Hypersensitivity Pneumonitis: Perspectives in Diagnosis and Management

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Awareness of hypersensitivity pneumonitis (HP) as a unique disease entity dates back to the 18th century (1). Since then, numerous inciting agents have been attributed to inducing HP, and the pathogenesis of the disease is now better understood (1, 2). HP is a disease of many facets and phenotypes, making its recognition and differentiation from other interstitial lung diseases (ILDs) challenging, in particular idiopathic pulmonary fibrosis (IPF). The clinician is often unable to distinguish features of chronic HP (CHP) from those of IPF, and some patients meeting the 2011 criteria for the diagnosis of IPF may in fact have CHP with pulmonary fibrosis (3). The high rate of screen failures in patients participating in IPF clinical trials highlights this diagnostic challenge, as pulmonologists may be misdiagnosing patients with CHP as having IPF, overlooking environmental factors that can contribute to the disease (4–8).

Despite recent data and reports suggesting new directions in the diagnosis, management, and treatment of HP (9–15), there remain substantial gaps in knowledge of epidemiology, pathogenesis, optimal diagnostic approach, and, ultimately, classification of this disease. Consensus among experts for diagnosis, treatment, and management are lacking, and the need for consensus guidelines is evident. In this Perspective, we propose diagnostic criteria and a novel classification of HP based on a combination of international clinical experience and available evidence. We believe that these criteria will be of use to the pulmonologist when confronted with patients suspected of having HP and promote further study to increase our understanding of how HP should be managed. The proposed criteria need to be validated in further studies, and therefore should not be interpreted as a guideline recommendation.

Epidemiology and Etiology of HP

Epidemiologic data on the incidence of HP range from 0.3 up to 0.9 per 100,000 individuals (16–18). A different perspective emerges from cohorts of patients investigated for new-onset ILDs where HP is part of differential diagnosis (19). In this setting, the clinical diagnosis of HP was made by multidisciplinary discussions in nearly half of patients with new-onset ILD in one study (19), with other reported incidence ranging from 18 to 30% (20, 21). These results emphasize the importance of a high clinical suspicion of HP diagnoses in patients manifesting ILD.

In a genetically predisposed individual, HP is a consequence of an immune-mediated reaction caused by recurrent exposure to overt or occult inducing environmental agents—HP inducers. This exposure can occur at home, in the workplace, related to hobbies, or sometimes indirectly, in another environment frequently visited by the patient (see Table E1 in the online supplement). It is likely that a mixture of antigens, rather than a single antigen, contributes to the sensitization and evolution of HP (8). Despite thorough investigations, the search for the occult HP inducer is reported as unsuccessful in up to 60% of cases (22–24). Feather bedding or down comforters may be an overlooked trigger of HP (25, 26).

Clinical Course of HP and New Proposed Classification

The division of HP into acute, subacute, and chronic categories is outdated (3 decades old), and of little prognostic value (23, 27). From a practical standpoint, it is difficult to stratify patients into these three distinct groups, and, in particular, subacute HP (22).

The knowledge from imaging, bronchoalveolar lavage (BAL), and clinical

studies has evolved since the original classification, and has been variably incorporated into clinical practice, without the benefit of consensus guidelines. We propose two main categories based on clinical–radiologic–pathologic correlation: acute/inflammatory HP and chronic/fibrotic HP (Table 1). Acute/inflammatory HP (symptom duration usually <6-mo or <∼24-wk duration) is often reversible, and is characterized by radiologic and histopathologic patterns. The presence of fibrotic changes in high-resolution computed tomography (HRCT) images or lung tissue (biopsy) defines chronic fibrotic HP, and reflects a prolonged or repetitive course of acute HP over several months, usually beyond 6 months or approximately 24-week duration (28, 29). The cut-off period of 6 months or approximately 24 weeks is arbitrary, but intended to reflect that, beyond this time period, the clinical course evolves to become chronic, either due to ongoing exposure or persistence of radiologic changes with/without treatment. In some cases, HP may initially present

clinically as an acute disease, but have radiologic and/or histopathologic signs of combined active inflammatory and chronic changes, and may have intermittent "flares." Some patients may manifest acute respiratory decline during their clinical course of CHP, similar to acute exacerbation in patients with IPF, and this may occasionally be the initial presentation of the disease.

Patients with well defined HP without an identifiable HP inducer tend to have a chronic course, and behave clinically similar to patients with IPF. Because the HP inducer(s) remains occult, we suggest the term "cryptogenic HP" for such patients (23).

Outcome of HP is highly variable and dependent on the type of initial clinical and radiological presentation, as well as clinical behavior patterns (Table 1). Patients with the acute form of HP who are able to avoid of further antigen exposure tend to have excellent outcome and prognosis; recovery is also possible. Patients with CHP may also experience partial recovery; however, in some individuals, the disease tends to progress despite avoidance of the HP

inducers and treatment. In general, outcome of patients with HP and their survival seem better than that in patients with IPF, even in those patients with HP with chronic progressive disease. Nevertheless, in the chronic progressive group, the median survival has been shown to be only 7 years (range, 4.4–14.5 yr) (15).

Predictors of unfavorable outcome have been associated with greater age, a history of cigarette smoking, crackles on lung examination, baseline low total lung capacity and diffusing capacity of carbon monoxide, absence of lymphocytosis in BAL fluid (BALF), presence of radiologic and/or histopathologic signs of fibrotic changes, and unidentified source of exposure (30–33).

