Hypersensitivity pneumonitis

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Abstract | Hypersensitivity pneumonitis (HP) is a complex syndrome caused by the inhalation of a variety of antigens in susceptible and sensitized individuals. These antigens are found in the environment, mostly derived from bird proteins and fungi. The prevalence and incidence of HP vary widely depending on the intensity of exposure, the geographical area and the local climate. Immunopathologically, HP is characterized by an exaggerated humoral and cellular immune response affecting the small airways and lung parenchyma. A complex interplay of genetic, host and environmental factors underlies the development and progression of HP. HP can be classified into acute, chronic non-fibrotic and chronic fibrotic forms. Acute HP results from intermittent, high-level exposure to the inducing antigen, usually within a few hours of exposure, whereas chronic HP mostly originates from long-term, low-level exposure (usually to birds or moulds in the home), is not easy to define in terms of time, and may occur within weeks, months or even years of exposure. Some patients with fibrotic HP may evolve to a progressive phenotype, even with complete exposure avoidance. Diagnosis is based on an accurate exposure history, clinical presentation, characteristic high-resolution CT findings, specific IgG antibodies to the offending antigen, bronchoalveolar lavage and pathological features. Complete antigen avoidance is the mainstay of treatment. The pharmacotherapy of chronic HP consists of immunosuppressive drugs such as corticosteroids, with antifibrotic therapy being a potential therapy for patients with progressive disease.

Susceptible
Increased risk of developing a disease, usually associated with genetic or host factors.

Sensitized
Presence of specific antibodies to the offending antigen.

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Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) resulting from an immune-mediated response in susceptible and sensitized individuals to a large variety of inhaled antigens found in the environment (TABLE 1). The antigens can be divided into predominantly organic antigens (such as bacteria, fungi, animal or plant proteins and enzymes) and inorganic agents (such as low-molecular-weight chemicals or metals). HP can also be referred to on the basis of the provoking condition such as 'farmer's lung' for HP caused by exposure to mouldy hay or straw or 'bird breeder's lung' caused by exposure to feather dust and bird droppings. The disease involves the terminal bronchioles, the alveoli and the interstitium and is characterized by a bronchiolocentric granulomatous and cellular interstitial pneumonia. The development, progression and clinical presentation are thought to be influenced by factors that include the nature and quantity of the inhaled antigen, the intensity and frequency of exposure, environmental cofactors, and the interaction of the offending antigens with the immune response[1–3]. Genetic and host factors may explain why only few individuals develop the disease; some individuals with similar exposure will become sensitized but remain healthy whereas others will not become sensitized[1].

HP may be classified as acute or chronic; the term subacute HP was previously used, yet it is difficult to distinguish from acute HP and has been eliminated from the classification. Acute HP is attributed to intermittent, high-level exposure to the inducing antigen[1,4]; symptoms typically occur abruptly (~4–12 hours after exposure) and patients often experience a flu-like syndrome. By contrast, chronic HP is thought to result from long-term, low-level exposure, usually to birds or moulds in the domestic environment[1,5,6]. Chronic HP is not easy to define in terms of time and may occur within weeks, months or even years of exposure. Thus, it has been suggested that it is more important to subclassify this clinical form as non-fibrotic or fibrotic, which has important prognostic and management implications[7]. The insidious onset of non-specific pulmonary symptoms, such as cough and dyspnoea, as well as fatigue and lack of or unnoticed acute episodes often leads to the misdiagnosis of patients as having other chronic ILDs such as idiopathic pulmonary fibrosis (IPF)[5,8]. Further complicating this differentiation, chronic fibrotic HP may show a similar histological pattern to IPF with a similar poor prognosis[9]. Antigen recognition and removal of exposure is of crucial importance to improve outcomes. Additionally, diagnostic criteria have been

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proposed that highlight the value of identifying a characteristic HP pattern on high-resolution CT (HRCT) and of identifying lymphocytosis upon bronchoalveolar lavage (BAL). This Primer provides a comprehensive review on recent advances in our understanding of HP epidemiology and pathogenesis as well as on the current diagnostic and therapeutic modalities.

Epidemiology

Incidence and prevalence

HP is a rare disease that can develop in people of all ages, including children, with a mean age at diagnosis of 50–60 years. Overall, an almost equal sex distribution has been noted[10] but there is some variation depending on the type of HP and the exposure conditions, with chronic HP being more frequent in males in some series[11,12]. Population-based national epidemiological studies show divergent results, with a female predominance of 58% in the United States[13] and a male predominance of 57% in Denmark[14]. HP is less frequent in smokers or ex-smokers[10]; the reasons for this are uncertain but it has been reported that nicotine dampens macrophage activation, decreases lymphocyte proliferation and impairs T cell function, all of which are necessary components of the immune processes implicated in HP pathogenesis[1]. The prevalence of HP is varied, reflecting the different causes and intensity of exposures, the geographical area, and the local climate and customs. An epidemiological survey in Spain revealed that the incidence of ILD is 7.6 per 100,000 persons annually, of which 6.6% of cases were HP, ranking fifth overall among ILDs in this country after IPF (38.6%), pulmonary sarcoidosis (14.9%), cryptogenic organizing pneumonitis (10.4%) and connective tissue disease-associated ILD (10.0%)[15]. However, in a recent ILD registry from India, HP was the most common cause of ILD (47.3%), followed by connective tissue disease-associated ILD (13.9%) and IPF (13.7%)[16]. Furthermore, in the United Kingdom, the incidence over the period 1991–2003 was shown to be 0.9 per 100,000 population[17], nearly twice that in the Spanish report.

In the late 1980s, the estimate of the annual incidence of HP was 0.5–0.6 per 100,000 in a population-based registry from New Mexico, United States[18]. A subsequent national population-based study from the United States (covering the period from 2004 to 2013) reported a yearly incidence in the range of 1.28–1.94 per 100,000 population, with relative stability over time[13]. Current data from Denmark are in line with this current US data, with incidence over the period 1998–2010 being 1.16 per 100,000 (REF.[14]). Prevalence ranged from 1.67 to 2.71 per 100,000 in the US study, and increased with age (11.2 per 100,000 among those aged ≥65 years)[13] but not over time. Data from the global south, including Australia, Africa and South America, are not available to the best of our knowledge.

Inciting antigens

Bird-related HP is likely to be the most frequent subtype of HP, with clinical symptoms of HP reported in 5–15% of all pigeon breeders[19]; another common form is farmer's lung. Indeed, according to a worldwide study of 116 cases, the incidence is highest for avian (bird-related disease), followed by bacterial (farmer's lung) and fungal (humidifier lung, summer-type HP) antigens[20]. Avian antigens also make up the highest proportion of HP cases in some regions, including in Mexico, Turkey and Europe[6,21,22]. The incidence of farmer's lung depends on geographical and seasonal conditions as well as on agricultural practices[23]. The annual incidence of farmer's lung caused by *Saccharopolyspora rectivirgula*, *Thermoactinomyces vulgaris*, *Absidia corymbifera*, *Eurotium amstelodami* or *Wallemia sebi* shows regional variations, ranging from 8 to 60 per 100,000 farmers in Finland, for example[24]. The Finish survey showed a prevalence of 1,400 per 100,000 farmers. According to survey data from 1976 in the United States, the prevalence of farmer's lung caused by *S. rectivirgula* is 3,000 per 100,000 farmers[25]; however, contemporary data are not available. In France, a survey from 1988 showed the prevalence to be 1,803–6,080 per 100,000 farmers[10].

Limited data specify the epidemiology of acute HP versus chronic HP, which can be attributed in part to divergent diagnostic criteria for HP. In Japan, according to an epidemiological study reported in 1991, 70–80% of acute HP cases are summer-type HP caused by *Trichosporon asahii*[26], whereas a nationwide epidemiological survey reported in 2013 revealed that ~50% of chronic HP cases correspond to bird-related disease caused by proteins from bird faeces or feathers[2]; furthermore, <40% of chronic HP cases are summer-type HP or house-related HP cases caused by fungi including *Trichosporon*[2]. Thus, the incidence according to the inciting antigen is different between acute and chronic HP, with most cases of acute HP being caused by fungi and about half of chronic HP caused by avian antigens[6]. Approximately 40–50% of chronic HP cases are fibrotic[9,11,13,27].

Mortality

In terms of outcome, the identification and avoidance of the offending antigen or antigens remains the most important measure as persistent antigen exposure is associated with increased mortality[3,28]. By contrast, antigen avoidance was shown to be associated with clinical improvement in 40% of patients with chronic fibrotic HP[29]. In a UK study, patients with HP carried a threefold increased risk of death compared with the

Bronchoalveolar lavage (BAL). A method to collect cells and fluid from the alveolar spaces for diagnostic or research purposes.

Summer-type HP
A subtype of HP mainly in Japan caused by the fungus *Trichosporon asahii* growing in decayed wood in housing.

House-related HP
A subtype of HP mainly caused by exposure to fungi in the home.

Table 1 | **Example antigens and antigen sources**[a]

Antigen	Antigen source	HP variant
Bacteria		
Thermophilic actinomycetes	Mouldy hay and straw	Farmer's lung
Klebsiella oxytoca	Humidifiers	Humidifier's lung
Thermophilic actinomycetes	Sugar cane dust	Bagassosis
Mycobacteria		
Mycobacterium avium complex	Outdoor hot tubs	Hot-tub lung
Mycobacterium immunogenum	Metal-working fluid	Machine operator's lung
Fungi		
Absidia corymbifera	Mouldy hay and straw	Farmer's lung
Trichosporon cutaneum	Indoor households	Summer-type HP
Penicillium roqueforti	Cheese washing and/or industrial source	Cheese-worker's lung
Animal proteins		
Feathers and excrements	Birds	Bird breeder's or fancier's lung
Serum and urine	Rats	Rat protein alveolitis
Plant proteins		
Nut dust	Processing of tiger nuts	Tiger nut alveolitis
Soy dust	Soy foods	Soy dust alveolitis
Enzymes		
Phytase	Animal feed	Phytase alveolitis
Enzymes from *Bacillus subtilis*	Detergent industry and/or cleaning products	Detergent worker's lung
Chemicals		
Toluene diisocyanate, methylene diphenyl isocyanate and hexamethylene diisocyanate	Paint and/or varnish	Isocyanate lung
Acid anhydrides	Plastic industry	Acid anhydride alveolitis
Metals		
Zinc vapour	Zinc welding	Zinc vapour alveolitis
Zirconium	Ceramic tile work	Zirconium silicate alveolitis

HP, hypersensitivity pneumonitis. [a]Some common examples from each category of antigens are provided.

general population[17]; a Danish study reported a two-fold increased risk[14]. The overall age-adjusted mortality of HP in the United States was reported to be 0.19 per million[30]. A US study using a national cause-of-death database showed an increase in the age-adjusted mortality of HP from 0.12 to 0.68 per million from 1988 to 2016, which may reflect increased disease recognition[31]. Fibrotic HP has a higher mortality than non-fibrotic HP, of 67.5 versus 45.2 per 1,000 person-years according to another US study[13]. A Finish study reported a mortality of 0.7% in patients with farmer's lung; death occurred on average 8 years after diagnosis[32]. The causes of death in patients with chronic HP are respiratory failure in ~42–62% of patients (including ~0–53% of whom experienced acute exacerbation (acute respiratory failure of unknown cause) as a contributing factor), infection in ~0–32% and cardiovascular diseases in ~0–6%[33–35]. The association between the type of causative antigen and death remains to be determined.

