Updates in Hypersensitivity Pneumonitis: A Narrative Review

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Abstract

Purpose of Review Hypersensitivity pneumonitis (HP) is an immune-mediated disease triggered by a known or unknown antigen. While reversible in the early stages of disease, progression toward irreversible pulmonary fibrosis may occur. This narrative review summarizes recent publications highlighting a methodical approach toward the diagnosis, classification, and management of fibrotic and nonfibrotic HP.

Recent Findings Establishing the diagnosis of HP is often challenging given its variable clinical course, extensive inciting agents, and overlapping features with other interstitial lung diseases. Recently, HP has been re-classified into nonfibrotic and fibrotic subtypes based on radiographic and histopathological features. Chronic fibrotic HP is associated with significant functional impairment and increased mortality. In addition to antigen avoidance, immunosuppression is the cornerstone of management in nonfibrotic HP. Antifibrotic agents have emerged as a therapeutic option in halting the progression of chronic fibrotic HP.

Summary The combination of clinical, radiographical, and histopathological data will assist in increasing the diagnostic certainty of HP. The new dichotomization of HP is thought to provide better prognostication for patients. This review provides clinicians with a current and evidence-based approach toward the management of patients with HP.

Keywords Hypersensitivity pneumonitis · Interstitial lung disease · Antifibrotic treatment, Immunosuppression

Introduction

Hypersensitivity pneumonitis (HP) is a subtype of interstitial lung disease (ILD). The rate of HP varies from 2 to 47%, depending on occupational or environmental exposure, geographical location, and inherent genetic host risk factors [1, 2]. The highest prevalence is noted in patients in the fifth or sixth decade of life [3•]. In the United States (US), HP
accounts for less than 2% of ILD [4]. The annual incidence of HP is approximately 30 per 100,000 persons [5]. ILD registries in Europe indicate that HP accounts for 4 to 15% of all ILD cases [1]. The National Center for Health Statistics of the US shows an increase in HP mortality from 0.09 to 0.29 per million between 1980 and 2002 for residents aged 15 years or older [6].

Clinical Presentation

Patients with HP can present with a variety of symptoms, depending on the time course of the disease. Common symptoms and signs include dyspnea, cough, chest tightness, wheezing, and mid-inspiratory squeaks [7•]. Infrequently, constitutional symptoms such as low-grade fever, weight loss, and malaise may occur. These symptoms may be episodic and recurrent. Due to its non-specific nature, the diagnosis of HP is often delayed or missed. Physical examination may be completely normal or show findings of high-pitched end-inspiratory wheeze, “squeaks,” crackles, or rales [8]. Patients with acute HP present with symptoms of several weeks to months (less than 6 months) whereas symptoms for chronic hypersensitivity pneumonitis (CHP) are present for a longer duration [7•].

Pathophysiology of HP

Pathophysiology and progression of HP are dependent on duration and type of exposure, and the host inflammatory response. Genetic predilection, combined with environmental factors, may yield a robust and significant immune response in the lungs. Increased expression of Th1 cytokines, TNF-alpha, IL-12, interferon-gamma, and toll-like receptor 9-mediated dendritic cell response appears to be implicated in the immune response to the inflammatory antigen (Fig. 1) in HP [7•]. The etiological agent that triggers the host response may be challenging to identify. Since its discovery in the 1700s, HP has been associated with many culprits [9]. Yet, the definite diagnosis of HP remains challenging as the inciting agent is not identified in up to 60% of patients [10].

Common infectious, organic, and inorganic trigger agents—ranging from most common to least common—are detailed in Table 1. It is critical that a thorough history, and an exploration of all possible exposures is conducted, as this may halt or reduce the likelihood of disease progression. Recurrent exposure leads to persistent inflammation and, consequently, disease progression into lung fibrosis.

In 2020, a list of potential inciting agents was derived from a Delphi systematic review of literature conducted by an international panel of ILD experts [11•]. All patients suspected of having CHP should be investigated for exposure to these agents. Examples include exposure to water damage, mold, air conditioners, hot tubs, organic matter, musical instruments, dentistry products, avian exposures, farming and food products, and chemical agents such as isocyanates, metal working fluids, and fumes [11•]. Patients should complete a comprehensive environmental and occupational questionnaire tailored to the local geographical prevalence. In a prospective study evaluating a cohort of 400 patients, exposure to identified inciting agent was found to be the strongest of six significant predictors of HP [12].