Diagnosis of HP

The diagnosis of HP requires a high index of suspicion by the clinician evaluating any patient with new onset of ILD of unknown cause. Diagnostic steps should include a thorough and targeted evaluation of the

Table 1. Suggested Novel Classification of Hypersensitivity Pneumonitis

	Clinical Behavior	Typical HRCT Image Patterns*	Histopathology Patterns
Acute HP[†‡]: symptom duration usually few weeks/months (<6 mo to ∼24 wk)	• Mostly reversible • Complete resolution possible • Symptoms related to exposure/s to the HP inducer, which can resolve completely after further avoidance (frequently seen in occupational HP)	Upper- and middle-lobe predominant ground-glass opacities, poorly defined centrilobular nodules; mosaic attenuation, air trapping or, rarely, consolidation	Inflammatory (cellular) HP Lymphoplasmocytic/mononuclear (macrophage) infiltrates Airway-centric lymphocytic infiltrates/peribronchiolar Poorly/loosely formed granulomas Multinucleated giant cells NSIP cellular–like
Chronic HP[†‡]: symptom duration usually several months (>6 mo to >∼24 wk)	• Potentially reversible to some extent • Risk of progression	Upper- and middle-lobe predominant fibrosis, peribronchovascular fibrosis, honeycombing, mosaic attenuation, air trapping, and centrilobular nodules, relative sparing of the bases	Fibrotic HP UIP-like NSIP fibrotic–like Airway-centered fibrosis, NOS Unclassifiable Histopathologic signs of inflammatory HP can be present on the background of fibrosis

Definition of abbreviations: HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; NOS = not otherwise specified; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.
*Patterns specific for other diseases excluded: significant hilar adenopathy with or without calcification, egg shell calcification, nodular infiltrates abutting upper-lobe fissure, and/or other features typical of sarcoid; bilateral cysts; lymphangioleiomyomatosis; pulmonary Langerhans cell histiocytosis; and lung mass.
[†]When inducer in interstitial lung disease, which otherwise shows typical signs of HP (clinical, radiologic, and/or histopathologic) cannot be identified, the term "cryptogenic HP" is proposed. The characteristics of the acute and chronic cryptogenic HP are similar to those for HP with known cause, but may have worse prognosis.
[‡]Some patients presenting with manifestations of acute HP may have severe lung function impairment and extensive radiographic signs of fibrosis, whereas some patients with chronic HP (CHP) may manifest acute respiratory decline similar to acute exacerbation seen in patients with idiopathic pulmonary fibrosis. Some patients with CHP can intermittently present with superimposed acute symptoms.

patient's history, seeking to identify exposures, physical examination, HRCT of the chest, serum specific IgGs (SsIgGs) for confirmation of exposure or as a screening tool, and BAL. A lung biopsy should be considered in patients in whom the diagnosis remains uncertain. Specific inhalation challenge (SIC) can confirm an etiology of the disease and might be helpful when a lung biopsy is contraindicated. The diagnostic interventions suggested in Figure 1 are based on our collective clinical experiences, and represent evidence that is either of low or very low quality, and must therefore not be considered as clinical recommendations (34). The algorithm and proposed clinical criteria stratify patients into four diagnostic categories before obtaining lung biopsy material: (1) confident clinical diagnosis of HP; (2) probable HP; (3) possible HP; and (4) HP unlikely. Although there can be confidence in the clinical diagnosis of HP based on the clinical features and imaging and BAL data, the diagnosis as definite HP requires histopathologic confirmation.

For the patient who is unable or unwilling to be subjected to lung biopsy or SIC, a diagnosis of "probable or possible HP" may be reasonable if the combination of given strong clinical and radiologic evidence is highly suggestive. Treatment interventions in this scenario should include the preventive and therapeutic measures used for those with confident clinical diagnosis of HP and definite HP.

In the recent clinical prediction model of Johannson and colleagues (11), a combination of compatible clinical features, exposure to birds and down, and typical HRCT features predicted a high-confidence diagnosis of CHP without need for biopsy or BAL. However, this study confined its analysis to bird and down exposures, which may limit its clinical applicability, particularly when no exposure can be identified (cryptogenic HP)—a scenario seen in more than 50% of patients with CHP based on one series (12).

Physical Examination
The physical examination may be completely normal; however in the advanced, fibrotic phase coarse inspiratory rales are usually heard on auscultation and in some cases high-pitched mid–end inspiratory wheeze known as "chirping rales" or "inspiratory squeaks" may be present (35). Pulmonary function tests are

useful to assess severity of lung function impairment at the time of diagnosis and to monitor disease course (36).

Role of Radiology in the Diagnosis of HP
The HRCT patterns typical for acute HP include a centrilobular diffuse micronodular pattern, ground-glass opacification and mosaic attenuation (reflecting coexistent small airways disease) predominantly in upper and middle lobes (11, 37) (Figure 2). The HRCT findings specifically in CHP are those of fibrosis, namely reticulation, architectural distortion and traction bronchiectasis with or without honeycomb change. The fibrosis may be patchy, peribronchovascular (Figure 3A), or subpleural (mimicking usual interstitial pneumonia [UIP]) (Figure 3B), and may occur in any zonal distribution (38, 40). Honeycombing has been reported in 16–69% of patients (38, 40, 41), and may have a subpleural or peribronchovascular distribution, although, compared with UIP in IPF, it less frequently has a basal predominance (40). In some cases, there are superimposed findings of acute HP and, more frequently, lobular areas of decreased attenuation (seen in 80% of cases) that help to separate the diagnosis of CHP from UIP/IPF (40, 42, 43) (Figure 3C). Although interstitial fibrosis is the most common feature of CHP, patients with chronic farmer's lung, including lifelong nonsmokers, appear to develop emphysema (44–46). Although it is possible to make a high-confidence, HRCT-based diagnosis of HP (88–92% accuracy and 44–61% sensitivity), the radiologic findings are often not specific, and other granulomatous and fibrosing ILDs with a predominantly upper lobe distribution need to be considered (37, 39, 40).

