

# Executive Summary Diagnosis and Evaluation of Hypersensitivity Pneumonitis

## CHEST Guideline and Expert Panel Report

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**BACKGROUND:** The purpose of this summary is to provide a synopsis of evidence-based and consensus-derived guidance for clinicians to improve individual diagnostic decision-making for hypersensitivity pneumonitis (HP) and decrease diagnostic practice variability.

**STUDY DESIGN AND METHODS:** Approved panelists developed key questions regarding the diagnosis of HP using the PICO (Population, Intervention, Comparator, and Outcome) format. MEDLINE (via PubMed) and the Cochrane Library were systematically searched for relevant literature, which was supplemented by manual searches. References were screened for inclusion and vetted evaluation tools were used to assess the quality of included studies, to extract data, and to grade the level of evidence supporting each recommendation or statement. The quality of the evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Graded recommendations and ungraded consensus-based statements were drafted and voted on using a modified Delphi technique to achieve consensus.

**RESULTS:** The systematic review of the literature based on 14 PICO questions resulted in 14 key action statements: 12 evidence-based, graded recommendations, and 2 ungraded consensus-based statements. All evidence was of very low quality.

**INTERPRETATION:** Diagnosis of HP should employ a patient-centered approach and include a multidisciplinary assessment that incorporates the environmental and occupational exposure history and CT pattern to establish diagnostic confidence prior to considering BAL and/or lung biopsy. Additional research is needed on the performance characteristics and generalizability of exposure assessment tools and traditional and new diagnostic tests in modifying clinical decision-making for HP, particularly among those with a provisional diagnosis.

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**KEY WORDS:** executive summary; guidelines; hypersensitivity pneumonitis

**ABBREVIATIONS:** HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IA = inciting antigen; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LPT = lymphocyte proliferation test; MDD = multidisciplinary discussion; PICO = population, intervention, comparator, outcome; SIC = specific inhalation challenge

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## Summary of Recommendations

**1. In patients with suspected hypersensitivity pneumonitis (HP), we suggest gathering a thorough clinical history of exposures focused on establishing the type, extent, and temporal relationship of exposure(s) to symptoms** (Ungraded Consensus-Based Statement).

*Remarks:* Accurate and timely HP diagnosis relies on gathering and integrating a detailed and comprehensive exposure history. Although an important factor in reducing diagnostic uncertainty is the identification of a compelling exposure, an unrevealing exposure history does not exclude HP. If the exposure history is unclear, the process of exposure history gathering, integration, and interpretation of possible exposure data should continue until an HP diagnosis or its exclusion is more certain. All patients should complete a comprehensive environmental and occupational questionnaire tailored to the geographic region.

*Remarks:* During the diagnostic workup of a patient with suspected HP, interpretation of a positive or negative diagnostic test is dependent upon the presence or absence of an identifiable exposure and disease prevalence (pretest probability).

**2. In patients with suspected HP, if the inciting antigen (IA) is thought to be related to occupational exposure, we suggest considering the inclusion of an occupational medicine specialist and an environmental hygienist during the multidisciplinary diagnostic workup, especially when the source of exposure**

**is obscure or unverified** (Ungraded Consensus-Based Statement).

**3. In patients with suspected HP, we suggest classifying patients based on the likelihood of an occupational or environmental inciting antigen exposure** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Correct identification of the IA and the subsequent elimination of that exposure facilitates the management and helps determine the prognosis of HP. Unless a thorough exposure history is performed, the IA may go unrecognized with resultant ongoing exposure possibly adversely impacting disease progression and survival. In some scenarios, the disease may flare or continue to progress despite apparent remediation of the suspected exposure(s). This suggests that other factors may be associated with disease progression, and/or that other exposure(s) may be contributing.

*Remarks:* Given the prognostic importance of antigen identification and avoidance, surveillance for exposure and patient education focused on antigen avoidance at every visit is the highest priority. This is particularly important for those unwilling to remove the antigen source despite the negative clinical consequences, patients with disease progression despite pharmacological or environmental management, those with a recurrence of symptoms after an initial appropriate response, in cases of disease clustering (e.g., multiple cases identified in one geographic area), and when symptoms are attributed to an occupational or suspected but unverified exposure. While the prognostic implications of a suspected but unverified exposure remain unclear, additional investigative strategies to identify a potential exposure (e.g., workplace inspection) may support the diagnosis and help guide management decisions.

**4. For patients with either newly diagnosed or a working diagnosis of HP, we suggest classifying the disease as fibrotic or nonfibrotic based on the presence or absence of fibrosis on high-resolution computed tomography (HRCT) of the chest** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* HRCT findings indicative of lung fibrosis include one or more of the following: reticular abnormality or ground-glass opacity associated with traction bronchiectasis, honeycombing, and loss of lobar volume.

*Remarks:* Several studies demonstrate that the presence or absence of lung fibrosis provides important prognostic information. Further, as chronic HP does not

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always follow acute disease and only a subgroup of HP patients with chronic disease will develop lung fibrosis, a time-based classification scheme (eg, acute, subacute, chronic) is inferior to the identification of the presence or absence of fibrosis as a prognostic marker.

Furthermore, in addition to prognosis, both fibrosis and antigen characterization have important diagnostic and treatment implications.

**5. In patients with suspected HP, if an IA exposure is identified and then completely avoided, we suggest using clinical improvement with antigen avoidance to support the diagnosis of HP, but not relying solely on the lack of clinical improvement with antigen avoidance to rule out the diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Clinically appreciable improvement in symptomatic, physiologic, and radiographic features may be seen only in patients with non-fibrotic HP. Measurable clinical improvement may not occur if the remediated antigen is not causative, if there are multiple exposures causing disease, if complete avoidance cannot be achieved, or in subjects with severe or progressive pulmonary fibrosis. Moreover, in a significant proportion of patients with fibrotic HP, an antigen will not be identified. Therefore, clinical improvement with antigen avoidance may support the diagnosis of HP, but the absence of clinical improvement does not rule it out.

**6. For patients with suspected HP, we suggest not relying solely on clinical improvement with medical therapy to confirm a diagnosis of HP or on the lack of clinical improvement with medical therapy alone to rule out the diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Clinical improvement refers to improvement in physiologic and radiologic features. Failure to respond to medical treatment (eg, systemic corticosteroids) alone does not necessarily exclude the diagnosis of HP as the response rate to medical therapy can be highly variable. For example, clinical improvement with medical treatment appears to occur frequently in nonfibrotic HP, while the lack of clinical improvement, regardless of therapy, is common in fibrotic HP. Clinical improvement with medical therapy supports but does not confirm the diagnosis of HP as other interstitial lung diseases with similar presentations, such as idiopathic NSIP, may also improve with immunosuppressive treatment.