Genetic risk factors

Although patients usually have sporadic HP, familial disease has been described in few reports, mostly from Japanese populations[36,37]. Interestingly, mutations in genes linked to telomere shortening, such as *TERT*, *TERC*, *RTEL1* and *PARN*, are detected in families with different ILDs, in which some of the affected individuals had HP[38]. To date, there are no studies evaluating genetic susceptibility through genome-wide association and few have been performed using targeted genotyping, primarily related to the highly polymorphic major histocompatibility complex (MHC)[39–42]. In general, these studies have indicated that common variants of the MHC class II region (HLA-DR and HLA-DQ), of proteins involved in antigen processing and presentation (namely, the transporter associated with antigen processing (TAP) complex) and of immunoproteasome components (for example, PSMB subunit, β-type 8) increase the risk of the disease[39–42]. More recently, an increased risk for chronic HP was shown to be associated with the *MUC5B* promoter polymorphism rs35705950 (REF.[43]).

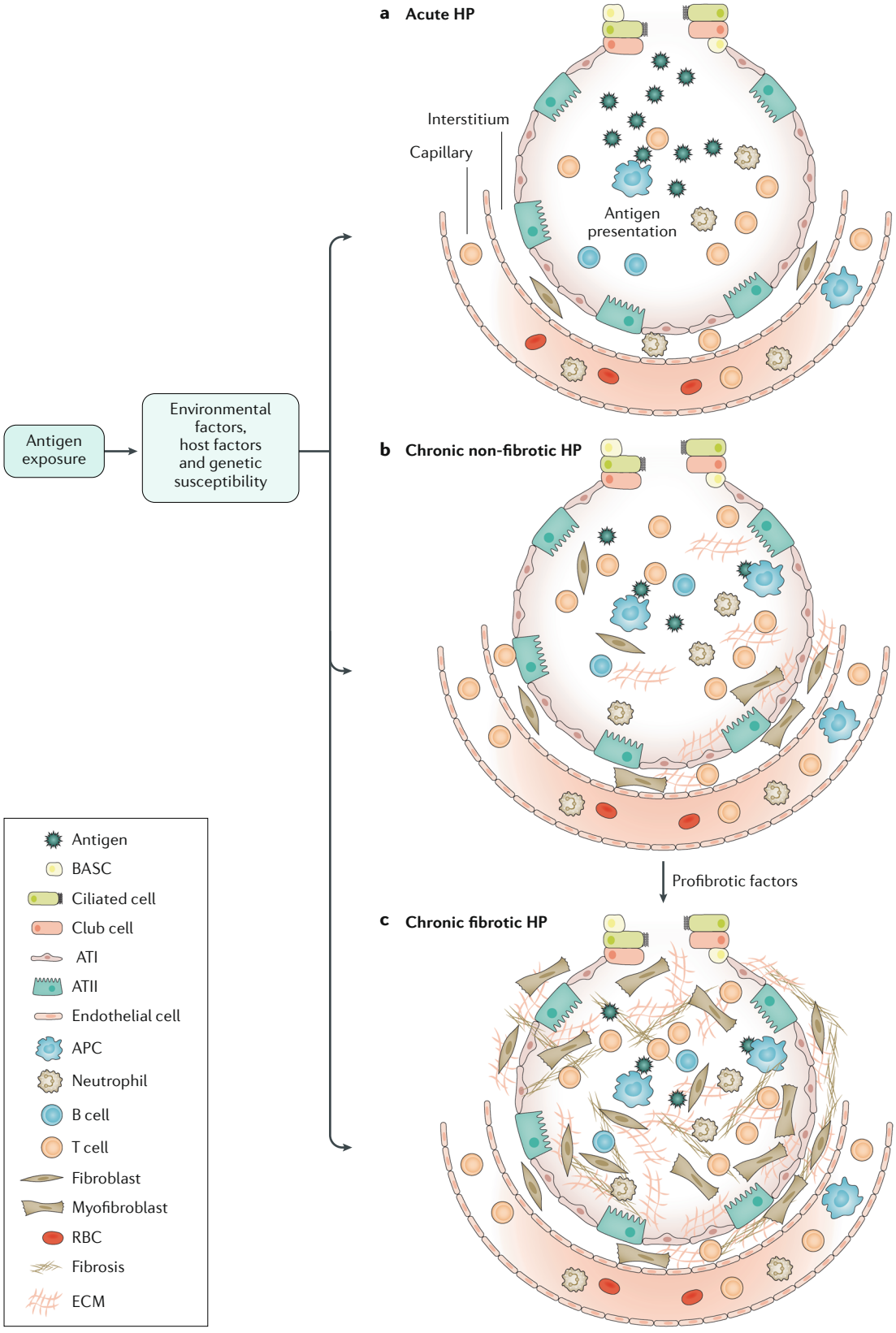
Mechanisms/pathophysiology

Inciting antigens

Bird breeder's lung. The sources of avian antigens are feather dust, excrement and serum from the animals. The most common bird types causing HP are pigeons[44] and budgerigars (parakeets)[45], with exposure to canaries[46], parrots[47], cockatiels[48] and love birds[49] observed less frequently. The reasons underlying this difference is not clear but may be due to budgerigars being common pets. Only a few cases have been reported to be caused by native, uncaged birds such as starlings[50] or owls[51,52]. Indirect antigen exposure can induce bird-related HP, caused by allergens being transported by a partner[53] or by exposure to feather-based products[54]. A specific form of bird-related HP — feather duvet lung — caused by exposure to feather duvets and pillows has been reported[55] and is associated with the presence of specific IgG antibodies to goose and duck feathers[56]. Cross-reactions between different avian antigens are common and, therefore, it is highly recommended to distance all feather duvets and pillows from every patient with bird fancier's lung[57]. Avian antigens can be detected for prolonged periods of time after removal of the bird and environmental clean-up[58], indicating that occult exposure to avian antigens is possible; for example, bird breeder's lung may develop even after moving into a new home where the former resident had kept birds[59].

Farmer's lung. The relationship between hay exposure and pulmonary symptoms was first described in 1932, with the immunological pathogenesis being suspected by the detection of specific IgG antibodies in 1962 (REFS[60,61]). The most frequent antigens are thermophilic actinomycetes (*S. rectivirgula* or *T. vulgaris*) and fungi (*A. corymbifera*, *E. amstelodami*, *W. sebi* and *Aspergillus fumigatus*), which grow in large numbers when wet stored hay begins to warm[62–65]. Exposure to other farming environments such as greenhouses[66] or compost[67] and stored maize corn[68] can also cause HP.

Humidifier lung. Humidifier lung was initially considered an occupational disease caused by contaminated humidifiers or air conditioners[69]. A variety of antigens were isolated in humidifier water or ventilator systems, including thermophilic actinomycetes and other bacteria, moulds and yeasts. Owing to the increasing regulations of occupational accident insurance, a decline in incidence of this disease type has been noted, for example, in the German occupational accident statistics records[70]. However, a new kind of humidifier



Granuloma
A focal collection of inflammatory cells, predominantly mature macrophages that form an aggregate in response to an antigen. It consists of a tightly formed conglomerate of epithelioid and multinucleated giant cells encircled by lymphocytes, especially $CD4^+$ T helper cells. In hypersensitivity pneumonitis, these are small poorly formed non-necrotizing epithelioid cell granulomas.

lung related to the use of domestic ultrasonic misting fountains has more recently emerged[71].

Mycobacteria-related HP. Some patients with hypersensitivity-like lung disease after exposure to water aerosols of hot tubs are shown to have non-tuberculous mycobacteria (NTM) in BAL fluid or even in lung specimens; NTM is frequently found in the water of the hot tubs[72,73]. Thus, so-called hot-tub lung can be difficult to differentiate from infection due to mycobacteria often being detected in the lung or BAL specimen, which is atypical in other HP types. Other outbreaks of hypersensitivity-like lung diseases and exposure to NTM have been related to occupational settings with metal work fluids of machining and grinding operations caused by *Mycobacterium immunogenum*[74] or observed in patients treated for intravesical immunotherapy of non-invasive bladder tumours with locally administered Bacillus Calmette–Guérin[75].

Emerging HP diseases. Various wind instruments have recently been identified as an antigen source for HP (so-called wind instrument's lung). Contamination with moulds, bacteria or mycobacteria (for example, *Ulocladium botrytis*, *Mycobacterium chelonae* and *Stenotrophomonas maltophilia*) has been found in a saxophone[76], trombone[77], bassoon[78], tenor horn[79] and bagpipe[80], having caused HP in the players and making this an important exposure to consider in new cases of HP.

Disease development

A complex interplay of genetic, host and environmental factors influences the development and progression of HP (FIG. 1). This complexity explains why, despite the worldwide distribution of the offending antigens, only few exposed individuals develop the disease[1]. Indeed, to develop HP, an exaggerated humoral and cellular immune response is also required, affecting the small airways and lung parenchyma. This hyper-response is at least partially related to an impaired lung immunosuppressive function by regulatory cells[81].

Antigen presentation. Antigen-presenting cells (namely, dendritic cells and alveolar macrophages) located close to the alveolar epithelial surface are activated by the presence of antigen and, in those with HP, induce the differentiation of T cells into a variety of effector subsets, primarily T helper 1 (T_H1) cells, in a process driven by IL-12, TNF and IFNγ expression (FIG. 2). Indeed, in patients with HP, increased expression of these T_H1-associated cytokines is found in lung macrophages; there is also a predominance of IFNγ-producing T cells[1,82,83].