Role of BALF Cellular Analyses in the Diagnosis of HP
BAL technique is used routinely in clinical practice in Europe and in some ILD centers and community practices in the United States; thus, we have addressed the possible clinical scenarios incorporating the BALF cellular analyses in the diagnostic process of HP (47). A predominantly lymphocytic pattern in BALF raises the probability of HP, as more than 80% of patients with CHP have more than 20% lymphocytes in BALF (48). However, BALF lymphocyte counts may be normal, or even lower than normal, in some patients with CHP

(48–50). Lymphocyte count also reflects the different histopathologic patterns seen in HP, with the highest counts present in organizing pneumonia and cellular nonspecific cellular interstitial pneumonia, and the lowest, but still increased, counts in a UIP-like pattern (51, 52). This is of particular importance in patients with CHP presenting with a UIP pattern on HRCT, as the presence of increased BALF lymphocytes raises the probability of the diagnosis of CHP (48–52). Although a low-lymphocyte CD4:CD8 ratio is suggestive for HP, this is nonspecific and insensitive, and thus, in keeping with the recommendations of the 2012 American Thoracic Society Clinical Practice Guidelines, we do not support the use of the T cell subsets in BALF as a routine test for patients undergoing evaluation for diagnosis of ILD (47, 53).

Role of Antigen Detection in Diagnosis of HP
Identifying the causative antigen is crucial for diagnosis, preventive measures, and prognosis of HP. The relationship between the exposure and the disease may be obvious in cases of occupational HP, but, in domestic cases, is often not immediately clear, making identification of the underlying trigger challenging (3):

- The first step in causative antigen identification is to meticulously collect a detailed patient history of exposure in their occupational and domestic environments, as well as any regularly visited places. The use of a standardized questionnaire as an aide may be very useful in identifying exposures otherwise missed in an informal discussion with the patient. Such a questionnaire would need to be validated before it could be used in routine clinical practice. A suggested questionnaire is shown in Table E2. The identification of environmental triggers may require input from ancillary specialists, such as occupational physicists or industrial/environmental hygienists, to collect reliable samples from the patient's environment for microscopic/microbiology analysis (54).
- The second step is laboratory investigation for confirmation of the suspect antigen by identification of SsIgG. Although the presence of SsIgG merely reflects the exposure and sensitization to the specific antigen by the patient, it is not diagnostic of HP.
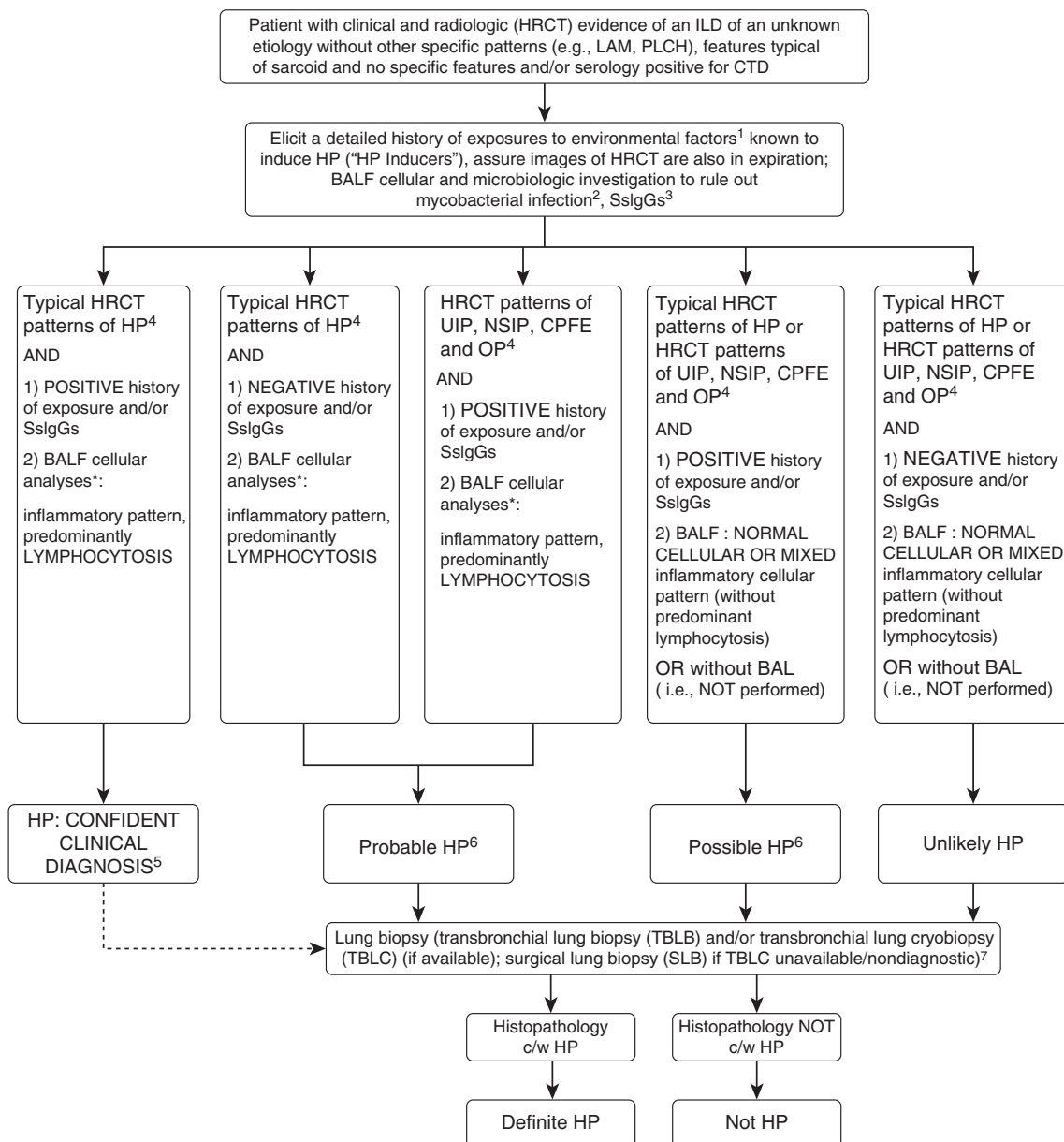
Patient with clinical and radiologic (HRCT) evidence of an ILD of an unknown etiology without other specific patterns (e.g., LAM, PLCH), features typical of sarcoid and no specific features and/or serology positive for CTD