**7. For patients with suspected HP, we suggest not relying solely on serum antigen-specific**

**immunoglobulin G (IgG) or immunoglobulin A (IgA) testing to confirm or rule out the diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Major limitations to the diagnostic utility of serum antigen-specific IgG/IgA testing in HP are the lack of standardized antigen preparations for most IAs, the lack of standardized immunoassays techniques, variable diagnostic cutoff thresholds for quantitative IgG assays, and validation of serum antigen-specific IgG test performance in limited population settings.

*Remarks:* When there is a questionable exposure based on the history (eg, indoor musty odor but no visible mold or the occasional exposure to mold with the significance of exposure uncertain), the detection of serum antigen-specific IgG/IgA may suggest a putative exposure and in the setting of other supporting diagnostic tests (eg, typical HRCT) or environmental assessment data (eg, indoor visual inspection, surface sampling, and culture), may raise the likelihood of HP. However, there is a lack of data consistently supporting the test as a reproducible and accurate diagnostic tool.

**8. For patients with suspected HP, we suggest not performing antigen-specific inhalation challenge testing to support the diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Major limitations to the diagnostic utility of antigen-specific inhalation challenge testing in HP are the lack of standardized and validated antigen preparations for most IAs, the lack of standardized challenge techniques (eg, challenge chamber, nebulization of suspected IA), and the absence of validated criteria for defining a positive response. Also, there is limited world-wide availability of appropriate facilities to perform the test and absence of studies evaluating the additional value of antigen-specific inhalation challenge in modifying the likelihood of suspected HP (eg, unidentified IA) during the multidisciplinary diagnostic process.

**9. For patients with suspected HP, we suggest not performing antigen-specific lymphocyte proliferation testing to support the diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Major limitations to the diagnostic utility of antigen-specific lymphocyte proliferation testing in HP include: the lack of standardized and validated antigen preparations for most IAs, the lack of standardized lymphocyte proliferation techniques, absence of validated criteria for defining a positive response, and

the absence of studies evaluating the additional value of antigen-specific lymphocyte proliferation testing in modifying the likelihood of HP during the diagnostic process.

**10. For patients with suspected HP, we suggest the integration of HRCT findings characteristic of HP with clinical findings to support the diagnosis of HP, but not using the CT findings in isolation to make a definite diagnosis** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* High-resolution CT findings characteristic of HP include profuse centrilobular nodules of ground glass attenuation, inspiratory mosaic attenuation and air-trapping, and the three-density sign.

*Remarks:* Assessment of the overall probability of HP should consider the prevalence of the disease in the particular setting (eg, referral center or primary care clinic, farming region), the clinical context, the exposure history, and the information contributed by the HRCT.

**11. For patients with suspected HP, we suggest using a multidisciplinary discussion (MDD) for diagnostic decision-making** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* If a high confidence diagnosis cannot be established by combining the history and clinical context, consider case discussion in the setting of an MDD.

*Remarks:* The inter-observer agreement for HP diagnosis between MDD and individual clinicians for typical HP cases (respiratory symptoms, known temporal relationship with a specific IA exposure, characteristic CT chest and histopathological findings) is unknown. However, in uncertain cases, MDD may increase diagnostic confidence and/or guide the appropriate use of subsequent tests such as bronchoscopy or surgical lung biopsy (SLB).

**12. For patients with suspected HP who have a compelling exposure history within the appropriate clinical context and a chest HRCT pattern typical for HP, we suggest not routinely using BAL fluid analysis to confirm a diagnosis of HP** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* BAL fluid analysis can narrow the differential diagnosis by excluding competing causes, particularly in nonfibrotic HP (eg, infection). However, in patients with a high pretest probability of HP, the BAL cellular

differential generally does not significantly alter the post-test probability and as a result adds little additional diagnostic information. In the appropriate clinical context, a history of clinically relevant exposure to a compelling IA with a typical high-resolution CT pattern allows for a confident diagnosis of HP.

*Remarks:* Lymphocytic alveolitis is not consistently present in patients with fibrotic HP and BAL fluid lymphocytosis is not sufficiently sensitive or specific to rule in or rule out the diagnosis of fibrotic HP. However, BAL fluid lymphocytosis may increase diagnostic confidence when the IA is identified and HRCT findings are compatible with HP. It may also increase diagnostic confidence and *should be considered when the exposure history and imaging data are discordant* (eg, unidentified exposure and typical CT for HP-provisional diagnosis), and may exclude common alternative diagnoses, such as IPF, when the lymphocyte differential count is high (eg,  $\geq 40\%$ ).

**13. In patients with suspected HP, we suggest considering histological lung biopsy for additional diagnostic evaluation when all available data such as clinical, laboratory and radiologic findings along with bronchoscopic results do not yield a confident diagnosis and results may help guide management** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* When possible, a consensus MDD should be considered before an SLB or TBC. SLB, TBC, and transbronchial biopsies (TBBs) have different diagnostic yields and benefit-risk profiles. The harm from the procedure must be weighed against the potentially useful information that can be gained, particularly in suspected non-fibrotic or advanced fibrotic HP cases.

*Remarks:* Some patients with fibrotic HP may show histopathologic findings of nonspecific interstitial pneumonia or usual interstitial pneumonia (UIP) pattern. Samples should be carefully examined for findings consistent with HP (eg, poorly formed non-necrotizing granulomas and/or multinucleated giant cells and fibrotic bronchiolocentric accentuation). Thus, when lung biopsy is performed, the histopathological information requires multidisciplinary reconciliation with the clinical and radiological information.

**14. For patients with suspected HP, we suggest integrating biopsy findings with clinical and radiological findings to support the diagnosis of HP in the context**



**of the MDD** (Weak Recommendation, Very Low-Quality Evidence).

*Remarks:* Pathologic findings characteristic of HP typically include a combination of cellular and/or fibrosing interstitial pneumonia with bronchiolocentric accentuation, poorly formed non-necrotizing granulomas with or without giant cells, with or without peribronchiolar metaplasia, and/or small foci of organizing pneumonia. Isolated histopathological findings such as non-necrotizing granulomas or inconspicuous foci of organizing pneumonia can occasionally be seen in other ILDs and are not specific enough for a diagnosis of HP. Potential limitations of lung biopsy include interobserver variation in the pathologic interpretation, biopsy size and number of specimens affecting the diagnostic yield of the biopsy procedure, sampling error, and the occasional presence of atypical findings such as NSIP or UIP-like patterns. Biopsy findings of HP or occasional isolated atypical patterns produced by HP require MDD to confirm the diagnosis.

