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REVIEW ARTICLE

Current management in hypersensitivity pneumonitis

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ABSTRACT

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease resulting from repeated inhalation of environmental antigens in genetically susceptible individuals. Its incidence and prevalence vary globally, influenced by geographic, occupational, and environmental factors. HP can present in non-fibrotic or fibrotic forms, the latter associated with a worse prognosis. Diagnosis involves a multidisciplinary approach, including clinical, radiological, serological, histopathological, and environmental data. Identification and elimination of the offending antigen are critical for management. Serological testing for specific immunoglobulin G, bronchoalveolar lavage lymphocytosis, and high-resolution computed tomography patterns are useful but have limitations. Specific inhalation challenge and lymphocyte proliferation tests are reserved for specialized centers. This article reviews current diagnostic strategies and discusses radiologic, bronchoscopy, and biopsy findings, emphasizing the role of antigen identification and classification into fibrotic or non-fibrotic forms to guide treatment and prognosis.

Keywords: Interstitial lung disease. Hypersensitivity pneumonitis. Evidence-based medicine. Pulmonary fibrosis.

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic disease of the lung parenchyma and small airways, triggered by an immune-mediated response to repeated inhalation of environmental antigens in genetically susceptible individuals[1].

The incidence of HP varies widely by geographic region, with estimated rates ranging from 0.13 to 1.94 cases/100,000 inhabitants and a prevalence of 0.45-2.71/100,000 inhabitants[2-5]. In high-risk occupational groups, prevalence can reach up to 81.3%[6]. The disease affects both men and women equally, with a predominant age of onset between 50 and 60 years[4,7,8].

Numerous antigens can trigger HP. These vary according to geographic, cultural, and occupational factors and may be of organic origin (avian proteins, bacteria, and fungi) or inorganic (metals, chemicals, and microplastics)[9,10]. Up to 30% of cases are attributed to avian antigen exposure[11].

The pathogenesis of HP is based on a persistent adaptive immune response to inhaled antigens. Activation of antigen-presenting cells, such as macrophages and dendritic cells, leads to immune-mediated alveolitis, which, in most individuals, is transient and reversible upon antigen removal. However, in some patients, continuous exposure perpetuates immune activation, favoring progression toward pulmonary fibrosis[9,12,13].

Modifying factors of the immune response

Susceptibility to HP development and progression may be influenced by genetic, environmental, and clinical factors. Variants in major histocompatibility complex (HLA) genes and *MUC5B* polymorphisms have been associated with a higher risk of fibrosis, including in the context of HP. Similarly, short telomere length has been linked to a worse prognosis and poorer response to immunosuppressive treatment in fibrotic forms[14-18].

Smoking, traditionally considered a protective factor, may reduce lymphocytosis in bronchoalveolar lavage (BAL) and complicate diagnosis. It has also been associated with fibrotic progression in certain subgroups[19-21].

Clinically, HP presents with non-specific symptoms, mainly exertional dyspnea and dry cough. During active phases, fever, fatigue, or weight loss may occur, whereas in advanced fibrotic stages, hypoxemia, bibasilar crackles, and clubbing are typically observed[22].

DIAGNOSIS

The diagnosis of HP is based on a multidisciplinary approach that integrates clinical, radiological, functional, histopathological, and environmental exposure data[1,12]. Historically, HP was classified as acute, subacute, or chronic based on exposure duration and symptom onset. However, this classification

has lost clinical utility, as it does not accurately reflect disease evolution. Today, two main clinical forms are recognized with distinct prognostic implications: fibrotic HP (fHP), which is associated with progression and poor survival, and non-fHP (nfHP), which generally has a more favorable course[12,23-31].

Antigen identification

Identifying the causal antigen is a cornerstone in HP diagnosis and has significant prognostic value. In a population-based study by Pérez et al., antigen identification was associated with improved survival compared to cases where the antigen remained unknown[32]. However, up to 50% of cases are considered cryptogenic due to failure to identify the causative antigen despite a detailed clinical history[32-38]. Both antigen load and exposure duration significantly influence clinical and radiologic progression. Intense or prolonged exposures are associated with a higher risk of fibrotic evolution and worse prognosis[25,39-41].