Several mechanisms contribute to the interstitial and intra-alveolar infiltration of immune cells, including increased local proliferation of T cells, abnormal inhibitory capacity of mesenchymal stem cells, diminished immunosuppressive regulatory T (T_{reg}) cell activity[81,84] and a resistance to apoptosis, at least in part attributed to an increase in the expression of the anti-apoptotic protein BCL-X_L[85]. Additionally, a complex programme for cell recruitment and homing that involves the upregulation of multiple chemokines, such as CCL5, CCL4, CXCL9 and CXCL10 (REFS[1,86]), contributes to interstitial and intra-alveolar immune cell infiltration. The sequence of events leading to granuloma formation is likely to be regulated by T_H1-associated mechanisms, mainly inducing the functional differentiation and survival of macrophages and dendritic cells[87]. Indeed, in a model of pulmonary granulomatosis in mice, inhibition of this pathway decreased the accumulation of T_H1 cells and attenuated granuloma formation[88].

In the acute form of the disease, usually related to intermittent high-level antigen exposure and likely to be mediated primarily by immune complexes, there is an increase of neutrophils attracted by several interleukins, including IL-8 (REF.[89]) and IL-17 (REF.[90]). A post-mortem study of human acute HP has revealed prominent interstitial neutrophilic infiltrates and fibrin deposition[91]. Experimental models of acute HP have shown that, in both BAL and lung tissue, neutrophils are the predominant infiltrating cell type and that they may contribute to the immunological response involved in granuloma formation, particularly in an early phase of the process[92]. The type (intermittent versus continuous) and the levels (high versus low) of antigen exposure are presumably important factors for the development of acute or chronic disease[5].

Sensitization. Environmental antigen exposure in genetically predisposed individuals may lead to sensitization that can be detected through the presence of specific antibodies (usually IgG) in the serum. Most sensitized individuals do not develop the disease but may occasionally have a small increase in BAL lymphocytes[93] without clinical relevance. Subsequent exposure may result in the production of high-affinity specific antibodies, in the formation of immune complexes and in the in situ generation of the complement activation product C5a. Activation of lung macrophages results in the production of IL-1 and TNF as well as in the upregulation of adhesion molecules that enhance the adhesion of neutrophils and facilitate their transmigration into the interstitial and alveolar spaces[94]. It is assumed that acute HP is mainly mediated by this mechanism.

Second hit. As well as antigen exposure in a genetically susceptible individual, an additional hit seems to contribute to the development of HP. Common respiratory viruses, mainly influenza A virus, have been frequently found in the distal airways of patients with

◀ Fig. 1 | **Pathogenesis of HP.** Exposure to antigens in an individual with genetic predisposition and certain environmental exposures (such as to viruses, pesticides or air pollution, mainly exposure to particulate matter <2.5 μm in diameter ($PM_{2.5}$)) may lead to the development of an exaggerated immune reaction that may result in acute lung inflammation, characterized by the recruitment of neutrophils as well as T cells and B cells (panel **a**). This immune reaction can become chronic (panel **b**), leading to the activation of myofibroblasts and the deposition of extracellular matrix (ECM). In some individuals, in the presence of progressing factors (such as ageing, further exposure or genetic predisposition), critical pathogenetic changes occur that result in the expansion and activation of fibroblast and myofibroblast cell populations as well as in the exaggerated accumulation of ECM and destruction of the lung architecture (panel **c**). APC, antigen-presenting cell; ATI, alveolar epithelial type I cell; ATII, alveolar epithelial type II cell; BASC, bronchioalveolar stem cell; HP, hypersensitivity pneumonitis; RBC, red blood cell.

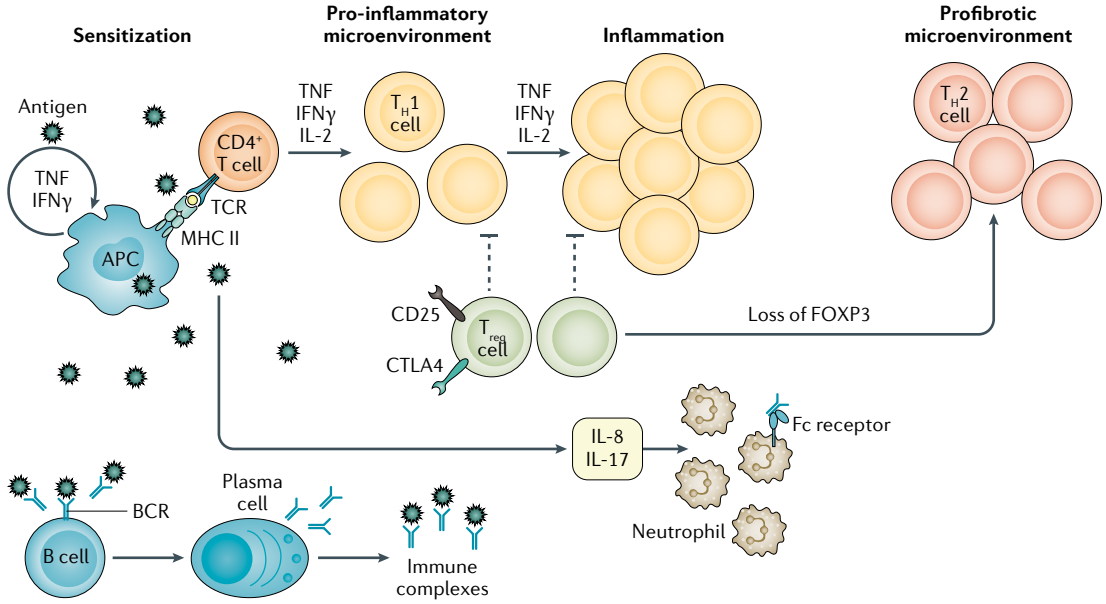


Fig. 2 | **Immunopathology in HP.** The immune responses to hypersensitivity pneumonitis (HP) antigens involve adaptive and innate immunity and include T cells and B cells. Following inhalation, the antigen is phagocytosed and degraded by antigen-presenting cells (APCs), such as macrophages and dendritic cells, and coupled to major histocompatibility complex (MHC) class II (MHC II) molecules. The antigen is then recognized by $CD4^+$ T cells through the T cell receptor (TCR). A T helper 1 (T_H1)-type differentiation of $CD4^+$ T cells is initiated through expression of the transcription factor T-bet, and cytokines such as TNF, IFNγ and IL-2 drive the proliferation and differentiation of these cells. Progression from sensitization to HP initially requires the accumulation of $CD4^+$ T_H1 cells in the lung, creating a pro-inflammatory microenvironment. IFNγ and TNF promote the accumulation, activation and aggregation of macrophages, resulting in the development of granulomatous inflammation. On the other hand, the suppressive activity of regulatory T (T_{reg}) cells is impaired, which facilitates the amplification of the inflammatory response. T_{reg} cells express the transcription factor FOXP3 as well as CD25 and CTLA4 on the cell surface. The decrease of FOXP3 expression reduces the suppressive function of T_{reg} cells (indicated by dashed lines) and some evidence indicates that T_{reg} cells expressing decreased FOXP3 preferentially become T_H2-type effectors (which express GATA3 and STAT6), even in an environment that favours T_H1 cells. During chronic HP, a switch from a T_H1 to T_H2 environment could contribute to the profibrotic response. A B cell response against the antigens also occurs, leading to the production of specific antibodies and the formation of immune complexes. IL-17 is likely to be produced by some subpopulations of $CD4^+$ T cells and IL-8 is mainly secreted by alveolar macrophages; both cytokines are potent chemoattractants for neutrophil recruitment and activation. Neutrophils express receptors for the constant region of IgG immunoglobulins (FcγRs), favouring the recruitment of these cells to the site of inflammation and the interaction with antigen–antibody immune complexes, a process involved mainly during acute HP. BCR, B cell receptor.

acute HP[95]. Similarly, mice receiving Sendai virus and simultaneously sensitized with HP antigens developed a marked enhanced inflammatory response to the antigen that persisted long after the transient viral infection had resolved[95,96]. Viral infections may affect antigen clearance, increasing the antigen-presenting capacity of alveolar macrophages through the upregulation of B7 co-stimulatory molecules and inducing the release of pro-inflammatory cytokines such as TNF and IL-1 (REF.[97]). A high exposure to pesticides is a potential risk factor for the development of HP in farmers[98]. Furthermore, a strong positive correlation between the percentage of HP cases and higher levels of air pollution (mainly atmospheric particulate matter with diameters <2.5 μm ($PM_{2.5}$)) has been revealed in several cities in India[99]; the reasons are unclear, but air pollutants may lead to airway inflammation and reduced mucociliary clearance with resultant lung retention of the antigens.

Some host-related conditions may also increase the risk for HP. For example, microchimerism, characterized by the persistence of foreign fetal cells, is frequently found in the lungs of parous female patients with HP[100]. Other as-yet unknown promoting factors are also likely to facilitate the initiation and/or development of HP.

Immunopathology. B cells are recruited to the site of inflammation from the peripheral blood and, through the B cell receptor, recognize antigens tethered to the surface of specialized antigen-presenting cells and differentiate into high-affinity, antibody-producing plasma cells[101]. After the lung immune-complex mediated reaction arises, strong evidence indicates that HP is associated with a T cell-mediated immune reaction. Natural and inducible $FOXP3^+$ T_{reg} cells are required for the maintenance of immune tolerance (preventing excessive inflammation) and are likely to be involved in the appropriate immune response in antigen-exposed individuals who do not develop HP or who have subclinical controlled, reversible inflammation. In this context, there is evidence with lymphocytes obtained from BAL and blood samples from healthy individuals, asymptomatic individuals and patients with HP suggesting that

Honeycombing
A form of lung fibrosis on high-resolution CT (HRCT) with cyst clusters having a bee honeycomb appearance.

Traction bronchiectasis
Widening of the bronchial lumen through traction exerted by shrinking fibrotic lung tissue as a sign of lung fibrosis on high-resolution CT.

Reticulation
A form of lung fibrosis on high-resolution CT with a net-like appearance.

Usual interstitial pneumonia
(UIP). A radiological and a histopathological pattern that is seen mainly in idiopathic pulmonary fibrosis but may be observed in other fibrotic lung disorders. On chest high-resolution CT, it is characterized by the presence of reticular changes, predominantly bilateral, peripheral and basal, and usually associated with traction bronchiectasis and honeycombing. Histopathologically, it is characterized by interstitial fibrosis showing spatial heterogeneity with patchy involvement of the lung parenchyma, areas of marked fibrosis, architectural distortion and microscopic honeycombing.