## Background

The definition and proposed diagnostic criteria for hypersensitivity pneumonitis (HP) have evolved substantially since their first published description in the 18th century.<sup>1-3</sup> HP is now understood as an immunologically mediated form of lung disease

resulting from inhalational exposure to a large variety of environmental and/or occupational organic (typically fungal, bacterial, or avian), and less often, nonorganic, inciting antigens (IAs). HP is a complex lung disease that can occur at any age in genetically susceptible individuals previously sensitized to the inhaled IA.

Over the years, the categorization of HP based on clinical features and disease duration coupled with traditional diagnostic criteria has been unhelpful, even when accurate, when separated from Bayesian principles and used equally in all individuals. Furthermore, a central source of practice variation and diagnostic disagreement across multidisciplinary teams and among physicians has been the absence of a comprehensive clinical practice guideline to optimize diagnostic consistency and decision-making in HP.

This paper provides an executive summary of the full guideline document<sup>4</sup> that describes the evidence base for the benefits and harm of diagnostic approaches to HP and details the pathogenesis, exposure assessment, imaging, pathology, and diagnostic evaluation. This evidence is used to inform recommendations and ungraded consensus-based statements. A diagnostic algorithm is also provided, incorporating the evidence and informed by expert consensus, to aid physicians in gauging the probability of HP.

## Methods

These guidelines were developed per American College of Chest Physicians (CHEST) policy.<sup>5,6</sup> In short, approved panelists developed research questions and a systematic literature review was

conducted. The Grading of Recommendations Assessment, Development and Evaluation approach was used to appraise the certainty of evidence and to formulate and grade recommendations.<sup>7,8</sup>

## Results

Sixty-four studies were identified that met inclusion criteria and were included in the narrative synthesis supporting the recommendations previously summarized (e-Fig 1).

### Clinical History Taking

#### Population, Intervention, Comparator, Outcome

**Question 1: For patients with suspected HP, should a clinical history be taken to support (or rule out) the diagnosis of HP?:** Two prospective studies and a retrospective study<sup>3,9,10</sup> were identified to provide evidence of the diagnostic utility of the clinical history (see e-Table 1 from Fernández Pérez et al<sup>4</sup>). These

studies did not directly evaluate clinical history taking as a diagnostic criterion.

Despite the complexity of gathering, integrating, and interpreting a thorough environmental and occupational exposure history, we placed a high value on the benefits of establishing the pretest likelihood of the disease based on the environmental and occupational history and minimizing the risk of misdiagnosing HP as idiopathic interstitial pneumonia. To ensure consistency and optimize patient recall during the history-taking process, we suggest using a clinically relevant environmental and occupational questionnaire to guide the interview and improve the sensitivity of detecting the IAs (Table 1).<sup>11-13</sup>

**TABLE 1 ]** Suggested Environmental Assessment Steps During the Evaluation of a Subject With or Suspected to Have Hypersensitivity Pneumonitis<sup>a</sup>

Steps	Characteristics	Comments
IA exposure assessment	<ul style="list-style-type: none"> <li>• Epidemiologic context: disease frequency, geographic area, climate, season</li> <li>• Structured questionnaire: with regional and cultural components</li> <li>• Comprehensive clinical history: assess for features of association and lack of refutability</li> </ul>	<ul style="list-style-type: none"> <li>• As part of the exposure assessment, the history and the structured questionnaire ideally include open-ended questions adapted to the epidemiologic context: regional and local geography, customs, climate, or season, all of which are associated with variations in the type of IA and HP prevalence.<sup>11</sup></li> <li>• When possible, the physician should consider including family members or caregivers in the exposure history-taking process. Visual reconstruction such as web-based geographic maps, pictures, and drawings of possible antigen sources can help to reduce recall bias. Dedicating a separate clinic visit to delve further into the environmental and work history may be beneficial.</li> <li>• Consider an exposure questionnaire that includes at least three components: exposure survey, work history, and environmental history. A questionnaire listing of specific types of antigens according to occupational and/or environmental setting may uncover exposures that are routine to the patient, despite their unfamiliarity to the physician.</li> </ul>
Characterization of IA type and sources	<ul style="list-style-type: none"> <li>• Workplace(s): understand current/prior jobs and type and extent of exposure(s)</li> <li>• Home(s): detailed indoor and surrounding space survey</li> <li>• Vocational activities, travel/migration, all animal contact</li> </ul>	<ul style="list-style-type: none"> <li>• For work-related cases, ask patient to bring lists of material/chemicals or materials safety data sheet for documentation and review.</li> </ul>
Determine the IA likelihood	<ul style="list-style-type: none"> <li>• Identifiable: causal relationship and absence of refutability or evidence against the suspected IA cause. Urge prevention and remediation.</li> <li>• Indeterminate: evidence is suggestive of an association. Consider trial away from the likely IA containing-environment and serologic testing.</li> <li>• Unidentified: consider serial exposure assessments. A high index of suspicion is needed, particularly for mycobacteria-related HP. A positive mycobacteria sputum culture may be the first clue to a previously thought indeterminate or unidentified IA exposure (eg, contaminated domestic well water).</li> </ul>	<ul style="list-style-type: none"> <li>• Search for inorganic or organic antigen type, sources, and geographic locations on web-based engines such as <a href="http://www.nlm.nih.gov/toxnet/index.html">www.nlm.nih.gov/toxnet/index.html</a>, <a href="http://www.epa.gov/iris">www.epa.gov/iris</a>, and <a href="http://www.hplung.com">www.hplung.com</a>.</li> <li>• Physician and patient web resource when indoor mold suspected: <a href="http://www.cdc.gov/mold/default.htm">www.cdc.gov/mold/default.htm</a>.</li> </ul>
Team-based evaluation	<ul style="list-style-type: none"> <li>• Consider referral to specialized center</li> <li>• Occupational medicine consultation: work-place related, disease progression, and suspicion for ongoing indeterminate IA exposure or multiple IA sources</li> <li>• Determine if site environmental assessment is required</li> </ul>	<ul style="list-style-type: none"> <li>• The occupational medicine specialist may help identify a certified indoor environmental quality consultant working at or outside the referral medical facility or for the patient's employer as compliance or safety officers.<sup>b</sup></li> <li>• Websites providing a geographic search of certified professionals include <a href="http://www.ioha.net">www.ioha.net</a> and <a href="http://www.aiha.org">www.aiha.org</a>.</li> </ul>
Determine the need for site environmental assessment	<ul style="list-style-type: none"> <li>• Establish the goal and objectives of the exposure assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Walkthrough or visual assessment: building, mechanical systems, appliances, and maintenance.</li> </ul>