Clinical and radiological improvement after antigen avoidance can support the diagnosis of HP, especially in non-fibrotic forms. However, lack of improvement does not rule out the diagnosis, particularly in patients with advanced disease[12,37,42,43].

Questionnaires

Currently, there are no validated clinical questionnaires for detecting causal antigens in HP. Nonetheless, given the importance of antigen identification for diagnosis and prognosis, a thorough and systematic evaluation of potential sources of exposure is recommended. Structured questionnaires adapted to regional, cultural, and occupational factors may be useful tools in clinical practice[44-46].

Serologic testing

Detection of specific serum IgG (SsIgG) against inhaled antigens, using techniques such as ELISA or chemiluminescence, is a complementary diagnostic tool in HP. However, these tests have major limitations: lack of standardization between laboratories, geographical variation in antigens, and cross-reactivity, especially between fungi and avian proteins, complicate interpretation.

A positive result indicates sensitization but does not confirm active disease, as up to 50% of exposed healthy individuals may have detectable SsIgG[47-49]. Likewise, the absence of SsIgG does not exclude the diagnosis, as not all exposed individuals develop a detectable humoral response. In addition, commercial antigen panels often do not reflect the patient's environmental exposure[12,50].

In specialized centers, the use of customized antigen extracts obtained from the patient's environment may enhance diagnostic performance when commercial panels are negative. SsIgG is particularly helpful in cases with unclear etiology, suspected occupational HP, or multiple exposures, always integrated with

clinical, radiological, and histopathological evaluation. Finally, lymphocyte proliferation tests are a promising research tool but require further validation before they can be incorporated into routine clinical practice[43,51].

Specific inhalation challenge (SIC)

The SIC consists of controlled exposure to the suspected antigen, followed by respiratory function testing and monitoring of clinical parameters, including onset of symptoms, leukocytosis, oxygen desaturation, and body temperature changes. Its use is restricted to specialized centers, with Mexico, Spain, and Japan being the countries where it is most commonly practiced. In studies conducted in Spain, SIC has shown high sensitivity (85.1%) and specificity (86.2%) in HP cases related to avian or fungal proteins, although performance decreases with other antigen types[52].

A major limitation, especially in occupational cases, is the need to use antigens obtained from the patient's environment in addition to commercially available ones. This requires collaboration with environmental hygienists and experienced centers familiar with the technique[12,53].

The wide diversity of potential antigens and the lack of standardized protocols for antigen preparation and test interpretation limit reproducibility. Methodology, dosage, exposure duration, and positivity criteria differ significantly between centers. For these reasons, international guidelines currently do not recommend routine use of SIC for HP diagnosis[1,12].

Radiological imaging

High-resolution computed tomography (HRCT) is recommended in patients with HP to characterize nfHP or fHP forms and classify findings according to the 2020 ATS/JRS/ALAT criteria into three categories: typical, compatible, or indeterminate pattern for HP (Table 1)[1].

In nfHP, the typical pattern includes inflammatory parenchymal infiltration such as ground-glass opacities or mosaic attenuation, along with small airway involvement (centrilobular nodules < 5 mm or air trapping). Both components should be diffusely distributed throughout the lung parenchyma. The compatible pattern may show pulmonary cysts, consolidations, or uniform faint ground-glass opacities, which are less specific findings. Non-specific interstitial pneumonia (NSIP)-like presentations may also be observed in nfHP, corresponding to cellular NSIP on histopathology and correlating with ground-glass opacities and fine reticulation on HRCT.

In fHP, the typical pattern must meet two criteria: signs of pulmonary fibrosis (reticulation, parenchymal distortion, traction bronchiectasis, or honeycombing) and small airway involvement, manifesting as centrilobular nodules, mosaic attenuation, three-density pattern, or air trapping. These findings often predominate in the middle lobes, although this is not definitive. The compatible pattern may include features of usual interstitial pneumonia (UIP) or extensive ground-glass opacities with mild superimposed fibrosis, potentially with axial, peribronchovascular, subpleural, or craniocaudal distribution.