Subtypes of HP

HP is historically subcategorized into acute, subacute, or chronic subtypes. Acute HP is often reversible secondary to an acute inflammatory process with complete resolution of symptoms following antigen avoidance and/or therapy [13]. However, this categorization provides little prognostic value [13]. To better predict prognosis, the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana del Tórax (ATS/JRS/ALAT) recently published guidelines categorizing HP into fibrotic and nonfibrotic subtypes, based on the presence or absence of radiographic or histopathological fibrosis [7•]. Table 2 illustrates key distinguishing features of the most recent dichotomization of HP.

Radiologic Features of HP

The radiographic features of HP are best determined by high-resolution computed tomogram (HRCT) of the chest [14]. Features of nonfibrotic HP include findings suggestive of parenchymal infiltration, such as ground glass opacity (GGO), and findings suggestive of air trapping, such as centrilobular diffuse micronodules on inspiration, and mosaicism [15]. The distribution of abnormalities is often diffuse, with or without basal sparing. On the other hand, airspace consolidations, subtle GGO, and lung cysts are radiographic findings that are compatible with nonfibrotic HP but are not specific to HP [7•]. Figure 2A, B depicts common features of nonfibrotic HP. “Three-density pattern” or the “head cheese signs” describes the combination of GGO, mosaic attenuation, and normal appearing lung that is highly specific for HP [16].

Meanwhile, the HRCT pattern of fibrotic HP is characterized by small airway diseases and fibrosis [17]. Examples include reticulation with architectural lung distortion, and traction bronchiectasis with or without honeycombing. The distribution of abnormalities can be patchy, peribronchovascular, subpleural, or in any zonal distribution. Honeycombing can be present and may have a subpleural distribution but is less frequently associated with a basal predominance as compared to idiopathic pulmonary fibrosis (IPF) [3•, 13]. Figure 3A, B depicts common features of fibrotic HP. Areas of mosaic
attenuation that is suggestive of small airway disease can be helpful in distinguishing it from that of IPF [18, 19]. Meanwhile, HRCT findings of fibrosis in fibrotic HP are considered nonspecific, and differentials of other granulomatous fibrosing ILD such as sarcoidosis and connective tissue disease-ILD should be considered.

**Histopathological Features of HP**

The histopathological alterations of HP can be heterogeneous. Nonfibrotic HP histopathology features bronchiocentric lymphohistocytic interstitial pneumonia, chronic bronchiolitis, and small poorly formed non-necrotizing granulomas [13]. The pulmonary infiltrate of interstitial pneumonia is typically polymorphic and includes predominantly small lymphocytes with smaller numbers of plasma cells and occasionally eosinophils [7•]. Cellular non-specific interstitial pneumonia (NSIP) pattern can also be present [20]. Histopathological features that suggest an alternative diagnosis include extensive lymphoid hyperplasia, more than focal peribronchiolar lymphoid aggregates with germinal centers, extensive well formed sarcoidal granulomas, necrotizing granuloma, and plasma cells predominant infiltrate [7•].

Fig. 1 Proposed mechanisms in the pathogenesis of hypersensitivity pneumonitis. This image illustrates the proposed mechanisms in the pathogenesis of hypersensitivity pneumonitis. It includes the interplay of genetic and environmental factors, inflammatory response in the alveoli, and fibroblastic activity leading to irreversible changes and fibrosis.
Fibrotic HP histopathology is associated with less inflammatory changes but exhibit more fibrotic changes with the presence of chronic interstitial pneumonia and bronchiolitis. These include airway fibrosis and poorly formed non-necrotizing granulomas. Subpleural and centriacinar fibrosis are typically seen, and there may be an absence of or sparsity of airway-centered granulomas [13]. Although the histopathological pattern might overlap with those of usual interstitial pneumonia (UIP), the presence of abnormality within and/or around the small airways is highly suggestive of HP [13]. Lung tissue for histopathological analysis may be obtained in several ways including fiberoptic transbronchial biopsy, transbronchial lung cryobiopsy, and surgical lung biopsy [7•]. The need for and the preferred method of obtaining tissue samples is often determined by individual patients’ profile, physicians’ clinical judgement, and the shared decision-making process between patient and physician. Balancing the risk vs. benefits of invasive procedures, and awareness of local expertise and availability of facilities, is important. If obtaining histopathological samples of the lung is important in determining treatment, and thus improving patients’ outcomes, then invasive procedures should be pursued.