Non-specific interstitial pneumonia
(NSIP). A lung disease characterized by histological features of varying amounts of interstitial inflammation and fibrosis with a uniform appearance.

patients with HP have dysfunctional lung and circulating $FOXP3^+CD4^+$ T_{reg} cells that are unable to suppress the proliferative response of activated T cells[81]. This finding suggests that a defect in T_{reg} cell function is involved in the pathogenesis of HP (FIG. 2). Preliminary observations with mesenchymal stem cells obtained from BAL in children with HP also suggest that these cells, which modulate the activity of antigen-presenting cells by suppressing lymphocyte proliferation, also fail to inhibit $CD4^+$ and $CD8^+$ T cell proliferation and activation in these patients, thereby enhancing inflammation[84].

The inflammatory response may be reversible through avoidance of further antigen exposure with or without corticosteroid treatment. However, some patients develop fibrosis and eventually die from the disease.

Progression to fibrosis

The processes, circumstances and mechanisms triggering irreversible fibrotic progression in HP remain uncertain. Epidemiological data suggest that fibrotic HP increases with age, in particular after 65 years[13]. The ageing-associated mechanisms are unknown but may be related to aberrant shortening of telomeres and T cell immunosenescence[43]. Age also influences the presence of fibrotic features, including honeycombing, traction bronchiectasis and reticulation, which are associated with shorter survival[9]. Similarly, in experimental models[102], aged mice exposed to sustained inhalation of organic dust displayed a higher upregulation of Toll-like receptors, chemokine ligands and genes involved in natural killer cell-mediated cytotoxicity than young mice[103]. Importantly, gene clustering studies indicated that the severity of the fibrotic response, at least at the transcriptional level, occurs much earlier in middle-aged mice than in younger littermates.

Although cigarette smoking is associated with a reduced risk of developing HP[1], chronic fibrotic HP is associated with smoking[1,11,104,105]. Indeed, patients with morphological features of usual interstitial pneumonia (UIP)-like or fibrotic non-specific interstitial pneumonia (NSIP)-like morphological patterns are predominantly current or former smokers[106]. Additionally, an inability to identify the inhaled antigen or the persistence of exposure to a known antigen have been associated with shorter survival, likely due to the development of fibrosis[11,28]. Finally, some patients display autoimmune features, including a higher prevalence of autoantibodies, such as antinuclear antibodies (ANAs), rheumatoid factor, cyclic citrullinated peptide, Scl-70, SS-A/Ro or SS-B/La, that are associated with worse outcomes[107,108]. Interestingly, the frequency of hypothyroidism is increased in patients with HP and is associated with an autoimmune serology[109]. Of note, hypothyroidism by itself has been shown to be an independent predictor of mortality in patients with HP[109].

Changes in the immune response. Several likely pathogenesis-associated T cell subsets are found in chronic fibrotic HP, including an increase of the $CD4^+$ to $CD8^+$ ratio and a switch from a predominant T_H1-like phenotype to a T_H2-like phenotype[110]. The triggers of the switch from T_H1 to T_H2 are unclear but there is evidence that decreased FOXP3 expression in T_{reg} cells affects the suppressive function of these cells, which acquire the phenotype of effector T_H2 cells[111] (FIG. 2). T_H2-associated cytokines, mainly IL-4 and IL-13, have been causally linked to the development of fibrosis in a variety of chronic inflammatory diseases[112]. A T_H2-biased genetic background is also implicated in fibrosing processes in experimental models of HP[113]. T_H2 cells secrete IL-4, IL-13 and other cytokines that are predominantly associated with profibrotic inflammatory responses. In particular, IL-13 seems to induce fibrosis by stimulating the production and activation of TGFβ1 and by directly activating the proliferation of fibroblasts[114,115].

Chronic fibrotic HP in humans is also characterized by a decrease of γδ T cells, a subset of lymphocytes that have immunoregulatory and antifibrotic activities[110,116]. In experimental models, an αβ $CD4^+$ T cell subset expressing an activated effector phenotype and polarized to T_H17 cytokine signalling enhanced the fibrotic response[117]. The development of pulmonary fibrosis is dependent on IL-17A and is attenuated by neutrophil depletion[118]. Indeed, in chronic fibrotic HP, increased neutrophil infiltration rich in matrix metalloproteinase 8 (MMP8) and MMP9 is evident, correlates with the development of lung fibrosis and might be a predictor of poor outcome[119].

Fibroblast migration, proliferation and activation. Chronic inflammation usually evolves to fibrosis after the expansion of the fibroblast population. Fibroblasts differentiate into myofibroblasts, which promote the accumulation of extracellular matrix and the destruction of the tissue architecture. In chronic fibrotic HP, the source of fibroblasts is unclear, although it is assumed that migrating local mesenchymal cells are the main source.

Bone marrow-derived fibrocytes and the epithelial-to-mesenchymal transition (EMT) might contribute to the increased fibroblast population at the damaged alveolar and interstitial sites in which the inflammatory response in not appropriately controlled[120,121]. In chronic fibrotic HP, a marked number of bone marrow-derived fibrocytes are found in the lungs, likely attracted by CXCL12 produced by epithelial cells via the CXCL12–CXCR4 axis[120]. These fibrocytes induce the differentiation of fibroblasts to myofibroblasts with the subsequent overexpression of several profibrotic molecules[120]. Regarding EMT, the cellular colocalization of epithelial and mesenchymal markers was observed in alveolar type II epithelial cells in chronic fibrotic HP[121]. In experimental models of HP, cells undergoing EMT were predominant in lungs from T_H2-prone A/J mice that develop strongly fibrotic disease in contrast to specimens from T_H1-prone C57BL/6 mice[121]. This finding suggests that, in a predominantly T_H2-like lung microenvironment, EMT contributes to the expansion of the fibroblast population and supports a role of T_H2 as a profibrotic pathway in this disease.

As mentioned, the *MUC5B* rs35705950 minor allele, which is a strong genetic risk factor for IPF[122] and a predisposing variant for lung fibrosis[123], is also associated with pulmonary fibrosis in patients with chronic HP[43].

Auscultation
The action of listening to sounds as a part of medical diagnosis.

Ground-glass opacity
An area of mildly increased attenuation in the lung on high-resolution CT, looking like ground glass.

Bronchiolitis
Inflammation of the bronchioles, the smallest airways of the lungs.

Patients with HP carrying this variant and with a short telomere length showed a greater extent of fibrosis, histopathological features of UIP and reduced survival[43]. Although the putative profibrotic mechanisms remain unclear, this polymorphism provokes excessive production of mucin 5B, which results in mucosal host defensive dysfunction in the distal airways and impaired mucociliary clearance that may contribute to the disruption of the reparative mechanisms in the distal lung.

ECM and MMPs. Major alterations of extracellular matrix (ECM) assembly and mechanical forces that occur during inflammation may also affect the immune response. For example, the extra domain A of the mechanosensitive protein fibronectin is a ligand for Toll-like receptor 4 (TLR4), facilitating the delivery of antigens to TLR4-expressing dendritic cells, inducing NF-κB activation and increasing specific T cell activation[124].

Studies on ECM and MMPs in HP are scanty but an increase in versican and tenascin-C, which are ECM components, is observed in chronic HP[125]. Moreover, tenascin-C levels correlated with fibroblastic foci content in HP lungs, suggesting a profibrotic role[125]. Versican and other components of the ECM bind to chemokines, growth factors, proteases and receptors on the surface of the immune cells, influencing cell phenotype and communication. These mediators may be released or activated by MMPs increasing the local concentrations and promoting tissue inflammation and fibrosis[126].

MMPs regulate several immune processes, such as leukocyte migration and processing of non-ECM proteins such as cytokines and chemokines[127]. Interestingly, MMP8 and MMP9 are elevated in BAL fluids of patients with chronic fibrotic HP and tissue neutrophils showing intense immunoreactive MMP8 and MMP9 staining are increased in HP, correlating with lung fibrosis[119,128]. Activated MMPs are inhibited by four mammalian tissue inhibitors of metalloproteinases (TIMPs). Interestingly, two promoter variants, –915A>G and –1296T>C, in *TIMP3* decrease the susceptibility to HP[129]. TIMP3 is localized to the ECM through interaction with heparan sulfate and other sulfated proteoglycans and, among other functions, may regulate inflammation[129].

Diagnosis, screening and prevention

The clinical manifestations of HP are heterogeneous. Although the clinical subtypes of HP have conventionally been distinguished by the duration or nature of symptoms, subacute HP is difficult to distinguish from acute HP based on a cluster analysis in a large prospective cohort study[4] and has hence been eliminated as a clinical subtype. Moreover, the duration of symptoms is not straightforward to define and can be extremely variable. As the presence of fibrosis is the primary determinant of prognosis, a recent guideline has proposed the categorization of HP as either fibrotic (usually mixed inflammatory plus fibrotic, less frequently purely fibrotic) or non-fibrotic (that is, purely inflammatory)[7]. However, we suggest continuing to recognize acute HP because it is useful to characterize outbreaks of HP observed in occupational, recreational and home environments[71].

Patients with acute HP typically have non-specific respiratory symptoms such as cough, dyspnoea on exertion, fever and general fatigue usually for weeks or a few months. The abrupt flu-like symptoms that occur in farmers or in pigeon breeders within 4–12 hours after exposure are often confused with a viral or bacterial infection, frequently resulting in empiric treatment with antibiotics[130]. Physical examination should be noted for diffuse fine crackles on chest auscultation. Centrilobular micronodules and ground-glass opacity with a mosaic pattern on chest HRCT are other characteristic findings[131]. Many manifestations will disappear entirely within days or weeks after antigen avoidance.

Patients with chronic HP typically have a slowly progressive course with a presentation that is similar to IPF[8]. Patients will rarely have acute symptoms and will instead present with gradually increasing dyspnoea on exertion, fatigue, anorexia, cough and weight loss over several months or even years[5]. The diagnosis of chronic fibrotic HP can be challenging as an inciting antigen cannot always be found, the HRCT features may or may not be suggestive of the diagnosis, and even the histological findings may be of UIP or NSIP, without specific features of HP. Thus, a substantial proportion of patients with fibrotic HP may be misdiagnosed as having IPF[8].

On physical examination, fine crackles are observed in 90% of patients and digital clubbing in up to 30%[2]. In contrast to IPF and other fibrotic ILDs, a rather unique finding in some patients is the presence of inspiratory 'squeaks' on auscultation, caused by the coexisting bronchiolitis. The progressive pulmonary fibrosis that characterizes chronic advanced HP may respond to antigen avoidance but only in a minority of patients[29,132]. Some patients with chronic HP can manifest acute respiratory deterioration and acute exacerbation similar to IPF, with a similarly high mortality[33,133].