(Continued)

TABLE 1 ] (Continued)

Steps	Characteristics	Comments
	<ul style="list-style-type: none"> <li>Evaluate the results and limitations of the qualitative assessment: establish IA likelihood for indeterminate exposures</li> <li>Provide recommendations and specific actions</li> </ul>	<ul style="list-style-type: none"> <li>Home inspection commonly includes three domains: (1) home exterior (eg, damaged roof, walls, windows, foundation); (2) heating, ventilation, air-conditioning system, evaporative cooler, and humidifier assessment; and (3) indoor space survey (eg, standing water, water damage, condensation).<sup>12,13</sup></li> </ul>

HP = hypersensitivity pneumonitis; IA = inciting antigen.

<sup>a</sup>See recommendations 1, 2, 3, 7, and 9.

<sup>b</sup>The term environmental hygienist is broadly used throughout this guide. However, other terms such as environmental hygienist or occupational hygienist are also used depending on the consultant specialization, indoor setting, and world geography.

### Specialist Consultation

#### Population, Intervention, Comparator, Outcome

##### Question 2: For patients with suspected HP, should an occupational medicine specialist and/or environmental hygienist be consulted to support (or rule out) the diagnosis of HP?:

The systematic review identified one longitudinal study that evaluated the effectiveness of interventions to address an HP outbreak at a metalworking facility (see e-Table 2 from Fernández Pérez et al<sup>4</sup>).<sup>12,14-16</sup>

Based on this indirect evidence and consensus generation, we reasoned inclusion of an occupational medicine specialist and an environmental hygienist during the multidisciplinary diagnostic workup of suspected occupational HP cases is beneficial because specialists can help determine the likelihood of occupational exposure as the cause of HP, assist in the removal of workers from further exposure, and suggest changes to improve work conditions and remove contaminants. In patients with nonoccupational HP, consultation with a certified environmental hygienist for visual inspection of an indoor environment may help identify an antigenic source.<sup>12</sup> We placed a high value on determining the likelihood of exposure and a relatively lower value on the environmental assessment cost, lack of validated quantitative environmental sampling methods, and limitations of interpreting environmental sampling. However, the panel recognizes the limitations of the feasibility of this recommendation because access to specialist consultation is limited in many health care settings.

### Identification of IAs

#### Population, Intervention, Comparator, Outcome

##### Question 3: In patients with suspected HP, does identification of the IA improve clinical outcomes?:

Five observational studies that compared prognostic outcomes (eg, survival, disease progression) between

subjects with HP with and without an identifiable IA were identified (see e-Table 3 from Fernández Pérez et al<sup>4</sup>).<sup>15-19</sup>

We weighed the benefits (ie, eliminating the IA at a relatively early stage may reduce the risk of HP disease progression) of establishing an IA exposure likelihood (ie, identified, indeterminate, or unidentified IA) (Fig 1, Table 1) against the undesirable consequences of not characterizing the IA, determining that the balance favors classifying patients based on IA exposure likelihood.

### Classification of HP

#### Population, Intervention, Comparator, Outcome

##### Question 4: In patients diagnosed with HP, should the disease be classified according to the presence or absence of fibrosis and IA characterization?:

The systematic review did not identify any studies that directly address the population, intervention, comparator, outcome (PICO) question focused on the combined effect of lung fibrosis and IA exposure status on HP-related mortality, adverse events, and disease progression. However, six observational studies that estimated survival over time or mortality rate between subjects with HP with or without lung fibrosis on CT scan of the chest and with or without an identified IA were identified and provided indirect evidence (see e-Table 4 from Fernández Pérez et al<sup>4</sup>).<sup>15,16,20-23</sup>

After assessing the image quality and the presence, distribution, and extent of CT features (Table 2),<sup>24-26</sup> we suggest classification of chest imaging patterns into nonfibrotic or fibrotic (Table 3). As a whole, this evidence suggests that the extent of high-resolution CT (HRCT) fibrotic change in HP has prognostic value. We placed a high value on the prognostic benefits of classifying HP cases on the presence or

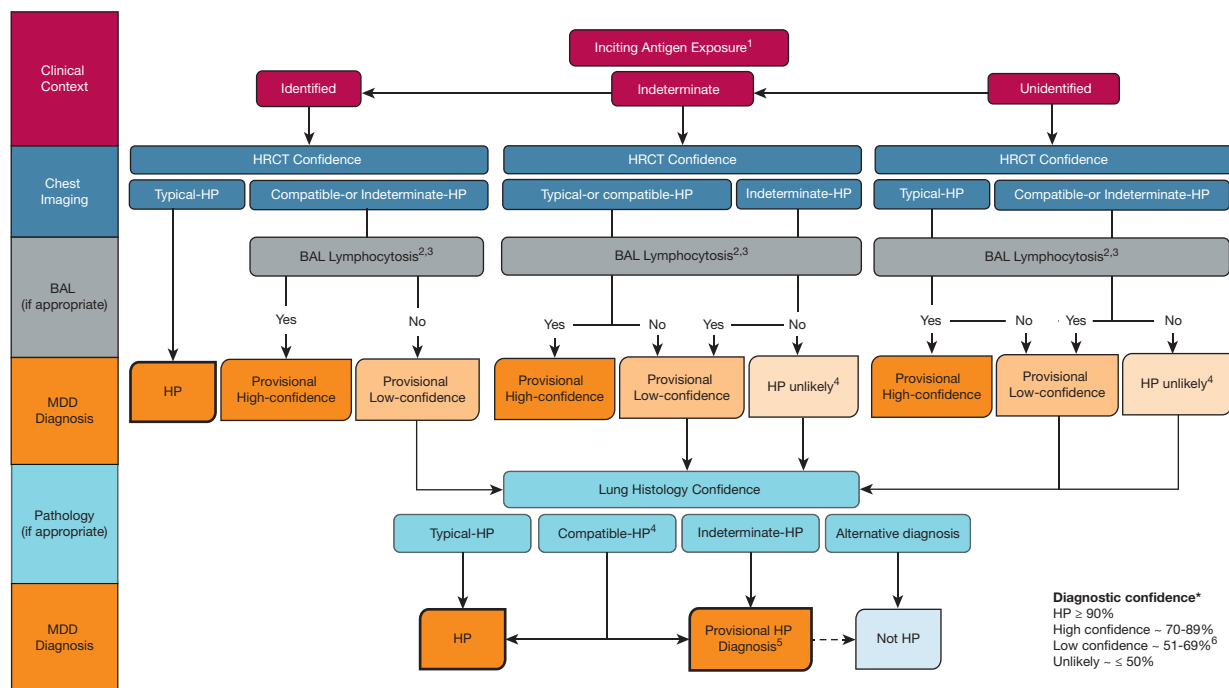


Figure 1 – Algorithm for the diagnosis of fibrotic and nonfibrotic HP. See full online version for more details.<sup>4</sup>