Elicit a detailed history of exposures to environmental factors[1] known to induce HP ("HP Inducers"), assure images of HRCT are also in expiration; BALF cellular and microbiologic investigation to rule out mycobacterial infection[2], SsIgGs[3]

Typical HRCT patterns of HP[4]

AND

1) POSITIVE history of exposure and/or SsIgGs

2) BALF cellular analyses*:

inflammatory pattern, predominantly LYMPHOCYTOSIS

Typical HRCT patterns of HP[4]

AND

1) NEGATIVE history of exposure and/or SsIgGs

2) BALF cellular analyses*:

inflammatory pattern, predominantly LYMPHOCYTOSIS

HRCT patterns of UIP, NSIP, CPFE and OP[4]

AND

1) POSITIVE history of exposure and/or SsIgGs

2) BALF cellular analyses*:

inflammatory pattern, predominantly LYMPHOCYTOSIS

Typical HRCT patterns of HP or HRCT patterns of UIP, NSIP, CPFE and OP[4]

AND

1) POSITIVE history of exposure and/or SsIgGs

2) BALF : NORMAL CELLULAR OR MIXED inflammatory cellular pattern (without predominant lymphocytosis)

OR without BAL (i.e., NOT performed)

Typical HRCT patterns of HP or HRCT patterns of UIP, NSIP, CPFE and OP[4]

AND

1) NEGATIVE history of exposure and/or SsIgGs

2) BALF : NORMAL CELLULAR OR MIXED inflammatory cellular pattern (without predominant lymphocytosis)

OR without BAL (i.e., NOT performed)

HP: CONFIDENT CLINICAL DIAGNOSIS[5]

Probable HP[6]

Possible HP[6]

Unlikely HP

Lung biopsy (transbronchial lung biopsy (TBLB) and/or transbronchial lung cryobiopsy (TBLC) (if available); surgical lung biopsy (SLB) if TBLC unavailable/nondiagnostic)[7]