**Serum and Bronchoscopic Evaluation**

Bronchoalveolar lavage (BAL) fluid cellular analysis often demonstrates an inflammatory pattern, predominantly lymphocytosis (> 30% in nonsmokers/former smokers and > 20% in current smokers) [21]. BAL lymphocytosis is

### Table 1 Causes of hypersensitivity pneumonitis

| Causes                                | Source                                                                 |
|---------------------------------------|------------------------------------------------------------------------|
| **Infectious**                        | - Bacteria: *Acinetobacter* spp., *Bacillus* spp., *Klebsiella* spp., *NTM*, *Pseudomonas* spp., *Stenotrophomonas* spp., *Streptomyces* spp., endotoxin from pool-water  
- Fungi/molds: *Aspergillus* spp., *Cryptococcus* spp., *Fusarium* spp., *Mucor* spp.  
- Yeasts: *Candida* spp., *Geotrichum candidum*, *Torulopsis glabrata*  
- Protozoa: Amoebae  
- Edible mushrooms: Shiitake, Pleurotus, Pholiota, *Agaricus* |
| **Organic agents**                    | - Animal proteins: Animal fur dust, Avian dropping/feathers, bats, cow milk, fish feed/meal, shell protein (oyster, sea snail, mussels)  
- Plant proteins: Grain flour (wheat, rye, oats, maize), malt, legumes, paprika, alginate, argan cake, esparto dust, spinach, Tiger nut, wood |
| **Inorganic agents**                  | - Chemicals: Acid anhydrides, acrylate compounds, copper sulfate, chloroethylene, isocyanates, tetrachlorophthalic acid, sodium diazobenzene  
- Pharmaceuticals: Penicillins, cephalosporins, methotrexate, alpha-IFN, lenalidomide, pravastatin, venlafaxine, temozolomide  
- Metals: Cobalt, zinc, zirconium, beryllium, TMI |
| **Genetic predisposition**            | Gene polymorphism involved in molecules processing and presenting external antigens:  
- Class II MHC molecules  
- Polymorphisms of genes potentially involved in altered lung homeostasis, wound repair, and telomere-related gene mutations |

**Alpha-IFN** interferon alpha, **MHC** major histocompatibility complex, **NTM** non-tuberculous mycobacterium, **TMI** trimethylindium

### Table 2 Fibrotic versus non-fibrotic hypersensitivity pneumonitis

| Characteristics | Nonfibrotic HP | Fibrotic HP |
|-----------------|---------------|------------|
| **Symptoms**    | Acute, with or without constitutional symptoms  
HRCT imaging findings | GGO, mosaic attenuation, plus at least one HRCT abnormality suggestive of small airway disease (ill-defined, small (5 mm) cen
trilobular nodules on inspiratory images and air trapping on expiratory images). “Three-density pattern” and/or “head cheese sign”  
Serum testing | Detection of serum immunoglobulin G against suspected antigens  
BAL features | Lymphocytosis > 25–30% on BAL  
Histological features | Granulomatous bronchiolocentric interstitial pneumonitis and chronic bronchiolitis |
|                 |              | Insidious onset in the setting of a specific exposure history  
Irregular fine or coarse reticulation with architectural lung distortion, septal thickening, traction bronchiectasis, honeycombing, GGO, and mosaic attenuation. Fibrotic changes are predominantly in the upper and middle lobes, in contrast to UIP  
Detection of serum immunoglobulin G against suspected antigens  
Lymphocytosis on BAL  
Architectural distortion with centriacinar fibrosis. UIP-like pattern, including patchy collagen fibrosis, fibroblastic foci, and subpleural-dominant honeycombing |

**BAL** bronchoalveolar lavage, **GGO** ground glass opacities, **HRCT** high-resolution computed tomogram, **UIP** usual interstitial pneumonia
strongly supportive of HP diagnosis, although not specific
[22]. Microbiological investigations must be pursued prior
to further workup. Other diagnostic modalities to consider
include serum immunoglobulin G (sIgG). sIgG testing may
assist with the identification of potentially relevant expo-
sures; however, its superiority over a comprehensive history
and/or the use of exposure questionnaires is debatable [23].
It is also an unreliable test when attempting to distinguish
HP from other types of ILD [23].

Pulmonary Function Testing (PFT)

The PFT profile of patients with HP share similarities with
other subtypes of ILD. Patients may exhibit a restrictive PFT
pattern with a low diffusion capacity of the lung for carbon
monoxide (DLCO). In certain types of CHP, including farm-
er’s lung, an obstructive defect secondary to emphysema may
observed [24]. Specific inhalation challenges (SIC) have been
explored as a confirmatory test. The sensitivity and specific-
ity of the test were 72.7% and 84%, respectively [25]. Thus,
positive SIC testing virtually confirms the diagnosis of HP,
while a negative testing does not rule it out, especially when
the antigenic sources are not birds or fungi [25].