Table 1. Radiological findings of hypersensitivity pneumonitis on HRCT*

Variable	Typical	Compatible	Indeterminate	Major differences
nfHP	**CHEST 2021:** Any of the following: profuse, poorly defined centrilobular nodules of ground-glass opacity affecting all the lung zones. Inspiratory mosaic attenuation with the three-density sign. Inspiratory mosaic attenuation and airtrapping associated with centrilobular nodules And: lack of features suggesting an alternative diagnosis.	Any of the following: centrilobular nodules of ground-glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air-trapping. Patchy or diffuse ground-glass opacity. Mosaic attenuation and lobular air-trapping without centrilobular nodules or ground-glass abnormality And: lack of features suggesting an alternative diagnosis.	Non-specific or absent findings. No features suggestive of HP were identified.	The ATS/JRS/ALAT guidelines require a combination of parenchymal infiltration and small-airways involvement with diffuse axial and craniocaudal distribution, whereas the CHEST guidelines do not mandate this distributional pattern. In the CHEST guidelines, the three-density sign appears in nfHP as a defining criterion, not only in fHP.
	ATS/JRS/ALAT 2020: Requires both: – HRCT abnormality indicative of parenchymal infiltration (ground-glass opacities or mosaic pattern) and small airway disease (centrilobular nodules or air trapping). – In addition, there must be diffuse axial and craniocaudal distribution.	Non-specific findings but compatible with HP in the appropriate clinical context, such as uniform and subtle ground-glass opacities, airspace consolidation, or pulmonary cysts. In addition, there must be diffuse axial and cranio-caudal distribution with lower or peribronchovascular predominance, respectively.	Radiological findings that do not allow HP to be distinguished from other interstitial lung diseases.	
fHP	**CHEST 2021:** CT signs of fibrosis with either of the following: Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones; inspiratory mosaic attenuation with three-density sign And: lack of features suggesting an alternative diagnosis.	CT signs of fibrosis with any of the following: Patchy or diffuse ground-glass opacity, or patchy, non-profuse centrilobular nodules of ground-glass attenuation or Mosaic attenuation and lobular airtrapping that do not meet criteria for typical fibrotic HP And: lack of features suggesting an alternative diagnosis.	CT signs of fibrosis without other features suggestive of HP	ATS/JRS/ALAT defines "typical" by emphasizing any robust evidence of small-airways disease together with fibrosis, while CHEST makes two findings operational and hierarchical for "typical" (profuse centrilobular nodules or the three-density sign) and assigns the rest to "compatible."
	ATS/JRS/ALAT 2020: Presence of both:– Pulmonary fibrosis (irregular linearopacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate) and small airway involvement: t mosaic attenuation, three-density pattern and/or air trapping, or centrilobular nodules and/or GGO. Distribution should be random or mid-lung zone predominant or relatively spared in the lower lung zones.	Compatible pattern such as fibrosis with atypical distribution (e.g., UIP pattern, Extensive GGO with superimposed subtle features of lung fibrosis). May coexist with signs of small airway involvement (centrilobular nodules or three-density pattern and/or air trapping) but without a specific HP pattern. Atypical distribution: basal/subpleural axial predominance, basal craniocaudal predominance.	Findings of UIP. Probable UIP, indeterminate UIP, fibrotic NSIP, or organizing pneumonia patterns without additional features (e.g., nodules, air trapping, or bronchiolocentric distribution) are also considered indeterminate if no other suggestive signs are present.	

*Based on ATS/JRS/ALAT 2020 and CHEST 2021 guidelines.
HRCT: high-resolution computed tomography; nfHP: non-fibrotic hypersensitivity pneumonitis; fHP: fibrotic hypersensitivity pneumonitis.

In addition, emphysema has been reported in 23% of patients with fHP, even in non-smokers. These findings constitute the combined pulmonary fibrosis and emphysema syndrome, which is associated with a higher risk of pulmonary hypertension (PH) and worse prognosis[33,54].