Histopathology c/w HP

Histopathology NOT c/w HP

Definite HP

Not HP

Figure 1. Diagnostic criteria/algorithm for hypersensitivity pneumonitis (HP) (suggested). [1]See Table E1 in the online supplement. [2]Positive cultures of *Mycobacterium tuberculosis* (in bronchoalveolar lavage fluid [BALF] or sputum) exclude HP; positive cultures of nontuberculous mycobacteria raise the possibility of HP caused by nontuberculous mycobacteria if the other criteria noted in the boxes are fulfilled. [3]Serum-specific IgGs (SsIgGs) may help to: (*1*) find a relationship between exposure and the disease and/or associate exposure with the disease; (*2*) screen for potential inducers in case of unknown exposure in patients in whom the clinical and high-resolution computed tomography (HRCT) findings do not rule out HP; and (*3*) decrease probability of feather or fungus etiology of interstitial lung disease (ILD) if negative. [4]See Table 2. [5]Although the clinical diagnosis of HP is confident based on the proposed criteria, the option to confirm the diagnosis as definite with histopathology is individualized based on the patient's need of/wanting/insistence on a secured diagnosis by histopathology and/or to be convinced of getting rid of the alleged inducer/source/environmental factor. [6]Specific inhalation challenge testing for patients with probable and possible HP in patients who prefer not to undergo procedures for lung biopsy and/or who have clinical conditions considered absolute contraindications (*see* online supplement for the procedure details). Specific inhalation challenge testing, when considered, must be performed only in experienced centers. [7]The preferred procedure of choice for acquisition of lung tissue is deferred to discussions of risks–benefits of the procedures with the patient and dependent on (*1*) the individual patient's clinical condition and ability to tolerate the procedure, (*2*) local expertise, and (*3*) experiences of experts performing the procedure. The diagnosis of HP is not excluded based on nondiagnostic histopathology in the transbronchial lung biopsy (TBLB) and/or transbronchial lung cryobiopsy (TBLC) specimens but is excluded if the histopathology does reveal features inconsistent with HP in the surgical lung biopsy. The conventional TBLB can be planned/performed immediately after the bronchoalveolar lavage (BAL), and thus the BAL and TBLB specimens can be collected via one fiberoptic bronchoscopy procedure. Likewise, in centers performing cryobiopsy, the BAL can also be performed immediately prior to TBLC. CPFE = combined pulmonary fibrosis and emphysema; CTD = connective tissue disease; c/w = consistent with; LAM = lymphangioleiomyomatosis; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; SLB = surgical lung biopsy; UIP = usual interstitial pneumonia.
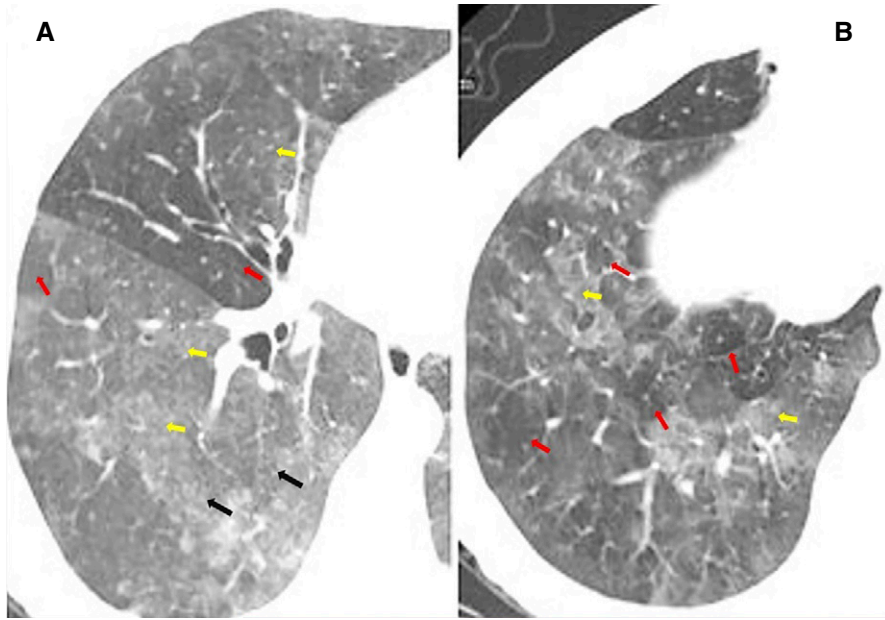
Figure 2. High-resolution computed tomography of acute hypersensitivity pneumonitis. (*A* and *B*) Ground-glass opacities as a sign of alveolitis (*yellow arrows*, *A* and *B*); centrilobular micronodules (*black arrows*, *A*) likely produced by a combination of small airway pathology and mosaic attenuation (hyperlucent areas within areas of normal density or ground-glass opacity) indicating air trapping (*red arrows*, *A* and *B*) based on bronchiolar involvement are shown.

chest radiologist, and BAL cellular analysis (if available) should be less than definitive for a confident diagnosis (Figure 1) (63). The ideal platform for the decision-making process for the most appropriate diagnostic evaluation of the patient is the multidisciplinary discussion. In the absence of diagnostic samples from transbronchial lung biopsy (TBLB) performed by flexible forceps, transbronchial cryobiopsy (TBLC), or surgical lung biopsy (SLB) should be considered. SLB is a well established method for obtaining adequate samples of lung tissue for histopathologic evaluation, and contributes substantially to the final diagnosis of HP, especially in cases of CHP (64). TBLB and the more recently introduced TBLC are less invasive than SLB. Although the diagnostic yield of TBLC in ILD is comparable to SLB in some centers (65–67), meta-analyses of available data on diagnostic yield of TBLC for the diagnosis of ILDs are limited to a few centers only. However, evidence on diagnostic efficacy of TBLC is accumulating (68). The meta-analysis by Sharp and colleagues (69) of 11 studies on TBLB, 11 on TBLC, and 24 on SLB revealed a diagnostic yield of 64.3, 84.4, and 91.1%, respectively, and the very recent meta-analysis by Iftikhar and colleagues (69, 70) comparing TBLC with SLB showed that diagnostic accuracy of TBLC is comparable with SLB, with an acceptable safety profile. Although such data are encouraging, TBLC for tissue diagnosis is currently only viable in a few experienced centers that have the required specialized skills (69–71). The preferred procedure of choice of acquisition of lung tissue is therefore best deferred to discussions of risks–benefits of the procedures with the patient, and dependent on: (*1*) individual patient's clinical condition and ability to tolerate the procedure; (*2*) local expertise; and (*3*) experiences of individuals performing the procedure. In this regard, we emphasize that the diagnosis of HP is not excluded based on nondiagnostic histopathology in the TBLB and/or TBLC specimens, but is excluded if the histopathology does reveal features inconsistent with HP in the SLB and/or other specific diagnosis.