\*This diagnostic approach is analogous to that suggested by the ontological framework for the classification of fibrotic interstitial lung disease (ILD).<sup>27</sup> This approach classifies both fibrotic and nonfibrotic HP diagnoses as either a confident ( $\geq 90\%$  overall probability of a diagnosis), provisional high confidence (70%-89%), or low confidence (51%-69%) diagnosis for HP. This framework provides a practical and straightforward empirical approach to estimating diagnostic likelihood for a complex disease. The term HP unlikely is used when there is  $\leq 50\%$  confidence in HP as a leading diagnosis. The diagnostic confidences are not intended to represent arbitrary estimates of the probability of HP diagnosis before and after testing but rather to provide a conceptual model for assessing discordant information and help optimize diagnostic clinical reasoning when evaluating patients with suspected HP. HP = hypersensitivity pneumonitis; HRCT = high resolution CT; MDD = multidisciplinary discussion.

<sup>1</sup>See Table 1, and the exposure assessment section on the full online version. The certainty of the IA cause and source may change over time after reevaluating additional exposure and clinical data.

<sup>2</sup>The BAL in this algorithm does not imply that every suspected HP case has to have this test. Instead, the objective is to show the estimated level of diagnostic confidence when the BAL fluid analysis results are combined with the clinical context and chest imaging confidence level (see recommendation 12). BAL lymphocytosis (eg,  $\geq 20\%$ ) alone would not rule in HP and should be interpreted in the context of the entire cellular count differential, sampling site, and protocol and the clinical context including age, smoking history, and treatment. A marked increase in BAL lymphocyte percentage is of additional value in distinguishing HP from some other forms of ILDs. Although in fibrotic HP the absence of BAL fluid lymphocytosis does not rule out the disease and the level of uncertainty generally remains unchanged, in nonfibrotic HP, the level of confidence is substantially reduced, especially when the inciting antigen exposure is indeterminate or unidentified. Cutoffs that define abnormal increases in BAL lymphocyte counts to accurately distinguish HP from other ILDs remain to be determined (see recommendation 14).

<sup>3</sup>Until further evidence becomes available, transbronchial biopsies may be considered (see recommendation 12).

<sup>4</sup>According to the clinical context, MDD diagnostic confidence and during serial evaluations the diagnosis can be provisional or ultimately HP. For example, when the biopsy is compatible with fibrotic HP, the overall probability of HP is lower if the exposure is unidentified and the chest CT is indeterminate for HP. The MDD consensus HP diagnosis may lead to a provisional diagnosis. In contrast, when the biopsy is compatible with fibrotic HP in a subject with an identifiable exposure and CT chest compatible with HP, the confidence may increase to an MDD consensus HP diagnosis. If the pre-VATS or TBC diagnosis confidence is unlikely for HP, a biopsy showing typical histopathology for HP may lead to an MDD provisional diagnosis. In this case, a confident diagnosis is sometimes made, especially when MDD prompts review and revision of the initial clinical context.

<sup>5</sup>This scenario is more likely in cases of fibrotic HP than in cases of nonfibrotic HP. During serial MDD evaluations, the diagnosis may change to not HP (dashed arrow), as more information becomes available.

When the inciting antigen exposure is indeterminate or unidentified, alternative nonfibrotic causes commonly not captured by history include primary bronchiolar disorders. A detailed history may help identify infections, recurrent aspiration, pneumoconiosis, other granulomatous lung diseases, smoking- or immunodeficiencies-related ILD, drug/dust inhalation, and connective tissue disorders.

absence of fibrosis considering HRCT scan of the chest is noninvasive. The present analysis indicates that the classification of HP cases should also include a designation of IA likelihood (Fig 1) because the evidence suggests that IA status has implications for management and prognosis.

### Clinical Improvement With Antigen Avoidance

**PICO Question 5: In patients with suspected HP, does clinical improvement with antigen avoidance support (or rule out) the diagnosis of HP?:** No studies that evaluated the diagnostic yield of a patient's response to antigen avoidance to facilitate a working HP diagnosis were identified. Alternatively, seven retrospective studies



**TABLE 2 ] CT Terms Used in the Diagnosis of HP**

Term	Definition	Comment
Centrilobular nodules	The characteristic centrilobular nodules of HP are profuse, poorly defined, measure < 3 mm, and are of ground-glass attenuation, reflecting a peribronchiolar predominance of inflammatory abnormality within the secondary pulmonary lobule.	Fig 2
GGO	GGO is increased lung attenuation through which normal pulmonary structures can still be identified. In HP, GGOs have a patchy or diffuse distribution in the axial plane and are often associated with mosaic attenuation and/or evidence of lung fibrosis.	Fig 3
Mosaic attenuation	Mosaic attenuation is defined as a sharply defined geographic patchwork of regions of differing attenuation on full inspiratory images. The term mosaic attenuation is reserved for findings on inspiratory CT scan. <sup>24</sup>	Figs 3-6
Three-density sign	The category of mosaic attenuation that is most specific for HP is the three-density sign (previously referred to as the headcheese sign). <sup>25,26</sup> This sign is characterized by a combination of lung lobules with preserved density, surrounded by patchy or lobular ground-glass attenuation, and interspersed with lobules of decreased density and decreased vessel size because of air-trapping, occurring within the same lobe. The lobules of decreased attenuation are accentuated on expiration.	Figs 3-5
Other forms of mosaic attenuation	A second category of mosaic attenuation that is common in HP is lobular decreased attenuation interspersed with normal lung and associated with lobular air-trapping on expiratory images. This pattern is probably less specific for HP than the three-density sign.	Fig 6
Lobular air-trapping	Lobular air-trapping is identified by sharply demarcated areas that fail to increase in density with expiration. This term is reserved for expiratory CT scan.	Fig 4, 5
Fibrosis	Fibrosis is identified by the presence of any or all of the following: reticular pattern or GGO with traction bronchiectasis or bronchiectasis, lobar volume loss, and honeycombing. The diagnosis of fibrosis should not be made when reticular abnormality is present without other confirmatory signs.	Figs 3E-F