Bronchoscopic techniques and BAL

Bronchoscopy is a minimally invasive procedure that allows sampling of the lower respiratory tract. In patients with HP, BAL and transbronchial biopsy help support the

diagnosis and rule out conditions with similar clinical and radiological presentations.

BAL plays a prominent role in the evaluation of HP. It is a safe, well-tolerated, minimally invasive technique with low technical difficulty[55]. Its main utility lies in distinguishing between nfHP and acute pulmonary infections. Alveolar lymphocytosis is considered a hallmark of HP, usually more pronounced in nfHP, but it can also be detected in fHP, where its presence has been associated with a more favorable prognosis[21,56,57].

Although the absence of lymphocytosis in BAL does not exclude the diagnosis[58,59] higher levels strengthen diagnostic confidence. In particular, values ≥ 30% support HP and are especially useful in differentiating fHP with a UIP pattern from idiopathic pulmonary fibrosis (IPF)[1,38,60].

According to current guidelines, there are relevant differences in the interpretation of BAL lymphocytosis: ATS/JRS/ALAT 2020 suggests that a threshold around 30% increases diagnostic confidence, while the CHEST 2021 guideline recognizes that even values as low as 20% may contribute to diagnosis in the appropriate clinical context[1,12]. However, current data do not allow for the establishment of a diagnostic threshold to differentiate HP from other interstitial lung diseases (ILDs)[12,61].

Regarding the immunological profile, lymphocytosis in HP is typically characterized by CD8+ lymphocyte predominance and a reduced CD4/CD8 ratio, with average values between 0.5 and 1.5[62,63]. Nevertheless, this ratio may be increased in some HP patients, limiting its sensitivity and specificity[64,65]. In addition, BAL may show other findings such as the presence of foamy macrophages, increased plasma cells, and mast cells, although these findings are non-specific[62,66].

Histological assessment

Lung biopsy is an invasive diagnostic tool that can be performed via surgical or bronchoscopy intervention and should be considered after multidisciplinary evaluation due to its associated morbidity[12]. Obtaining a high-quality, representative sample is essential for the histological diagnosis of HP. Transbronchial lung cryobiopsy (TBLC) has become the preferred technique in many centers, as it shows high concordance with surgical biopsy and a low in-hospital mortality rate (0.5-0.8%)[67,68]. In contrast, transbronchial forceps biopsy has a low diagnostic yield in HP and should not be routinely employed[61,69,70]. Surgical lung biopsy provides a larger sample but carries multiple complications, with an in-hospital mortality rate of up to 1.7%[71]. Recent evidence further supports the role of TBLC as a safe and effective alternative to surgical biopsy. A comprehensive review by Rodrigues et al. highlighted that TBLC yields histopathologic samples of sufficient size and quality for multidisciplinary diagnosis in the majority of ILD cases, with diagnostic agreement rates approaching those of surgical lung biopsy and a more favorable safety profile[70].

Pathology

The histological classification of HP varies depending on the predominant pattern of involvement. In nfHP, characteristic findings