Although the adequacy of the sample size and the selected sites of the biopsy specimens is important for the diagnostic yield of the lung biopsy, histopathological features consistent with HP can be present in the lung tissue obtained by
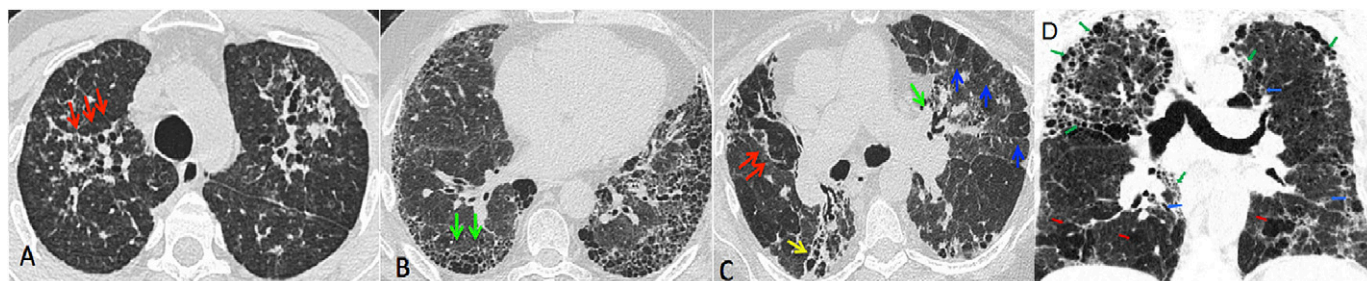
The most frequent laboratory method used for identification of SsIgGs is ELISA, but immunodiffusion and ImmunoCAP (Thermo Fisher Scientific Inc., Waltham, MA) can be used as well (55, 56). The antigens can be obtained as commercially available extracts, or can be prepared from collected material in specialized laboratories (57). The cut-off values are not arbitrary, and depend on comparison of values detected in sensitized but healthy individuals with those of patients with HP. The data on sensitivity and specificity of serum values of specific IgGs differ in the literature, and reflect the HP inducers and the method used for detection (58, 59).

Specific IgGs may help to:

1. Find a relationship between exposure and the disease and/or associate exposure with the disease.
2. Screen for potential inducers where an inducer has not been identified, but where clinical and imaging data are compatible with HP.
3. Decrease probability of feather or fungus etiology of ILD if negative.

The presence of increased SsIgG revealed during screening of extrinsic causes of ILD should prompt further evaluation and diagnostic interventions that could lead to securing the diagnosis of HP (60). The panels of SsIgGs used in different centers are determined by practice location. An example of a panel of SsIgGs can be found in Table E3.

- The third step to confirm the causality between a suspected antigen and the disease is the SIC test, which can be performed by natural exposure to the environment where the antigen is thought to be present, by direct challenge with inhalation of the alleged HP inducer obtained from the patient's environment, or by commercially available extracts (3). However, this test is not standardized or validated, and requires experienced personnel and laboratories (3, 61, 62) (Text Box E1). We propose the use of SIC, particularly in patients for whom histopathologic diagnosis is unavailable or where a biopsy has been performed, but is nondiagnostic. It may also be performed to confirm a suspected etiologic agent (Table E1).

Role of Histopathology in Diagnosis of HP

Before considering a lung biopsy, careful physical examination, pulmonary function tests, interpretation of HRCT images by a

Figure 3. High-resolution computed tomography (HRCT) of chronic hypersensitivity pneumonitis (HP). (*A*) Axial HRCT image at the level of the upper lobes, depicting peribronchovascular reticulation and ground-glass opacities containing traction bronchiectasis in a patient with chronic HP (CHP). These parenchymal patterns are centered on the bronchovascular bundles (*red arrows*). The subpleural lung is conspicuously spared. (*B*) Axial HRCT image at the level of the lower lobes demonstrating subpleural honeycombing, reticulation, and traction bronchiectasis (*green arrows*), typical of usual interstitial pneumonia, in a patient with CHP. This patient was a bird keeper and also had a marked lymphocytosis on bronchoalveolar lavage. (*C*) Axial HRCT image at the level of the carina demonstrating patchy peribronchovascular fibrosis (*green arrow*) and peripheral subpleural fibrosis (*yellow arrow*) typical of CHP. There is also parenchymal mosaicism manifesting as areas of lobular air trapping (*blue arrows*), which reflects the small airways component of the disease. Caution must be exercised when identifying air trapping when lung fibrosis is present; occasionally, fibrosis adjacent to normal lung parenchyma may give the appearance of air trapping (*red arrows*), and this is because of the low-density appearance of the normal lung parenchyma in contrast to the dense image pattern of the adjacent fibrotic tissue. (*D*) Coronal HRCT image showing typical distribution of the changes in CHP. Predominantly upper lobe involvement and reticulation with traction bronchiectasis corresponding to fibrotic changes (*blue arrows*), honeycombing localized predominantly in subpleural areas of upper lobes HP (*green arrow*), and mosaic attenuation indicating air trapping (*red arrows*) are shown.

conventional/traditional transbronchial forceps biopsy. Characteristic histopathological features of HP in its active phase (inflammatory/cellular form in our construct) include the triad of bronchiolocentric lymphohistiocytic interstitial pneumonia with chronic bronchiolitis and typical small, poorly formed, nonnecrotising granulomas, best appreciated near the bronchovascular sheaths and sometimes consisting of no more than two to three aggregated giant cells (72) (Figure 4). This triad represents the histopathological pattern of inflammatory (cellular) HP. The clinician's index of suspicion for the diagnosis of HP must be increased whenever the histopathology reveals nonspecific cellular interstitial pneumonia, lymphoplasmocytic infiltrate, and/or peribronchiolar lymphocytic infiltrates, lymphocyte aggregates without germinal centers, and peribronchial metaplasia (31). In the chronic form of HP (histopathological pattern of fibrotic HP), inflammatory infiltrates are less developed and fibrosis dominates the histopathology; airway-centered granulomas may be absent or sparse. The fibrosis has a "branched" appearance at very low magnification, as the scar with attendant peribronchiolar metaplasia tracks along the bronchovascular bundles. When a UIP pattern ("patchy" parenchymal fibrosis) is found in the lung biopsy, this does not exclude HP, as CHP can be patchy in an airway-centered distribution simulating the

patchwork of scar alternating with normal appearing lung seen in UIP of IPF. In the setting of advanced fibrosis in patients with CHP, the search for normal airways in SLB will help confirm CHP, as these are rarely (if ever) present. In fact, in a recent study, histopathology features of HP documented some degree of abnormality within and/or around the small airways in 100% of patients with HP (15). In short, normal-appearing small airways are rare in the lung biopsy of a patient with CHP (in contrast to UIP in IPF where fibrosis tends to spare the airways) (72, 73) (Figure 5).