Diagnostic criteria

A number of non-validated diagnostic criteria recommendations for HP have been published[134–138]. The criteria for HP typically include exposure to a potential antigen, elevated IgG (precipitating) antibodies to the antigen, inspiratory crackles on auscultation, and an HRCT pattern compatible with HP and BAL lymphocytosis (BOX 1). Recently, two groups proposed diagnostic algorithms with the distinctions of 'unlikely', 'less likely', 'possible', 'probable', 'likely' and 'definite'[139,140], which seems impractical in consideration of the therapeutic consequences. A recent consensus-based approach for the diagnosis of chronic HP[141] may be more feasible for clinical use. In this international modified Delphi survey, two different case scenarios emerged as representing a confident diagnosis of chronic HP: first, identified exposure on history combined with HRCT features suggestive of chronic HP and lymphocyte counts >40% of total cells on BAL; second, any scenario that included an identified exposure and lung biopsy with characteristics of chronic HP. None of the scenarios that lacked exposure were thought to represent a confident diagnosis (even after inclusion of histopathological features)[141]. The recent guideline emphasized the necessity of a multidisciplinary discussion and defined the

Box 1 | **Proposed diagnostic criteria for HP**

Acute hypersensitivity pneumonitis (HP)

- Can be diagnosed if the following features are fulfilled
  - Exposure to a potentially offending antigen source
  - Recurrent episodes of symptoms, occurring 4–8 h after exposure
  - Elevated titre of specific IgG (precipitating) antibodies to an antigen
  - Inspiratory crackles on physical examination
  - High-resolution CT (HRCT) pattern compatible with acute or subacute HP[a]
- If all these features are not fulfilled, one of the following criteria can function as a substitute
  - Bronchoalveolar lavage lymphocytosis
  - Pathology of lung specimen consistent with acute HP
  - Positive laboratory inhalation challenge test (ICT), positive workplace challenge or improvement after avoidance of the suspected exposure

Chronic HP

- Can be diagnosed if four or more of the following criteria are fulfilled
  - Exposure to a potentially offending antigen source
  - Elevated titre of specific IgG (precipitating) antibodies to an antigen or bronchoalveolar lavage lymphocytosis
  - Reduced diffusing capacity for carbon monoxide and/or hypoxaemia at rest or exercise
  - HRCT pattern compatible with chronic HP
  - Pathology of lung specimen compatible with chronic HP
  - Positive laboratory ICT, positive workplace challenge or improvement after avoidance of the suspected exposure

From REF.[138]. [a]Difficult to distinguish from acute HP and has hence been eliminated from the classification.

diagnosis with different confidence levels according to the combination of imaging, exposure assessment, BAL lymphocytosis and histopathological findings[7].

Alongside diagnostic criteria, other studies have attempted to identify the features that would increase diagnostic confidence. In one early study, six predictors of a diagnosis of HP were identified by regression analysis: exposure to a known offending antigen (OR 38.8), symptoms occurring at 4–8 hours after exposure (OR 7.2), positive precipitating antibodies to the offending antigen (OR 5.3), inspiratory crackles on physical examination (OR 4.5), recurrent episodes of symptoms (OR 3.3) and weight loss (OR 2.0). If all predictors were present, the probability of HP would be 98%, without the evidence of a known antigen exposure, the probability of HP would be 62%, and with only four or fewer of these six predictors present, the probability of HP would be <50%[20]. This analysis emphasizes the crucial role of a detailed history of antigen exposure in patients with ILD suspected to have HP.

Differential diagnosis

The differential diagnosis of HP depends on the clinical presentation as acute or chronic disease. Patients with acute HP can be misdiagnosed as having viral or bacterial infections owing to the symptoms of recurrent fever, chills and dyspnoea. Organic dust toxic syndrome may also mimic an acute HP; it is a non-infectious illness with fever, dry cough, mild dyspnoea, headache and malaise but mostly without radiological signs, lung functional impairment or specific IgG antibodies[142]. The disease is caused by endotoxins from Gram-negative bacteria in patients exposed to biologic aerosols as in HP conditions[142–144].

The differential diagnosis of chronic non-fibrotic HP includes, among others, some granulomatous diseases such as sarcoidosis or tuberculosis. For patients with chronic fibrotic HP, all other chronic fibrosing ILDs must be considered as part of the differential diagnosis. Sometimes only an extensive work-up leads to the correct diagnosis of HP even in patients with suspected IPF[8]. The challenge to reach a correct diagnosis of HP is highlighted by a study on multidisciplinary team agreement on first-choice diagnoses in ILDs. In contrast to IPF (weighted $\kappa = 0.73$), the agreement between clinicians, radiologists and pathologists for a diagnosis of HP was low (weighted $\kappa = 0.29$), probably reflecting the lack of standardization of the diagnostic process in HP[145].

Diagnostic work-up

In the diagnostic work-up for suspected HP, a detailed exposure history is of crucial importance. Clinical features, HRCT, lung function, laboratory tests, BAL cell differentials and, potentially after multidisciplinary case review, histopathology are also helpful to establish the diagnosis and assess disease severity. If the results are inconclusive, an antigen inhalation challenge test (BOX 2), a workplace challenge or an antigen avoidance test can be helpful[132,146–149]. Reproduction of clinical symptoms along with laboratory and functional abnormalities after re-exposure to the suspected antigen can also support a diagnosis of HP[132,146].

Exposure history. Exposures can occur at home or in the workplace, be related to hobbies or sometimes occur indirectly in another environment frequently visited by the patient. Thus, a detailed patient history is needed to determine exposures at home and in other situations. A standardized questionnaire is useful for determining exposure; however, some items on such questionnaires are geographically specific. Several respiratory medicine societies and academic institutions have developed questionnaires related to ILDs in general but not specifically for HP[150]. One comprehensive questionnaire included all potential sources of HP exposure, encompassing the workplace, household, hobbies, environment and neighbourhood[139]; it is clinically useful because it contains a step-by-step questionnaire on the amount and frequency of antigens that may be used or encountered in daily life. Feather bedding and down comforters or duvets are often overlooked as triggers of HP and should also be considered in every patient with a newly identified ILD[55,56,151].

Radiology. HRCT is generally the standard of care in the radiological evaluation of HP and other ILDs; acute and chronic HP show some overlapping features (TABLE 2). The distribution of HRCT findings in acute HP and chronic non-fibrotic HP is mostly diffuse with no predominant lung zones. By contrast, chronic fibrotic HP may show predominant findings in the mid-to-upper lung zones, with a lower lobe predominance in up to 50% of patients[9,152,153] and, compared with IPF, a more frequent upper-zone and mid-zone distribution and relative sparing of basal lung zones[9,152,154,155]. The typical

Box 2 | **Antigen inhalation challenge tests**

To identify the causative antigen, symptoms and laboratory and lung function abnormalities are analysed in a controlled laboratory setting following the inhalation of a nebulized solution of the suspected antigen (for example, avian proteins and moulds) or exposure in a challenge chamber (for example, to isocyanates, wood dust or feathers). The procedure is neither standardized nor validated but can, when the result is positive, confirm the diagnosis of hypersensitivity pneumonitis (HP), whereas a negative test does not rule it out. Various response criteria are applied and typically include respiratory symptoms (such as cough and dyspnoea), increase in body temperature, increase in C-reactive protein levels (as a marker of inflammation), increase in blood leukocyte count, decrease in forced vital capacity and oxygen saturation occurring 8–12 hours after provocation. A positive test is usually diagnostic, although false-negative results may occur in ~25% of patients[149]; these are patients who have a final diagnosis of HP but in whom the inhalation challenge test returned a negative result. Sensitivity varies from 73% to 100% and specificity from 84% to 100%[147–149,249]. Owing to the risk of severe reactions, the test should only be performed in experienced specialized centres and after other investigations have proven inconclusive. Patients are monitored for up to 24 hours. Limitations to routine use include the lack of experienced laboratories and of standardized antigen preparations as well as the absence of validated criteria for a positive response[138].

HRCT features in acute HP and chronic non-fibrotic HP include ill-defined centrilobular micronodules, patchy or diffuse ground-glass opacities, and mosaic attenuation (reflecting coexisting bronchiolitis; FIG. 3). HRCT can be normal between episodes of acute HP[156]. HRCT alterations from acute HP and non-fibrotic HP may resolve after antigen avoidance but usually persist, mainly in chronic cases.

In chronic fibrotic HP, reticulation, traction bronchiectasis and, sometimes, honeycombing are superimposed with findings that are thought to represent inflammatory disease[157] (FIG. 4). A UIP pattern on HRCT can be seen in one-third of these patients, with an NSIP pattern being observed less frequently (in ~15% of patients)[153]. Mosaic attenuation or air-trapping and diffuse axial distribution of disease are key features that can discriminate chronic HP from other fibrosing ILDs[158]. In this regard, an HRCT diagnosis of chronic HP can be made with high confidence, with an accuracy of 88–92% and a sensitivity of 44–61% in the differentiation against IPF or NSIP[154,155]. Performing expiratory CT images can help detect areas of air-trapping. Emphysema can be found in some non-smoking patients with chronic HP, particularly in farmers[159,160]. Chest radiographic findings of HP are non-specific and include bilateral reticular and/or micronodular densities.

Lung function. Lung function tests are not specific in HP and are, therefore, not helpful in the differential diagnosis of patients with ILD. However, they are useful in the assessment of the initial impact of the disease, to monitor the clinical course under treatment and as a prognostic parameter. Lung function tests can return to normal after or in between episodes of acute HP. In all subtypes of HP, a restrictive pattern (reduced forced vital capacity (FVC) and reduced total lung capacity) combined with impaired gas exchange (a reduction of the diffusing capacity for carbon monoxide (DLCO) and/or hypoxaemia on exercise or at rest) is common[20,161–163]. An increase of alveolar to arterial oxygen difference on exercise tests is a more sensitive parameter of impaired gas exchange than DLCO[164]. In patients with farmer's lung, an obstructive pattern is possible and usually occurs in association with emphysema[165]. Bronchial hyper-responsiveness (defined as an increase in sensitivity to a wide variety of airway-narrowing stimuli) can occur in patients with farmer's lung, highlighting the frequent difficulty in distinguishing this disease from asthma[166].

Diffusing capacity for carbon monoxide (DLCO). A highly sensitive method to determine the ability of the lung itself to perform normal gas exchange.