GGO = ground-glass opacification; HP = hypersensitivity pneumonitis.

that assessed clinical response to antigen avoidance in subjects already diagnosed with HP were identified and provided indirect evidence of the diagnostic utility of antigen avoidance (see e-Table 5 from Fernández Pérez et al<sup>4</sup>).<sup>16,19,28-32</sup>

Although prospective studies are needed to directly ascertain the diagnostic utility of antigen avoidance, we concluded that the threshold for using a patient's response to immediate antigen avoidance as a diagnostic test is low because complete resolution of early detected nonfibrotic HP may be observed with the timely elimination of the IA exposure. However, the absence of clinical improvement with antigen avoidance does not exclude the diagnosis of HP because many patients with fibrotic HP fail to improve with antigen avoidance.

#### *Clinical Improvement with Medical Therapy*

**PICO Question 6: In patients with suspected HP, does clinical improvement with medical therapy support the diagnosis of HP?:** The systematic review identified one randomized trial<sup>33</sup> and nine observational studies<sup>16,31,34-40</sup> that evaluated the responses of patients with HP to medical therapy but not directly the

diagnostic utility of clinical improvement with medical therapy (see e-Tables 6a and 6b from Fernández Pérez et al<sup>4</sup>).

Our confidence in using a patient's response to treatment as an informative step when investigating potential HP was diminished for several reasons. First, none of the studies enrolled patients with true diagnostic uncertainty. Second, the clinical course of disease and response to treatment vary greatly from one patient to another. Third, an improvement could be observed even if treatment was ineffective (eg, regression to the mean—treatment response because of chance or patient selection bias). Finally, treatment initiation may coincide with the patient's clinical improvement but may not be causative. For these reasons, we suggest not making a clinical diagnosis of HP based on clinical improvement with medical therapy alone.

#### *Antigen-Specific Antibody Testing*

**PICO Question 7: In patients with suspected HP, should antigen-specific IgA and/or IgG testing be performed?:** Three observational studies evaluating the diagnostic value of antigen-specific antibody testing in

**TABLE 3 ] Diagnostic CT Categories of Nonfibrotic and Fibrotic HP Based on CT Patterns**

HRCT Scan	Features
Typical nonfibrotic HP	Any of the following: <ul style="list-style-type: none"> <li>• Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones</li> <li>• Inspiratory mosaic attenuation with three-density sign</li> <li>• Inspiratory mosaic attenuation and air-trapping associated with centrilobular nodules and Lack of features suggesting an alternative diagnosis</li> </ul>
Compatible with nonfibrotic HP	Any of the following: <ul style="list-style-type: none"> <li>• Centrilobular nodules of ground-glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air-trapping</li> <li>• Patchy or diffuse ground-glass opacity</li> <li>• Mosaic attenuation and lobular air-trapping without centrilobular nodules or ground-glass abnormality</li> </ul> and Lack of features suggesting an alternative diagnosis
Typical fibrotic HP	CT signs of fibrosis with either of the following: <ul style="list-style-type: none"> <li>• Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones</li> <li>• Inspiratory mosaic attenuation with three-density sign</li> </ul> and Lack of features suggesting an alternative diagnosis
Compatible with fibrotic HP	CT signs of fibrosis with any of the following: <ul style="list-style-type: none"> <li>• Patchy or diffuse ground-glass opacity</li> <li>• Patchy, nonprofuse centrilobular nodules of ground-glass attenuation</li> <li>• Mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP and Lack of features suggesting an alternative diagnosis</li> </ul>
Indeterminate for fibrotic HP	CT signs of fibrosis without other features suggestive of HP

In a nonsmoker, the presence of diffuse, profuse, poorly defined ground-glass centrilobular nodules is highly suggestive of the diagnosis of HP; similar findings may occasionally occur for example in infections, pulmonary hemorrhage, metastatic pulmonary calcification, or severe group 1 pulmonary hypertension, but the clinical context will usually identify these rare causes. The distribution alone is not pathognomonic of HP. CT signs of fibrosis include any of the following: reticular or ground-glass abnormality with traction bronchiectasis, lobar volume loss, and honeycombing. The distribution of fibrotic HP is quite variable and often not diagnostically helpful. However, a midlung predominant distribution of fibrosis is suggestive of fibrotic HP, and an upper lobe predominance is much more common in fibrotic HP than in idiopathic pulmonary fibrosis. HP = hypersensitivity pneumonitis.

HP and nine observational studies providing data on the diagnostic yield of serum antigen-specific IgG/IgA testing were identified (see e-Table 7 from Fernández Pérez et al<sup>4</sup>).<sup>3,41-51</sup>

We identified limitations of the diagnostic yield data from these studies including small samples, limited clinical context (eg, unclear exposure status, disease severity), inappropriate reference standards, test incorporation bias, and minimal reporting of testing information, and noted limitations to the use of serum antigen-specific tests including cross-reactivity among ubiquitous fungal species and avian antigens (increasing the risk of false-positive results), and poorly standardized techniques and antigen preparations (increasing the risk of false-negative results).<sup>49,52-57</sup>

We concluded there is insufficient evidence to support the use of serum antigen-specific antibody testing results to reliably confirm or rule out the diagnosis of HP in the

absence of an identifiable IA or consistently identify the particular type of antigen (eg, mold) involved in the disease process.

#### *Antigen-Specific Inhalation Challenge Testing*

**PICO Question 8: In patients with suspected HP, should antigen-specific inhalation challenge (SIC) testing be performed?:** Six observational studies evaluating the diagnostic yield of antigen-SIC met inclusion criteria (see e-Table 8 from Fernández Pérez et al<sup>4</sup>).<sup>48,49,58-61</sup> Based on this evidence, documented limitations of the diagnostic utility of SIC for HP, and potential patient-important adverse effects, we suggest not making a clinical diagnosis of HP based on SIC findings exclusively. This suggestion is reflective of the lack of evidence reliably demonstrating that SIC findings can confirm a diagnosis of HP. It is also unclear what additive discriminative value SIC provides beyond a positive exposure history. Evidence is also lacking regarding the utility of SIC findings to

establish a working diagnosis of HP when histopathologic data are unavailable or nondiagnostic on multidisciplinary evaluation, particularly when the IA is unidentified.