Regardless of such nuances, in every case of lung fibrosis, it is essential to correlate clinical and radiological findings with histopathology for accurate diagnosis (7, 10, 36, 74, 75).

Treatment of HP

To our knowledge, there is only one 25-year-old clinical trial demonstrating the effectiveness of corticosteroids in acute HP (75). To date, there are no reported/published results from
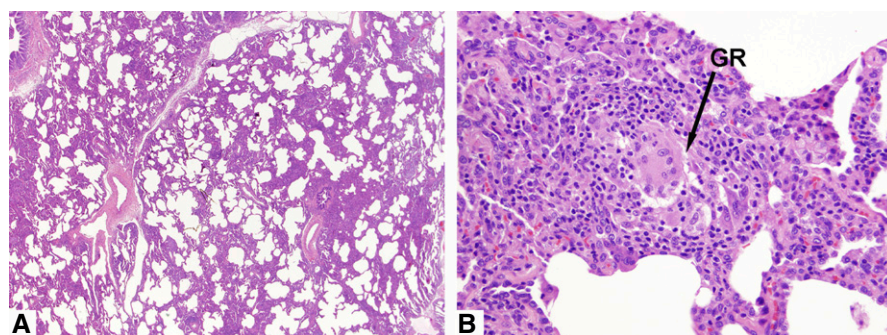

Figure 4. (*A* and *B*) Hypersensitivity pneumonitis (HP), active/inflammatory–cellular phase. (*A*) The diffuse lymphohistiocytic infiltrate resembling "nonspecific interstitial pneumonia–cellular" at very low magnification. The infiltrates are vaguely airway centered under the microscope, but not dramatically so (at this early stage of disease, the high-resolution computed tomography usually demonstrates "fuzzy" 3- to 5-mm centrilobular nodules in the lung periphery of the middle and upper lung zones). Hematoxylin and eosin stain (original magnification, ×20). (*B*) A characteristic, poorly formed, interstitial granuloma of HP (GR). These are easily overlooked, and may be represented by as few as one or two interstitial multinucleated histiocytes. Calcified inclusions can be seen in the giant cells (so-called Schaumann bodies), but are not essential to the diagnosis. Hematoxylin and eosin stain (original magnification, ×400).

randomized, controlled clinical trials on pharmacological treatment for CHP.

Exposure Avoidance

The first treatment intervention is prompt and complete avoidance of further exposure to the inducer, usually by eradicating it from the patient's environment, preferably with the help of environmental/industrial hygienists. Patients must be alerted to the importance of a domestic clean air environment and the absolute need to avoid further exposures to known HP inducers, including concealed antigens in feather duvets, pillows, ventilation systems, furnaces, air conditioners, filters, evaporative air coolers, and humidifiers, exposures to bird droppings in their immediate outdoor environments (e.g., patios and porches), window sills, yards, other landscapes they may attend, et cetera.

Pharmacological Treatment

Corticosteroids. Currently, systemic corticosteroids are the mainstay of pharmacology treatment. Although the general goal is to aim for the lowest-possible dose and shortest duration, the dosage and duration of treatment have not been determined in any study (76). Varying doses and duration, starting at 0.5 mg/kg (ideal body weight) for a few days and slow tapering to the lowest possible dose over several months to a year or longer, have been used. Pending clinical trials, a recommendation based on consensus of opinions among experts regarding the dose, and duration treatment is needed.

Immune-modulating agents. In patients with CHP, especially those with a progressive course, adjunct immunosuppressive agents may be considered. However, one must be aware of their off-label use in this context and the lack of randomized clinical trials to make specific treatment recommendations. By virtue of azathioprine and mycophenolate being available for clinical use in lung diseases mediated by autoimmune mechanisms, pulmonologists may be more comfortable with the use of azathioprine (and, more recently, mycophenolate) rather than other immune-modulating drugs, such as leflunamide, rituximab, et cetera. In a retrospective study by Morisset and colleagues (13), treatment with azathioprine and mycophenolate mofetil was associated with an improvement of gas exchange and reduction of prednisone, which supports the use of these drugs in the treatment of chronic progressive HP. Although the harmful effects of combined azothioprine, prednisone, and N-acetyl cysteine have been well documented in patients with IPF (77), it is unknown if prednisone plus azathioprine is harmful for patients with CHP. We express caution with the use of this combination treatment for patients with fibrotic CHP showing a UIP-like pattern. Very low quality evidence (case reports, small case series) suggest the use of rituximab and leflunomide in HP, and the use of these agents is deferred to the physicians who are especially confronted with patients who have not tolerated and/or not responded to the use of azathioprine or mycophenolate (78).