Laboratory tests. Despite only being markers of sensitization and indicators of antigen exposure and not of disease, in an appropriate clinical setting, elevated specific IgG antibodies support the diagnosis of HP and can facilitate the identification of the responsible antigen source[20]. Although various qualitative and quantitative commercial methods exist to test specific IgG antibodies, these tests have different sensitivities and specificities and are only available for a limited number of antigens, for example, some specific avian antigens, moulds or bacteria. Specific IgG antibodies to cultured fungi can be measured concurrently with an environmental gravity air culture[167]. The choice of the antibody panel used in the laboratory tests depends on the geographical region. For example, electrosyneresis on cellulose acetate with *A. corymbifera* antigens is an applicable diagnostic tool for farmer's lung in France[168], whereas ELISA for *T. asahii* is useful to diagnose summer-type HP in Japan[169,170].

For quantitative methods, it is necessary to establish specific IgG reference values of healthy controls, particularly for newly detected antigens[56,171]. More than 50% of healthy farmers have specific IgG antibodies to antigens of the farming environment but without any manifestations of the disease and with the same prognosis as those without antibodies[172]. Specific IgG antibodies are not found in at least 10–15% of patients with HP, which may be due to inappropriate antigen testing[173]. In those with suspected bird fancier's lung or bird-related HP, specific IgG antibodies are less useful in chronic fibrotic cases because of a low sensitivity (26–79%)[174]. The relevance of specific IgG antibodies in chronic fibrotic HP remains unclear.

Bronchoalveolar lavage. As a sensitive diagnostic test for HP, a normal BAL cell differential can widely exclude the diagnosis and is only occasionally found in those with chronic fibrotic HP[175,176]. The characteristic but not specific finding of HP is a marked lymphocytosis (usually >50% of total cells), which can be present but less pronounced in chronic fibrotic HP[177–179] and higher than in other ILDs[176,180]. Lymphocytosis may also be found in sensitized but asymptomatic individuals (that is, in those with subclinical alveolitis)[93]. Such a lymphocyte increase is unusual in purely fibrotic ILDs such as IPF and, in this context, it has been proposed that a BAL lymphocytosis of >30% might discriminate between chronic fibrotic HP showing a UIP pattern on HRCT and IPF[181]. This view was recently confirmed by a large meta-analysis of BAL lymphocytosis in patients with chronic (mostly fibrotic) HP, which included 42 studies and found that the pooled estimate for the BAL lymphocyte proportion was 43%, significantly higher than in

IPF and other ILDs[182]. A lymphocytosis of >20% in BAL discriminated between chronic HP and other ILDs with a sensitivity of 68% and a specificity of 65%. In addition, neutrophils, eosinophils, mast cells and, more characteristically, plasma cells may be mildly elevated[177,183,184]. An increase in $CD8^+$ T cell numbers in BAL fluid of patients with HP results in a low $CD4^+$ to $CD8^+$ ratio, with mean values ranging between 0.5 and 1.5, which had been suggested to be helpful for the differentiation from pulmonary sarcoidosis, another granulomatous disorder with BAL lymphocytosis and, usually, a high $CD4^+$ to $CD8^+$ ratio[185]. However, the clinical utility of this ratio is limited by its high variability and frequent elevation in chronic HP[110,186]. The cellular morphological features in BAL fluid include signs of T cell activation (such as folded nuclei and broad cytoplasm) and foamy macrophages[185].

Histopathology. The histopathological evaluation of lung tissue is usually unnecessary for the diagnosis of acute HP; however, some patients without obvious exposures will have typical histopathological findings of HP and a diagnosis of HP on that basis can be suggested. If biopsy is needed in unclear cases with a low pre-test probability of HP, the preferred approach is through surgical or transbronchial lung cryobiopsy, depending on the local expertise; the alternative approach, transbronchial forceps biopsy, generates smaller specimens that are of limited diagnostic accuracy[187]. The risks and complications of surgical lung biopsy need to be considered[188,189], taking into account the comorbidities and functional impairment of the patient, including procedure-related mortality risk, acute exacerbations of the ILD, bleeding and prolonged air leak.

The characteristic histopathological patterns of acute, inflammatory and chronic non-fibrotic HP are cellular interstitial pneumonia (cellular NSIP), cellular bronchiolitis, and poorly or loosely formed granulomas and focal organizing pneumonia (FIG. 5). This histological triad can be accompanied by randomly scattered multinucleated giant cells within the interstitial inflammation and/or bronchiolar walls. Characteristically, the central regions of the secondary pulmonary lobule are predominantly involved[190].

In chronic fibrotic HP, histological changes can mimic the patterns of other fibrotic ILDs (FIG. 6). The characteristic pathological findings supporting HP include bronchiolocentric inflammation, peribronchiolar fibrosis, bronchiolar epithelial hyperplasia, and the presence of granulomas or multinucleated giant cells[191]. Cases with isolated UIP-like or fibrotic NSIP-like patterns have been reported[5,179,191–193], indicating that HP cannot be excluded based on these patterns. Recently, 119 cases of chronic HP were classified according to the major histopathological pattern (cellular NSIP, fibrotic NSIP, peribronchiolar inflammation with poorly formed granuloma, bronchiolocentric fibrosis and a UIP-like pattern); the fibrotic patterns, including fibrotic NSIP, bronchiolocentric fibrosis and UIP-like patterns, were associated with poor prognosis[27]. Similar findings have been revealed in other cohorts[179]. A Japanese autopsy study that compared patients with chronic fibrotic HP and patients with IPF found that the histological pattern in HP closely resembled the UIP pattern in IPF; centrilobular fibrosis was the hallmark in all cases, often bridging to perilobular areas but this was not specific for HP and was also observed in those with IPF[194].

Prognostication

The prognosis of HP is highly variable and depends on the type and duration of antigen exposure, the dose of the inhaled antigen and the clinical form of the disease[195]. In general, acute HP seems to have a favourable prognosis. After acute attacks, if diagnosis and treatment are prompt, patients usually experience complete remission[196]. However, in some patients with farmer's lung, frequent relapses of disease can lead to airway distortion and emphysema[197]. In chronic non-fibrotic HP, the minimization of antigen exposure is important to avoid relapse and progression of fibrosis[196]. The prognosis of chronic HP has generally been thought to be better than that of IPF but the presence of several clinical

Table 2 | **HRCT features**

Acute HP and chronic non-fibrotic HP	Chronic fibrotic HP
Features	
Ground-glass opacities	Reticular opacities, traction bronchiectasis and honeycombing
Centrilobular nodules of ground-glass attenuation that are small and poorly defined	Superimposed with findings of acute HP (for example, combination of ground-glass opacities, centrilobular nodules and mosaic pattern)
Areas of decreased attenuation represent a mosaic pattern secondary to air-trapping[a], corresponding to areas of bronchiolitis	Emphysema, alone or in combination with other features of chronic HP possible[b]
Head-cheese sign (a combination of ground-glass opacities, mosaic pattern and normal lung tissue)[c]	Thin-walled pulmonary cysts, few and not dominant (may also occur in patients with chronic non-fibrotic HP)
Distribution	
Mostly diffuse, usually bilateral, sometimes patchy and predominantly in the lower lung areas	Mostly lower lung zone predominance, sometimes diffuse or in mid-to-upper lung zones, with a subpleural and peribronchovascular distribution; usually bilateral, with relative sparing of the lower lung zones

HP, hypersensitivity pneumonitis; HRCT, high-resolution CT. [a]Additional expiratory CT images are helpful. [b]Particularly in patients with chronic farmer's lung. [c]Highly specific for HP.

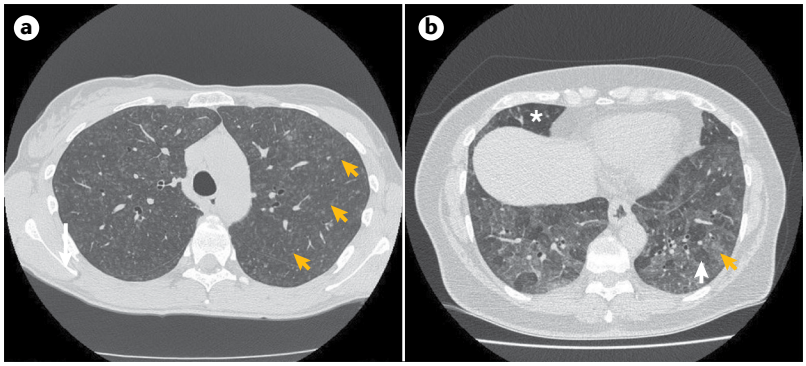


Fig. 3 | **HRCT of acute HP. a** | The upper lungs can show diffuse centrilobular nodules of ground-glass attenuation (arrows) bilaterally. **b** | The lower lungs can show bilateral combination of ground-glass opacities (yellow arrow), mosaic pattern (white arrow) and normal lung tissue (asterisk) — the so-called head-cheese sign. In chronic non-fibrotic hypersensitivity pneumonitis (HP), similar findings would be observed. HRCT, high-resolution CT.

factors and radiological or histological fibrotic features are associated with reduced survival[9,198,199] (TABLE 3).

Identified antigen. Identification of the inciting antigen represents the most important clinical factor shown to have a positive impact on survival[29]. A Japanese study found that the amount of avian antigen in household dust was associated with the prognosis of chronic bird-related HP[28]. Unfortunately, an inciting antigen cannot be always found[11,162]. In a study in 142 patients with well-characterized chronic HP, 37% of them with fibrosis on HRCT, the inability to identify an inciting antigen was independently associated with a 50% shortened survival (9 years versus 18 years)[11].

Radiological features. The radiological appearance is strongly associated with prognosis. On HRCT, signs of fibrosis, such as traction bronchiectasis and honeycombing, are the most important predictors of reduced survival in chronic HP[153,199–201]. Mosaic attenuation and/or air-trapping are associated with better survival[153]. One HRCT study showed that patients with chronic non-fibrotic HP had a median lung transplant-free survival of >14.7 years, compared with >8.0 years for those with chronic fibrotic HP without honeycombing and 2.8 years in those with honeycombing[9]. Automated computer-based CT stratification tools, such as CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating), represent the new frontier in machine learning-driven radiology assessment in those with ILD[202]. Recent studies have shown that CALIPER-derived variables, in particular reticular patterns, are the strongest CT predictors of mortality in HP in comparison with visual CT analysis[203,204]. Validation of these promising results is needed.

Lung function. Lung function tests, in particular FVC, are strongly correlated with survival. Patients with lower FVC at baseline and those with a ≥10% decline in FVC after 6–12 months have a significantly increased risk of all-cause mortality[29]. DLCO is also an independent predictor of mortality in chronic HP[204].

Histopathology. Similar to HRCT findings, several studies have shown that the presence of fibrosis on pathology, as honeycombing and/or fibrotic NSIP, is associated with reduced survival[27,106,205], while pure peribronchiolar fibrosis may portend a longer survival[106]. A recent study confirmed that a cellular NSIP pattern or peribronchiolar inflammation with poorly formed granulomas is associated with a better transplant-free survival than fibrotic patterns[27].