### Specific Lymphocyte Proliferation Testing

**PICO Question 9: In patients with suspected HP, should antigen-specific lymphocyte proliferation testing be performed?:** Four observational studies assessing the utility of antigen-specific lymphocyte proliferation test (LPT) in subjects with HP were identified (see e-Table 9 from Fernández Pérez et al<sup>4</sup>).<sup>44,49,58,62</sup>

Evidence of the diagnostic yield of LPT provided by the observational studies included in this analysis is of very low quality. Moreover, we were concerned that the performance characteristics of LPT are misleadingly high in the identified evidence because they were derived from a select sample and limited

only to responses to avian antigens. In addition to the diagnostic limitations of LPT outlined in the recommendation remark, our confidence was further lowered because the utility of the LPT as a potential HP diagnostic tool depends on the accuracy of the exposure history and knowledge of the suspected IA.

### HRCT Pattern

**PICO Question 10: Should patients be clinically diagnosed with HP based on HRCT findings alone if they have ground-glass opacities, and/or mosaic attenuation, and/or expiratory air-trapping, and/or centrilobular nodules, and/or peribronchovascular disease distribution, and/or upper lobe predominance?:** Nine studies evaluating the performance characteristics of HRCT scan of the chest for establishing the diagnosis of HP in patients with

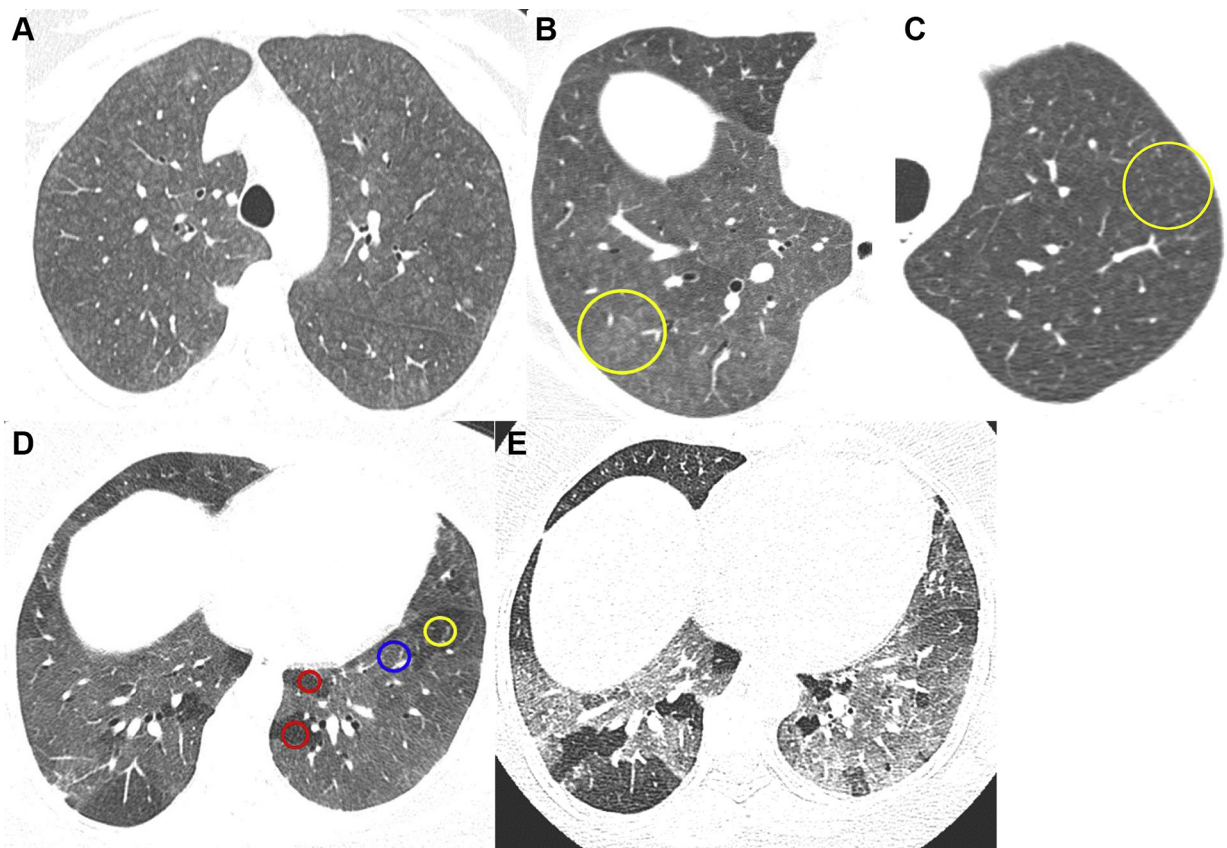


Figure 2 – A-C, Poorly defined centrilobular nodules of ground-glass attenuation in three different patients with nonfibrotic hypersensitivity pneumonitis (HP), selected to show the range of CT appearances for this finding. A, **Typical nonfibrotic HP** with profuse centrilobular nodules in the upper lobes. The centrilobular location is recognized by the fact that the nodules are separated by a clear zone from each other and from the pleural margin. B, **Typical nonfibrotic HP** with more subtle ground-glass nodules in the right lower lobe, (circle). C, Sparse nodules in the left upper lobe (circle), compatible with HP. D-E, **Typical nonfibrotic HP** with three-density sign. D, Inspiratory CT scan shows diffuse ground-glass attenuation (blue circle). An adjacent lobule is of preserved (normal) attenuation (yellow circle), and there are multiple lobules with decreased attenuation (red circle). No signs of fibrosis are present. E, Expiratory CT scan accentuates numerous lobules of decreased attenuation representing air-trapping.



interstitial lung disease (ILD) were identified (see e-Table 10 from Fernández Pérez et al<sup>4</sup>).<sup>10,63-70</sup>

Although a high-probability scan is virtually diagnostic for HP in subjects with compelling exposure history, in patients with an indeterminate or unidentified

environmental exposure, differentiating fibrotic HP from idiopathic pulmonary fibrosis (IPF) can be challenging. In this context, our confidence in the estimated performance characteristic of CT evidence was low for three reasons. First, several studies enrolled neither subjects with true diagnostic uncertainty nor