Antifibrotic treatment. For patients with progressive fibrotic CHP, especially with a UIP-like pattern, it may be appropriate to consider newer antifibrotic agents indicated for IPF, recognizing that this will be off-label and cost concerning. Randomized, controlled trials with either nintedanib or pirfenidone are appropriate and, hopefully, these will be conducted soon for these patients, as also discussed in the concurrent perspective by Salisbury and colleagues (12).

Lung Transplantation

Patients with progressive disease should be evaluated early for lung transplantation, as they have excellent post-transplant medium-term survival and, relative to IPF, a reduced risk for death (14).

Future Directions

Identification of Causal Antigen and Proof of Causality between Antigen and HP

Although methods of antigen exposure detection (presence of the antigen in patient's surroundings, SsIgGs in patient's blood) need to be standardized (see online supplement) and exposures must be sought, it is important to prove hypersensitivity to the suspected HP inducer/antigen. In this regards, the *in vitro* (lymphocyte proliferation test) or biologic *in vivo* (SIC and a skin test of delayed type of hypersensitivity) tests are promising for the future. However, availability of suitable standardized inducers will need to be resolved (3, 54, 79, 80). The normal values for microbiological contamination of homes and different working environments are not defined, and we also do not know if sensitization depends on concentration and duration of exposure to potential inducers in the environment. Animal models of HP to ascertain etiology and to study the relationship between pathologic lesions and exposure burden should be explored.

Biomarkers in the Peripheral Blood, BALF, and Lung Tissue

The biomarkers from BALF and peripheral blood need to be investigated for the potentials of minimally invasive diagnosis and prediction of prognosis of HP. Laboratory analysis of molecules, especially involved in alveolar damage and inflammation (Krebs von den Lungen [KL]-6, surfactant protein D, and chitinase
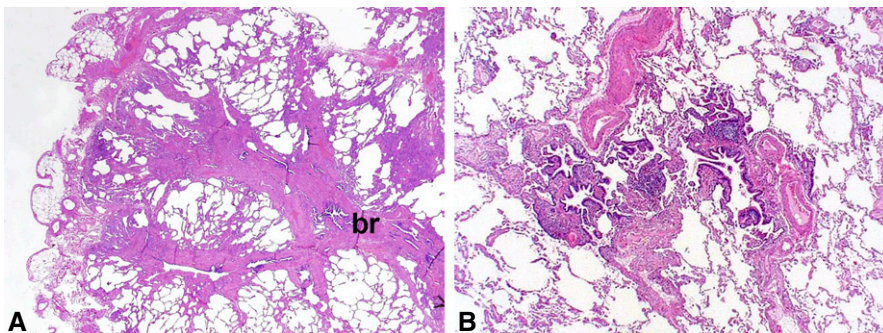

Figure 5. (*A* and *B*) Hypersensitivity pneumonitis, chronic-fibrotic phase. (*A*) The characteristic branching pattern on fibrosis following the bronchovascular bundles (br). Hematoxylin and eosin stain (original magnification, ×20). (*B*) The so-called "peribronchiolar metaplasia" commonly present in chronic hypersensitivity pneumonitis. This phenomenon occurs as a result of severe damage to the small airways, most commonly from an inhalational insult. The very peripheral ends on the bronchioles become redundant with reparative proliferation of the epithelium. Most inhalational injuries will show this finding to a variable degree. Hematoxylin and eosin stain (original magnification, ×100).

3–like protein 1 [YKL-40]) and chemokines (CCL17, CCL18, vascular endothelial growth factor, IL-8, epithelial neutrophil-activating peptide 78 [ENA-78]) may reflect inflammatory activity and predict progression and outcome (YKL-40) (81–83). The potential for cathepsin-K as a differentiating diagnostic marker for granulomas in CHP needs to be studied (84).

Diagnosis by Molecular Signatures

Molecular genetic analysis of BALF and lung tissue may reveal distinct patterns of expression profiles distinguishing HP, IPF, and other entities (85). Although this approach is promising, the feasibility, specificity, and sensitivity of a diagnosis using molecular probes need to be evaluated.

Genetic Predisposition, Genetic Factors, and Phenotypes

Currently, data on susceptibility genes in HP are scarce; risk genes will need to be identified and will be helpful, not only for diagnosis, but also for counseling in career choices and lifestyle of family members of patients with HP (86). With the advent of precision medicine and genetic testing, it is conceivable that HP can be prevented by pre-emptive avoidance of exposures to known HP inducers in susceptible people who would otherwise manifest HP. These methodologies and pharmacogenomics may also help estimate prognosis and predict outcomes/therapeutic responses.

Clinical Trials

As no evidence-based treatment recommendations are available for HP, there is an urgent need for well designed, randomized clinical trials in HP, especially for CHP. We believe that existing antifibrotic treatments for IPF and novel antiinflammatory/fibrotic agents currently being tested in IPF are also appropriate agents for randomized clinical trials for patients with CHP.

Conclusions

HP has multiple clinical phenotypes, and remains a challenge for general pulmonologists and for ILD experts. We have discussed what is known and highlighted uncertainties related to this disease. We outline our perspectives for establishing the diagnosis of HP and have proposed a classification schema, diagnostic algorithm, and criteria for making a confident clinical diagnosis of HP. Every effort must be undertaken to identify the HP inducer(s) in the patient's environment and eradicate the source to prevent further exposure and minimize risk of progression. Clinical trials with existing and/or new antifibrotic agents are needed to determine a safe and efficacious regimen for patients with CHP. It is our hope that this shared Perspectives article will enhance clinical awareness of HP and provoke much-needed clinical studies and lead to understanding for accurate diagnosis and better management of HP. ■

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