Pulmonary hypertension. Pulmonary hypertension is common in chronic fibrotic HP, present in 20–50% of patients and related to the severity of the disease; its presence is associated with poor prognosis[33,206,207]. Patients with pulmonary hypertension had a median survival of only 23 months compared with 98 months in those without pulmonary hypertension[206].

Other biomarkers. During the past decade, circulating biomarkers, such as lung epithelium-derived proteins and ANAs, have been investigated as stratifying or prognostic factors in HP. Proteins released by regenerating alveolar type II epithelial cells and cytokines released by alveolar macrophages have been thought to be early disease markers, reflecting epithelial damage and macrophage activation, respectively. Thus, three biomarkers, namely KL-6 (REFS[33,208,209]), YKL-40 (REF.[210]) and CCL17 (REF.[211]), have been extensively studied in sera and BAL samples to evaluate outcome in patients with HP. Serum KL-6 (REFS[33,209]) and YKL-40 (REF.[210]) predict disease progression and survival in HP, whereas serum CCL17 was shown to be a predictor of disease progression but not of survival[211]. ANA positivity has been reported in ~15–20% of patients with HP and is likely to be associated with worse outcomes compared with those of ANA-negative patients with HP[107]. Autoimmune hypothyroidism has also been reported as a negative prognostic factor but validation is needed[109]. The reasons

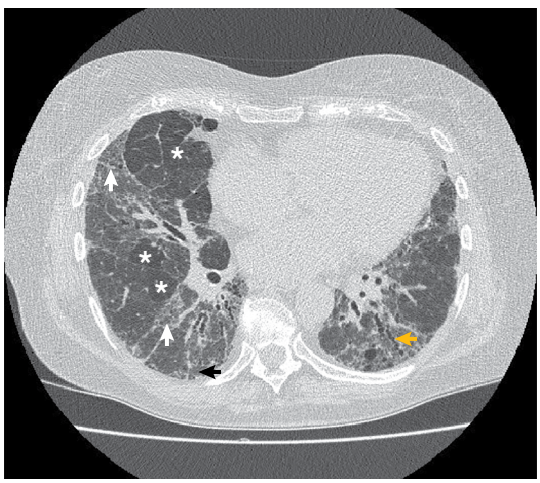


Fig. 4 | **HRCT in chronic fibrotic HP.** The lower lungs of a patient with chronic fibrotic hypersensitivity pneumonitis (HP) showing a combination of ground-glass opacities (white arrows), mosaic pattern (asterisks), and fibrotic lung disease with reticulation (black arrow) and traction bronchiectasis (yellow arrow). HRCT, high-resolution CT.

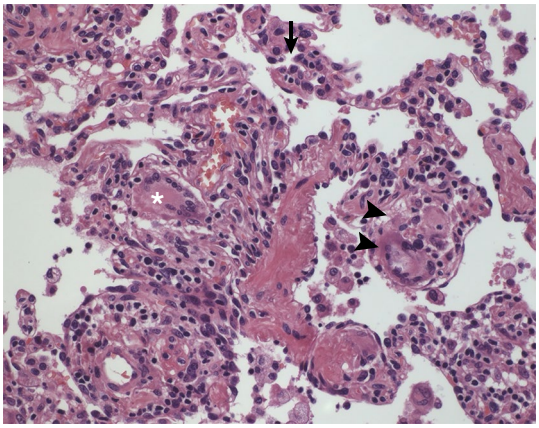


Fig. 5 | **Histopathology of acute inflammatory HP.** Cellular interstitial infiltrate (arrow) with loosely formed granuloma (arrowheads) and multinucleated giant cells (asterisk). In chronic non-fibrotic hypersensitivity pneumonitis (HP), similar findings would be observed. Haematoxylin and eosin stain, original magnification ×100. Image courtesy of D. Theegarten, University Hospital Essen, Germany.

underlying an association between autoimmunity and HP are unclear. It has been hypothesized that epithelial damage induced by antigen exposure can lead to post-translational modifications, alteration of mucosal proteins and production of citrullinated self-proteins[109]. However, none of these biomarkers has been validated for clinical use or proven to convey prognostic information beyond that suggested by readily available clinical and physiological features.

Other biomarkers that have been associated with reduced transplant-free survival in those with chronic HP include variants in telomere-related genes, which engender short peripheral blood telomere length[212]. The aforementioned rs35705950 variant in the promoter of *MUC5B* is also associated with the extent of fibrosis, histopathological features of UIP and reduced survival in patients with chronic HP[43].

Prevention

Diminishing or avoiding exposure to inciting antigens is crucial to prevent HP, as are routine inspections to identify potential sources of antigens in bioaerosols in the work place[1]. The removal or reduction of antigens from the environment is an important measure to prevent HP, particularly HP caused by bacteria or fungi. In bagassosis (TABLE 1), antimicrobial solutions were effectively used for the reduction of thermophilic actinomycetes during sugar cane processing[213]. In ventilation pneumonitis, air conditioner lung and humidifier lung, machinery should be drained daily, all 'slime' should be removed and the equipment sterilized frequently (for example, using bleach)[214]. Indoors, furnishings, drywall or carpeting that has become water-damaged should be removed[213]. Developments in haymaking and silage-making techniques have reduced the incidence of farmer's lung[22]. In summer-type HP, the causative antigen of which is *T. asahii*, cleaning, disinfecting and removing the colonizing locations have proven effective[215].

Personal protective equipment, for example, air-purifying respirators and masks that limit inhalation of the inciting antigens, can be considered when complete elimination of these antigens is impossible because of their professions (for example, farmers) or hobbies (for example, bird fanciers)[216–219]. Dust respirators, which are masks used to prevent diseases such as pneumoconiosis caused by the inhalation of airborne particulate matter, provide poor protection against organic particles and are not useful once sensitization has occurred[214].

Management

Complete antigen avoidance is the mainstay of treatment and patients should be advised in the strongest terms to avoid further exposure. However, identification of the causative antigen or antigens may not be straightforward and drastic measures (such as relocation to a new job or house) do not guarantee disease regression or even stability. Indeed, avian antigens may persist in the home despite removal of the offending animals and professional cleaning[58,220]. Other patients can have ongoing progression of disease even with complete exposure avoidance[165,221], suggesting a self-perpetuating aspect to the disease in some cases. Conversely, the disease may not progress despite continued exposure as shown in some farmers[217].

Acute HP

Most acute episodes of HP are self-limited, with patients fully recovering after antigen removal. Corticosteroids are often used, the rationale being suppression of the immune response, but the evidence supporting this approach is scant. In an 8-week study of patients with acute farmer's lung randomly assigned to the corticosteroid prednisolone ($n = 20$) or placebo ($n = 16$), DLCO improved significantly after 1 month in the prednisolone group; however, after 5 years of follow-up, no significant differences between treated and untreated farmers were observed in FVC, forced expiratory volume

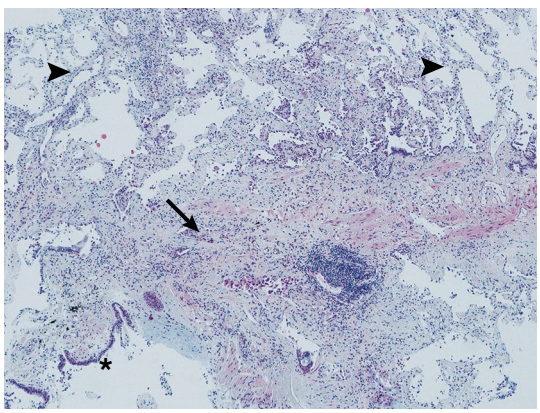


Fig. 6 | **Histopathology of chronic fibrotic HP.** Bronchiolocentric fibrosis with dense fibrosis (arrow) adjacent to a bronchiole (asterisk) and features of fibrotic non-specific interstitial pneumonia with alveolar septal thickening by fibrosis (arrowheads). Haematoxylin and eosin stain, original magnification ×20. HP, hypersensitivity pneumonitis. Image courtesy of D. Theegarten, University Hospital Essen, Germany.

Table 3 | **Factors associated with prognosis and/or survival in HP**

Factor	Disease progression[a] or acute exacerbation	Refs	Survival[b]	Refs
Antigen identification	Yes (++)	28,245	Yes (++)	11,28,245
Fibrosis on HRCT[c]	Yes (+)	245	Yes (++)	9,193,198,200, 204,205,245,246
Fibrosis on pathology	Unknown	NA	Yes (++)	27,152,193
FVC %pred	No (++)	210,245	Yes (++)	29,200,204,210
DLCO %pred	Yes (++)	210	Yes (++)	33,204,200,245
BAL lymphocytosis	Unknown	NA	Yes (++)	205,246
Pulmonary hypertension	Yes (+)	206	Yes (++)	206,207
Circulating KL-6	Yes (++)	209,247	No (+)	247
Circulating YKL-40	Yes (+)	210	Yes (+)	210
Circulating CCL17	Yes (+)	211,248	No (+)	211
Circulating ANAs	No (+)	107	Yes (++)	107,109
MUC5B rs35705950	Unknown	NA	Yes[d] (+)	43
Short telomeres	Unknown	NA	Yes[d] (+)	212

+, non-replicated results; ++, replicated results; %pred, percentage predicted, calculated as (observed ÷ predicted) × 100, whereby the predicted value is derived from reference equations; ANAs, antinuclear antibodies; BAL, bronchoalveolar lavage; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HRCT, high-resolution CT; KL-6, Krebs von den Lungen 6; NA, not applicable; YKL-40, a chitinase-like protein mainly secreted by macrophages, neutrophils and epithelial cells. [a]Heterogeneously defined as deterioration of lung function tests (FVC and sometimes DLCO), worsening of dyspnoea (generally self-reported) and/or chest imaging (chest X-ray radiography or HCRT) during the observational time). [b]Overall or cumulative survival. [c]Usual interstitial pneumonia and traction bronchiectasis. [d]Transplant-free survival.

in 1 second (FEV_1) or DLCO[222]. Notably, most participants in the trial continued farming throughout the study period. In a prospective study in patients with farmer's lung ($n = 93$), patients were treated with a 4-week or a 12-week glucocorticoid regimen or not at all if they had milder disease. Corticosteroid treatment was associated with faster symptom resolution than no treatment, but the 12-week regimen did not produce an additional benefit over the 4-week regimen. Moreover, corticosteroid treatment did not provide any significant long-term advantage in disease course in terms of symptoms, lung function or working capacity after an average follow-up period of 18.6 months[223]. However, at the last evaluation, fibrotic changes on chest radiographs were more frequently observed in patients who had not received corticosteroid treatment. In addition, systemic corticosteroid use is associated with a number of adverse effects, including skin thinning, weight gain, increased risk of cataracts and glaucoma, fluid retention, hypertension, accelerated reduction in bone mineral density, hyperglycaemia, increased risk of gastritis and ulcer formation, increased risk of infection, myopathy, and mood disorders. As such, corticosteroids may not be tolerated by some patients.