Table 2. Histopathological patterns of hypersensitivity pneumonitis

Patterns	Typical	Compatible/ Probable	Indeterminate	Differences
nfHP	**CHEST 2021:** Requires all four: (1) Bronchiolocentric distribution. (2) Uniform cellular interstitial inflammation (may include cellular NSIP pattern). (3) Lymphocyte predominance. (4) Poorly formed non-necrotizing granulomas and/or giant cells.	Presence of the first three criteria without granulomas or giant cells.	Mild inflammation, bronchiolitis, or non-specific interstitial pneumonia without clear bronchiolocentric distribution or granulomas.	The CHEST guidelines require uniformity of the interstitial infiltrate and a low plasmacytic component as part of the "typical" pattern, whereas the ATS/JRS/ALAT guidelines do not. In addition, CHEST highlights that atypical features (e.g., NSIP-/UIP-like patterns in fHP) require multidisciplinary discussion (MDD) to confirm HP.
	ATS/JRS/ALAT 2020: Same as CHEST, no significant differences.	Peribronchiolar lymphocytic interstitial inflammation without granulomas or giant cells.	Minimal or patchy inflammation, with findings that do not allow pattern classification.	
fHP	**CHEST 2021:** Requires all of the following: (1) Airway-centered (bronchiolocentric) fibrosis. (2) Chronic fibrosing interstitial pneumonia (may be NSIP or UIP-like). (3) Poorly formed non-necrotizing granulomas and/or giant cells. (4) No findings suggestive of an alternative diagnosis.	Presence of airway-centered fibrosis and chronic interstitial pattern without granulomas/ giant cells, and no features suggesting an alternative diagnosis.	Presence of nonspecific pulmonary fibrosis (NSIP/UIP) without bronchiolocentric accentuation or granulomas. Foci of organizing pneumonia may coexist.	ATS/JRS/ALAT emphasizes multisite sampling, whereas CHEST allows histo-radiologic synergy to explicitly exclude IPF (e.g., UIP pattern in one area + bronchiolocentricity in another + typical HRCT pattern).
	ATS/JRS/ALAT 2020: Same requirements as CHEST 2021.	-	Fibrotic findings without distinctive features for HP or for any specific alternative diagnosis.	

nfHP: non-fibrotic hypersensitivity pneumonitis; fHP: fibrotic hypersensitivity pneumonitis.

include cellular interstitial pneumonia with bronchiolocentric distribution, bronchiolitis, and poorly formed non-necrotizing inflammatory granulomas. The absence of histopathological features suggesting an alternative diagnosis supports a typical pattern. Evidence of the same inflammatory pattern without granulomas defines a probable pattern, while isolated findings of bronchiolocentric interstitial pneumonia or bronchiolitis without other distinctive features are classified as indeterminate[72-76].

In fHP, the typical pattern is defined by the presence of chronic fibrosing interstitial pneumonia, airway-centered fibrosis, non-necrotizing granulomas, and absence of histopathological findings supporting an alternative diagnosis. When granulomas are not identified but the other features are present, the pattern is considered probable. Cases showing only chronic fibrosing interstitial pneumonia without additional features are considered indeterminate[30,77].

The described radiological and histological patterns are based on the ATS/JRS/ALAT 2020 guideline. The classification proposed by CHEST in 2021 has similar features but presents slight differences in the definition of diagnostic patterns, particularly in intermediate categories. The main discrepancies between the two guidelines are summarized below (Table 2).

Real-world impact of guideline selection

Beyond theoretical differences, real-world evidence highlights the clinical consequences of applying one guideline over another. In a large multicenter cohort of patients with fHP, Ferreira et al. (2025)[78] compared the diagnostic yield of ATS/JRS/ALAT 2020[1] and CHEST 2021[12] criteria. The use of CHEST criteria significantly increased the proportion of cases classified as high-confidence or definite fHP, largely by reclassifying patients deemed "compatible" or "indeterminate" under ATS/JRS/ALAT. Importantly, this shift translated into a ~43% reduction in referrals for TBLC, with many patients reaching a confident diagnosis without the need for invasive sampling. These findings underscore how guideline selection directly affects patient management, biopsy referral rates, and ultimately clinical decision-making in multidisciplinary practice. While CHEST criteria appear more sensitive and pragmatic in clinical practice, ATS/JRS/ALAT retain greater specificity, and the optimal approach may depend on local disease prevalence and expertise of the multidisciplinary discussion team.

PROGNOSIS

The course of HP is heterogeneous and unpredictable. Patients with nfHP who improve after antigen avoidance tend to have a more favorable prognosis[32,79,80]. Since lymphocytosis in BAL is associated with nfHP and increased inflammatory activity, some studies suggest that this finding may predict response to immunomodulatory treatment[81].

Conversely, fHP is associated with a worse prognosis. The presence of honeycombing on HRCT, the extent of fibrosis, evidence of a UIP pattern, and fibroblastic foci are all poor prognostic indicators in HP[25,27,41,82]. In addition, patients who develop progressive pulmonary fibrosis (PPF) show survival rates comparable to those with IPF[83,84]. A significant proportion of patients with fHP eventually develop PPF, although reported rates vary considerably depending on cohort and methodology. In a recent multicenter study applying ATS/ERS consensus criteria for PPF, Cano-Jiménez et al. reported progression in 56% of patients with fHP, while other series have described higher proportions, up to 86%. Collectively, these findings underscore that PPF is a frequent and clinically relevant outcome in fHP[57].