The Role of the ILD Multidisciplinary Meeting (MDM)

The ILD multidisciplinary meeting (MDM) is broadly
accepted as the gold standard for ILD diagnosis worldwide
[26]. Team members include pulmonologists, radiologists,
pathologists, and/or rheumatologists. Due to the heterogene-
ity of ILD, accurately diagnosing ILD may be challenging
[27]. The role of the MDD is to collaboratively discuss and
integrate available clinical data to generate a consensus diag-
nosis for the patient [27]. MDM has consistently been shown
to change ILD diagnosis in approximately 50% of patients
presented and consequently is more reflective of patient out-
comes [28, 29].

It is noteworthy that the ILD MDD is not universally
available, especially outside large academic centers. In
practice, utilization of an algorithmic approach (Fig. 4) for
the diagnosis, treatment, and management of patients with
HP is recommended to avoid delays which may adversely
affect patient outcomes [30]. For instance, should clinical,
radiological, and exposure history align with the diagnosis
of HP, further testing is unnecessary. However, should there
be a discordance, additional testing, like BAL fluid cellular
analysis, and histopathological testing should be considered.

Treatment

The early diagnosis of HP, and the institution of strict meas-
ures toward antigen elimination are key components of the
management of nonfibrotic HP to halt the inflammatory cas-
cade of the host immune response. Lifestyle modifications to
mitigate antigen exposure is warranted to aid in minimizing
symptoms and improve quality of life (QoL) [31]. Depend-
ing on the causative antigen, some studies suggest that Bird
Fancier’s HP may be associated with a worse prognosis than
Farmer’s Lung [32]. Prolonged exposure to antigen, older
age, digital clubbing, a histopathologic pattern of fibrotic
NSIP, and UIP pattern on imaging are associated with worse
outcomes [33].
Corticosteroids (CS) have been used to treat HP; however, it may not necessarily affect long-term outcomes of the disease [34]. In a cohort study, a recommended dose of oral prednisone of 40 to 60 mg (0.5 mg/kg/d) was administered for 2 weeks in acute versus 4 to 6 weeks in subacute to chronic forms of HP, followed by a gradual taper to a daily maintenance dose of 10 mg prior to discontinuation based on clinical response [35]. Four weeks of CS was found as efficacious as an extended course of CS [35]. A large single-center cohort study demonstrated that nonfibrotic HP patients exhibited an overall increase in forced vital capacity (FVC) and DLCO with CS use, but no therapeutic effect was noted in patients with fibrotic HP [36•]. Additionally, patients with fibrotic HP had a dismal prognosis (median survival of 9.2 years) while nonfibrotic HP patients demonstrated an excellent survival [36•]. Notably, long-term outcomes of CS treatment have not been validated by randomized control studies [2].

Immunosuppressive and/or immunomodulatory agents have been utilized as an alternative to CS. Unfortunately, evidence for their efficacy is scant. Mycophenolate mofetil (MMF) and azathioprine (AZA) use has been associated with an increase in DLCO and a decrease in treatment-associated adverse effects compared with CS therapy in HP [37]. However, no consistent improvement in the incidence of death, lung transplantation, and respiratory hospitalization was demonstrated. In a single-center retrospective study, the addition of leflunomide to prednisone, AZA, or MMF showed an increase in FVC after 12 months of treatment in patients with nonfibrotic HP [38]. Rituximab, an anti-CD20 monoclonal antibody, has been shown to improve 6-min walk distance and stabilize HRCT progression in patients with CHP [39]. In a more recent retrospective study, rituximab use in patients with CHP was also associated with stabilization of FVC and improvement of DLCO [40].

Macrolides have been used for their immunomodulatory and CS-sparing effect in cases of organizing pneumonia and IPF [41]. However, high-quality research is needed to evaluate its role in HP [42]. Supportive therapy including oxygen supplementation for persistent hypoxia below 90%, use of bronchodilators, and opiates may be considered for refractory dyspnea.