Chronic HP

Although antigen avoidance is often sufficient to improve symptoms and lung function in acute HP, the optimal management of chronic HP, especially chronic fibrotic HP, is not well established. Treatment decisions are guided mainly from observational data and expert opinion. Alongside removing the antigen, the amount of exposure is also relevant; for example, patients with bird-related HP who are exposed to higher amounts of avian antigens are more likely to experience functional and radiographic progression over time and worse prognosis compared with patients exposed to lower amounts of avian antigens (11.18 ± 6.77 per 1 g of dust and 0.55 ± 0.33 µg per 1 g of dust, respectively; $P = 0.023$)[28]. Similarly, patients with a longer history of exposure (>2 years) to avian antigens are less likely to experience complete remission or significant improvement than patients with a shorter exposure[224]. However, bird-related HP may also progress to end-stage lung fibrosis despite avoidance of the exposure and treatment[225].

Patients with features suggestive of non-fibrotic disease and persistent active inflammation, such as ground-glass opacities on HRCT, BAL lymphocytosis (>20%) and/or histopathological cellular interstitial pneumonia or granulomatous inflammation, are more likely to respond to glucocorticoid therapy than patients without these features[140]; however, the treatment dose and duration have not been formally studied. The absence of clinical response or disease progression despite glucocorticoid treatment may prompt the use of immunosuppressive therapy directed at suppression of the ongoing inflammatory and immune responses. In a retrospective longitudinal analysis of patients with chronic fibrotic HP across four independent tertiary medical centres in the United States, the requirement for immunosuppressive therapy was associated with increased mortality[226]. However, compared with high-dose prednisone monotherapy, the addition of azathioprine or mycophenolate mofetil (MMF) to prednisone was associated with a similar incidence of death and with a need for lung transplant and respiratory hospitalization, yet with fewer adverse events, suggesting that consideration of transition to MMF or azathioprine in patients requiring long-term treatment is warranted[226]. Moreover, a multicentre retrospective study involving four ILD centres in Canada and the United States showed that treatment of chronic HP with MMF ($n = 51$) or azathioprine ($n = 19$) was associated with improved DLCO and a reduced prednisone dose after 1 year of therapy; MMF and azathioprine were well tolerated with low rates of drug discontinuation[12]. Despite these promising data, the role of MMF and azathioprine in the long-term management of chronic HP remains uncertain. In addition, because combined treatment with azathioprine, prednisone and the mucolytic *N*-acetylcysteine has proven harmful in patients with IPF[227], it is necessary to be particularly cautious when using combined prednisone and azathioprine in patients with chronic fibrotic HP and a UIP-like pattern of fibrosis.

In a small series ($n = 6$) of patients with refractory severe fibrotic disease, the use of rituximab was associated with disease improvement or stabilization in three patients (and with progression in the remaining three), suggesting that B cell depletion may represent an effective therapeutic strategy in at least some patients with chronic fibrotic HP[228]. However, because T cells are also involved in the complex pathogenesis of chronic progressive disease[229], B cell depletion may not be broadly

beneficial. Antifibrotic drugs that have proven effective in slowing functional decline and disease progression in IPF[230,231] may also be beneficial in progressive chronic fibrotic HP as shown in a recent trial with nintedanib (a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor, fibroblast growth factor receptor and platelet-derived growth factor receptor) in patients with progressive non-IPF fibrotic ILD, including chronic fibrotic HP[232]. Pirfenidone, a compound with anti-inflammatory, antioxidant and antifibrotic properties, has been shown to reduce the rate of FVC decline in patients with progressive fibrosing unclassifiable ILD and may potentially also benefit patients with chronic fibrotic HP[233], although a recent small open-label study of pirfenidone in combination with prednisone and azathioprine (versus prednisone and azathioprine) in patients with chronic HP was inconclusive[234].

Similar to other end-stage lung diseases, lung transplantation should be considered in patients with progressive chronic fibrotic HP, with some evidence that post-transplant survival is greater for those with HP than for those with IPF[235]. In a study in 183 patients undergoing lung transplantation for ILD (including 31 with HP and 91 with IPF), 1-year, 3-year and 5-year survival was 96%, 89% and 86% for those with HP and 86%, 67% and 49% for those with IPF, respectively. Overall, patients with HP had a lower risk of death than patients with IPF (HR 0.25; $P = 0.013$). Of note, in 5 out of 31 cases (16%), the diagnosis of HP was made only after explant pathology review, whereas 2 patients developed recurrent disease in their allografts, despite immunosuppressive therapy. Notably, both patients returned to the same residence, highlighting the importance of vigilance for persistent antigen exposure after lung transplant.

Quality of life

Health-related quality of life is defined by the WHO as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns"[236]. Although many quality-of-life tools have been used in chronic lung disease, none of these is validated in HP and few have been developed or comprehensively studied in other fibrotic ILD subtypes. Accordingly, without a standardized approach to measuring quality of life in patients with chronic fibrotic HP, the available options include both general (such as the Medical Outcomes Survey Short Form-36 (REF.[237])) and disease-specific questionnaires (such as the King's Brief Interstitial Lung Disease questionnaire[238]).

There are no data on how qualify of life is affected in patients with acute HP. Patients with chronic fibrotic HP have a poor quality of life, with its primary drivers being the typical symptoms of fibrotic ILD (namely dyspnoea and cough)[35,239,240]. Compared with IPF, patients with chronic fibrotic HP seem to have a worse quality of life[239], even with adjustment for important potential confounders such as age and lung function. This seems to be driven by relatively worse quality of life reported in women than in men with fibrotic ILD and the female predominance in patients with chronic fibrotic HP compared with patients with IPF, as well as the patients experiencing worse fatigue and dyspnoea for a given lung function[239]. Similar studies have also suggested an important impact of anxiety and possibly depressive symptoms on the quality of life of patients[35], and some authors have suggested a negative impact on quality of life arising from exposure remediation (for example, related to moving residence or abandoning a particular job or hobby)[241]. Medication adverse effects may be another contributor to a reduced quality of life in chronic fibrotic HP.

The prevalence and severity of impaired quality of life in chronic fibrotic HP indicates the need for physicians to address its root causes, particularly in patients with substantial symptoms of ILD. As described above, several approaches can be used in an attempt to slow progression or alleviate the symptoms of fibrotic HP, with the expectation that this benefit would likely translate into an improved quality of life. Some of these benefits relate to the slowing of progression rather than actual improvement[232], highlighting the importance of setting appropriate expectations when initiating a new therapy. Furthermore, the potential benefit of these therapies must be balanced against their potential adverse effects, reflecting the need for shared decision-making and consideration of how each therapy might affect general quality of life on a case-by-case basis.

Outlook

Although advances have been made in better understanding the basic mechanisms and clinical presentation of HP, a number of open questions remain that need to be addressed in future research.

Inciting antigens

The number of newly identified environmental exposure settings causing HP will continue to increase. As an example, the first evidence of HP related to argan powder was recently reported in two of nine workers from a cosmetic factory[242]. Argan, the fruit (nut) of a tree growing in Morocco, is now used worldwide in numerous cosmetic products[242]. Such new exposure routes will imply preventive measures and clinical surveys to diagnose other affected workers. The list of multiple causative agents and environments should be continuously updated and made available through web-based platforms.

Mechanisms

How genetic, host and environmental factors interact in the development and progression of HP is still incompletely understood. Additional research efforts are needed to clarify which mechanisms lead to sensitization and why disease develops only in a minority of exposed individuals. Up to now, genetic susceptibility has not been determined through genome-wide association studies. Beyond known risk factors, such as virus infection, exposure to pesticides or higher levels of air pollution, which contribute as a second hit to the initiation of HP, other yet unknown promoting factors are likely to be identified in the future. The intriguing and often ignored finding of emphysema in some non-smokers with chronic HP might be considered as an area for future mechanistic study.

Although several factors associated with fibrosis in HP have been recognized, it remains unclear why some patients evolve to a relentlessly progressive fibrotic phenotype, even with complete exposure avoidance. The mechanisms triggering this self-perpetuating process should be the objective of future basic research. Also important would be to elucidate which molecular targets are associated with the different histological subtypes of HP.

Diagnosis

One of the problems in the field of HP until most recently has been the lack of international diagnostic guidelines. Although several different diagnostic criteria have been proposed, none has been validated. Two guidelines on HP (recently from the American Thoracic Society[7] and, forthcoming, from the American College of Chest Physicians) may help to reduce uncertainties in the diagnostic approach to HP and contribute to avoiding misdiagnosis with other ILDs. In the future, the distinction between fibrotic and non-fibrotic HP will become increasingly important for prognostication and treatment. Both aspects — a precise diagnosis based on improved diagnostic criteria and better prognostication — will be crucial, not only for individual patients but also for obtaining a homogeneous study population in future clinical trials.

In terms of diagnostic techniques, transbronchial lung cryobiopsy using a flexible bronchoscope to sample the lung parenchyma will be increasingly applied by experienced teams instead of surgical lung biopsy, based on promising data of lower morbidity and mortality but equivalent contribution to confident multidisciplinary team diagnoses[243]. Molecular classifiers correlating with the histological subtype or even with the clinical diagnosis are urgently needed to avoid invasive procedures and increase the diagnostic power of the existing ones[244].

Treatment

As the optimal pharmacological treatment of HP remains undetermined, antigen avoidance will continue to be the mainstay of treatment. Indeed, prospective clinical trials are needed to clarify the role of immunosuppressive therapy in chronic HP. In patients with progressive disease despite immunosuppressive standard treatment, additional antifibrotic therapy with nintedanib or pirfenidone may be beneficial as shown by the results of a recent clinical trial with nintedanib for patients with progressive fibrosing ILD including HP[232]. Other antifibrotic drugs currently under evaluation for IPF should also be tested in progressive chronic HP. Moreover, the impact of exposure elimination and pharmacotherapy on the quality of life of patients should be systematically assessed. Finally, future research should focus on circulating or imaging biomarkers that will identify patients at risk of progression and those who will respond to a given therapy, with the ultimate goal of realizing the concept of individualized precision medicine.

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