The development of complications such as PH or acute exacerbations of HP (AE-HP) is also associated with poor prognosis. PH has been documented in up to 50% of patients with fHP and is linked to significantly reduced survival[85-87]. AE-HP is often associated with intense antigen exposures such as household mold and cryptogenic sources[88]. Emerging evidence also suggests that exposure to microplastics may contribute to HP and other respiratory disorders[10], while extensive fibrosis and honeycombing on HRCT are additional clinical variables associated with increased risk[89]. AE-HP may respond to antigen avoidance and high-dose corticosteroids; however, fulminant cases have been reported despite treatment[48], with in-hospital mortality rates reaching up to 44.4% in some series[90].

TREATMENTS

Antigen avoidance

Antigen avoidance is the cornerstone of HP treatment and is associated with improved lung function and increased transplant-free survival[32,37,91]. If available, antigen identification should be carried out with the help of an occupational medicine specialist or industrial hygienist to determine the likelihood of exposure as a cause of HP, prevent future exposure for the patient or others, and monitor the patient in future work environments to ensure safety[12,92].

Immunosuppressive therapy

Currently, there is no standardized algorithm for the pharmacologic treatment of HP. One suggested regimen includes prednisone at 0.5-1 mg/kg/day for 1-2 weeks, followed by a gradual taper to a maintenance dose of 10 mg/day[93]. The optimal duration of corticosteroid therapy is unclear; however, if proper antigen avoidance has been achieved and clinical and radiologic improvement is evident, a gradual withdrawal may be reasonable[91].

Inflammatory-predominant forms, mostly corresponding to nfHP, tend to respond better to immunosuppressive treatment and typically require moderate-to-high doses of systemic corticosteroids[93]. However, in patients with fHP, the role of corticosteroids is limited, with little evidence supporting their long-term use[37,93].

For patients who do not respond to corticosteroids or require prolonged treatment, immunomodulatory agents have been proposed[94]. Evidence for this approach comes from retrospective studies showing functional improvement, particularly in DLCO, after 1 year of therapy[37,94-96]. The main agents used are mycophenolate mofetil (MMF) and azathioprine (AZA). AZA is frequently associated with gastrointestinal intolerance, hepatotoxicity, and myelosuppression, with an increased risk of opportunistic infections and, in long-term use, possible malignancy. MMF, while not devoid of adverse events, is generally better tolerated, with gastrointestinal disturbances and leukopenia being the most common complications, and a lower incidence of hepatotoxicity compared with AZA. Observational studies suggest comparable efficacy between the two agents, but the more favorable tolerability of mycophenolate has led many centers to prefer it as a first-line steroid-sparing option[94,95]. In IPF patients receiving combination therapy with AZA, prednisone, and N-acetylcysteine, increased mortality and hospitalization risk have been observed, so this combination should be used cautiously in fHP patients with a UIP pattern[97].

Rituximab has also been used as immunosuppressive therapy in chronic HP, with evidence restricted to retrospective series. In the Royal Brompton cohort reported by Keir *et al.*[98], 50 patients with severe, treatment-refractory ILD (including six with HP) received rituximab, with stabilization or improvement in lung function, but also serious infections and 20% mortality largely due to disease progression. In the multicenter study by Ferreira *et al.*[99], 20 patients with chronic HP refractory to antigen avoidance and corticosteroids were treated with

rituximab, showing attenuation of forced vital capacity (FVC) decline and stabilization of DLCO at 6-12 months, with one infection-related death reported. Overall, these data suggest a potential role in selected patients, but the risk of adverse events, particularly infections, is considerable. No randomized controlled data are available, and an ongoing trial (NCT05596786) will help to clarify its role. (ClinicalTrials.gov ID: NCT05596786).