Treatment response failure may lead to progression of fibrosis with the eventual consideration for lung transplantation. Compared to patients with IPF, patients with HP who underwent lung transplant have reduced risk for death in 1, 3, and 5 years [43]. However, there remains significant risk for continued allergic inflammatory response against the transplanted lung [43]. The recurrence of HP has been reported after lung transplantation, usually presenting in the
Table 3  Current research trials on hypersensitivity pneumonitis

| Name                                           | Type of trial       | Location            | Recruitment         | Outcome                                                                 |
|------------------------------------------------|---------------------|---------------------|---------------------|-------------------------------------------------------------------------|
| PREDICT-HP                                     | Observational       | Multicenter         | Over 100 patients   | Correlate biomarkers with patients at risk for disease progression toward irreversible pulmonary fibrosis |
| PF Contact Registry                            | Observational       | National Jewish Health, US | Anticipate over 50,000 patients | Collect, analyze, and disseminate de-identified, group-level data on the clinical phenotypes of PF patients Connect and aid in enrollment in future research opportunities |
| Safety and Efficacy of Pirfenidone in patients with Fibrotic Hypersensitivity Pneumonitis | Single center, randomized, double-blind | National Jewish Health, US | 40 patients, prescribed Pirfenidone (2403 mg daily) versus placebo, followed for 52 weeks | Primary outcome–mean change in percentage FVC from baseline Secondary outcomes – progression-free survival (relative decline from baseline FVC or DLCO, acute exacerbation of fibrotic HP, decrease in 6MWT versus death) |
| Health-related quality of life instrument for patients with CHP | Observational       | Weill Cornell, US   | 120 participants    | Utilizing a newly developed survey versus Short Form survey versus King’s Brief Interstitial Lung Disease Questionnaire |

6MWT 6-min walk test, CHP chronic hypersensitivity pneumonitis, DLCO diffusion capacity of carbon monoxide, FVC forced vital capacity, HP hypersensitivity pneumonitis, PF pulmonary fibrosis
form of bronchiolitis obliterans syndrome [43]. This signifies the importance of exposure avoidance as well as the challenges in preventing recurrence of HP in cases where the inciting agent cannot be identified [43].

Recently, antifibrotics have been studied in patients who experience disease progression despite antigen avoidance and immunosuppressive therapy. Nintedanib is an intracellular inhibitor of tyrosine kinase that has shown promise in reducing rate of decline of FVC in patients with IPF and systemic sclerosis-associated ILD [44]. The INBUILD trial was a multicenter, randomized double blinded, placebo-controlled trial. Twenty-six percent of participants in this study had CHP. It demonstrated that in patients with progressive fibrosing ILD (>10% of the lung volume affected on HRCT, FVC of >45%, DLCO of 30 to 80%), the annual rate of decline in FVC in patients who received at least one dose of Nintedanib was significantly lower than those who received placebo [45•]. Despite this, there was no significant changes in QoL measures [45•]. Nintedanib was associated with a higher frequency of GI adverse events such as diarrhea, nausea, and vomiting [45•].

Pirfenidone is an antifibrotic agent frequently used for the treatment of IPF [46]. It is known to reduce the decline in vital capacity (VC) and improve progression-free survival [47]. Pirfenidone demonstrated decreased disease progression in the ASCEND study, as reflected by lung function, exercise tolerance, and progression-free survival [48]. It has also been considered effective therapy for other fibrotic lung diseases such as amyopathic dermatomyositis and scleroderma [49, 50]. In the RELIEF study, patients with fibrotic HP demonstrated a slower disease progression as measured by loss of FVC upon addition of Pirfenidone [51]. In 2018, 23 patients with avian-related CHP were enrolled in a study to monitor change in VC with administration of pirfenidone [52]. Pirfenidone reduced the decline of VC in patients with chronic fibrotic HP without significant adverse events, as observed in patients with IPF [47, 52]. Table 3 illustrates ongoing clinical trials involving patients with HP.

**Conclusion**

HP is an immune-mediated disease caused by exposure to a large variety of organic and inorganic materials in genetically susceptible patients. The disease has a heterogenous clinical presentation with a variable radiological and histopathological pattern on chest imaging and lung biopsy. The severity, persistence, and duration of antigen exposure influence the severity and progression of HP. It is imperative to obtain an extensive and exhaustive history to identify the inciting antigen. Utilizing published HP-specific questionnaires may augment the search to identify trigger agents. The combination of clinical, radiographical, and histopathological data will assist in determining the diagnosis in a timely manner [53]. More randomized control trials are needed to better understand and characterize HP. This would aid in standardizing management, identifying prognostic factors, and determining targets for future therapeutic interventions to improve survival and QoL.

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**Compliance with Ethical Standards**

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