Choosing the appropriate immunosuppressive treatment should be individualized based on patient characteristics. Recent studies suggest that the type of causative antigen or genetic features, such as telomere length, may influence response to therapy[100,101].

Antifibrotic therapy

In fHP, inhibiting fibrotic pathways is essential. The INBUILD trial evaluated the efficacy of nintedanib versus placebo in patients with fibrotic ILDs, including 173 (26%) with fHP[102]. Although the study was not specifically designed for individual diseases, subgroup analysis showed that HP patients treated with nintedanib had improved functional outcomes[103], leading the FDA to approve nintedanib in 2020 as a second-line treatment for chronic progressive fibrosing ILDs.

Pirfenidone has been studied in small cohorts of HP patients, showing reduced FVC decline at 6 and 12 months[104,105]. The RELIEF trial was prematurely terminated due to low enrollment. It included 127 patients with progressive ILD, of whom 57 (45%) had HP. The results showed a significant reduction in FVC decline at 6 and 12 months in fHP patients.

Recently, the FIBRONEER trial evaluated nerandomilast, an oral selective phosphodiesterase 4B inhibitor, in patients with PPF, including cases of fHP. The study demonstrated a significant preservation of FVC over 52 weeks compared with placebo, suggesting that nerandomilast may represent an additional therapeutic option in the management of fHP[106].

Therefore, although more clinical trials are needed to assess antifibrotic efficacy in HP, clinical practice currently follows a phenotype-based approach.

Lung transplantation

Lung transplantation should be considered in patients with progressive fibrosing HP, and early referral to a transplant center is recommended to maximize the chances of being listed[105]. Referral criteria include any form of pulmonary fibrosis with FVC < 80% or DLCO < 40% predicted, oxygen requirement at rest or with exertion, disease progression, or–within the past two years–relative declines of ≥ 10% in FVC, ≥ 15% in DLCO, or ≥ 5% in FVC with worsening symptoms or radiologic progression.

Transplanted HP patients show excellent survival rates (85-96% at 1 year, 75-89% at 3 years, and 70-89% at 5 years), better than those observed in IPF[107,108]. However, recurrence of the disease has been documented. In the study by Kern et al.[107], among 31 HP patients, 2 (6%) experienced recurrence after re-exposure to the antigen.

Other treatments

Non-pharmacologic interventions, such as vaccination, rehabilitation, patient support groups, and palliative care, are integral parts of ILD management[109,110].

HP patients may develop hypoxemia in the setting of progressive fibrosis. For patients with severe chronic resting hypoxemia, long-term oxygen therapy (at least 15 h/day) is recommended. Ambulatory oxygen may be considered for those who require oxygen with exertion or are able to leave the home[111]. Evidence for ambulatory oxygen in HP is limited. In the AmbOx trial, ambulatory oxygen improved exercise tolerance and patient-reported quality of life in ILD, including fHP, but the magnitude of benefit was modest and the certainty of evidence was low[112].

FUTURE DIRECTIONS

Despite recent advances in the diagnosis and management of HP, key areas still require targeted research to improve patient care. Accurate epidemiological data on incidence, prevalence, and geographic distribution are needed to identify regional risk factors and optimize prevention strategies. A better understanding of etiology and immunopathogenesis, including genetic factors, antigen-specific immune responses, and mechanisms of fibrosis progression, is necessary to refine patient classification and treatment.

Standardization of SIC and serological testing protocols in terms of preparation, execution, and interpretation would enhance diagnostic accuracy and inter-center reproducibility. Finally, randomized controlled trials are urgently needed to rigorously evaluate the impact of immunosuppressive and antifibrotic therapies in HP.

Developing treatment strategies tailored to the inflammatory or fibrosing profile of the disease will promote a more personalized and evidence-based approach to patient care.

CONCLUSIONS

The diagnosis of HP is complex and relies on a multidisciplinary and consensus-based approach. Integrating clinical, radiological, and serological findings with antigen identification allows for more precise disease management. Further studies are needed to strengthen the current diagnostic and therapeutic evidence base.

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CONFLICTS OF INTEREST

None.

ETHICAL CONSIDERATIONS

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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