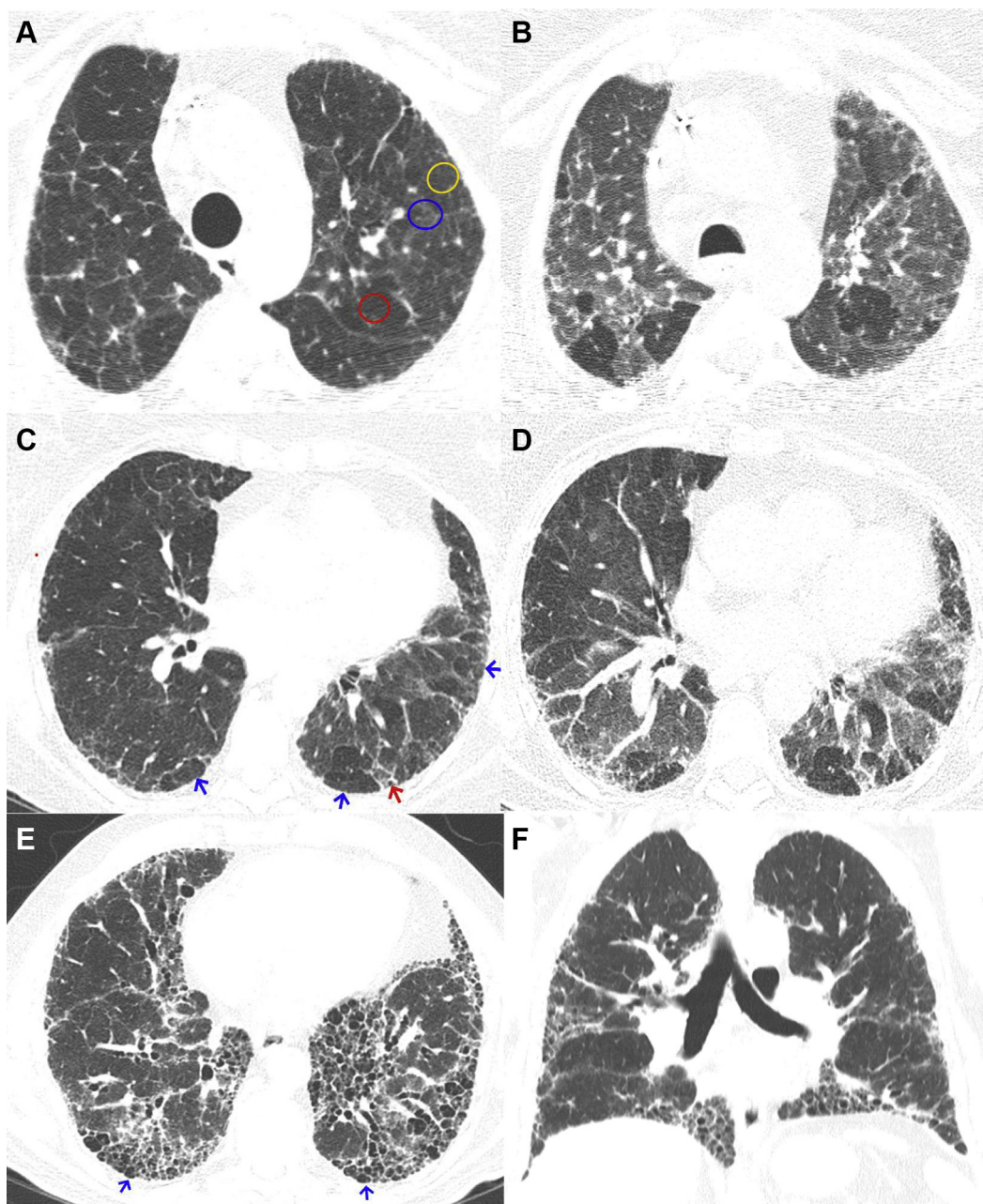


Figure 3 – A-B, **Typical fibrotic hypersensitivity pneumonitis (HP)** with three-density sign. A, CT scan shows patchy ground-glass attenuation (blue circle). Other lobules are of normal attenuation (yellow circle), and there are several lobules of decreased attenuation (red circle). Mild subpleural reticulation is present. B, Expiratory CT scan accentuates numerous lobules of decreased attenuation representing air-trapping. C-D, Mosaic attenuation and air-trapping compatible with fibrotic HP. C, CT scan shows reticular abnormality with architectural distortion and mild traction bronchiolectasis (red arrow) indicating fibrosis. Multifocal lobular mosaic attenuation is present (blue arrows). D, Expiratory CT scan confirms multifocal air-trapping. E-F, Usual interstitial pneumonia pattern, **indeterminate for fibrotic HP**. Axial and coronal CT images show lower lung predominant, subpleural predominant reticular abnormality with traction bronchiectasis and subpleural honeycombing (arrows). There are no imaging features to suggest HP; the diagnosis was based on exposure and surgical biopsy.

used consistent CT techniques negatively impacting the subjectivity of visual determinations for both the pattern and distribution of disease. Second, the results may not be generalizable to facilities that do not have access to an expert thoracic radiologist to interpret HRCT findings. Third, the mingling of subjects with fibrotic and nonfibrotic HP in several cohorts likely inflated the precision of CT features in distinguishing fibrotic HP from IPF. Moreover, despite the high specificity of HRCT features such as the three-density sign in endorsing a provisional diagnosis, we suggest a clinical diagnosis of fibrotic HP not be made based on HRCT findings alone, and consulting with an expert ILD center may help increase confidence in the diagnosis of fibrotic HP.

We suggest classifying nonfibrotic abnormalities as typical for HP (Figs 2A-E) or compatible with HP (Fig 2C), and fibrotic abnormality as typical for HP (Figs 3A, 3B), compatible with HP (Figs 3C, 3D), or indeterminate (Figs 3E, 3F). The indeterminate category is used when pulmonary fibrosis of any pattern is present without specific features of HP. The radiologic confidence level

may then be integrated with the patient's exposure likelihood and clinical information, with subsequent review by multidisciplinary discussion (MDD). We suggest such a review occur prior to determining if invasive testing will significantly alter the posttest probability of HP and optimize decision-making (Fig 1).

### MDD

**PICO Question 11: For patients with suspected HP, should MDD compared with clinical judgment alone be used for diagnostic decision-making?:** The

systematic review identified six observational studies that described the use of MDD for the diagnosis of HP (see e-Table 11 from Fernández Pérez et al<sup>4</sup>).<sup>71-76</sup> The evidence suggests that MDD provided a new or altered the preexisting pre-MDD HP diagnosis in a significant proportion of patients and that it may be associated with improved accuracy over individual physician diagnoses. However, improved accuracy may be attributed to reevaluation at regular intervals in the context of the MDD. Also, the included study designs did not provide conclusive supportive evidence of the HP MDD

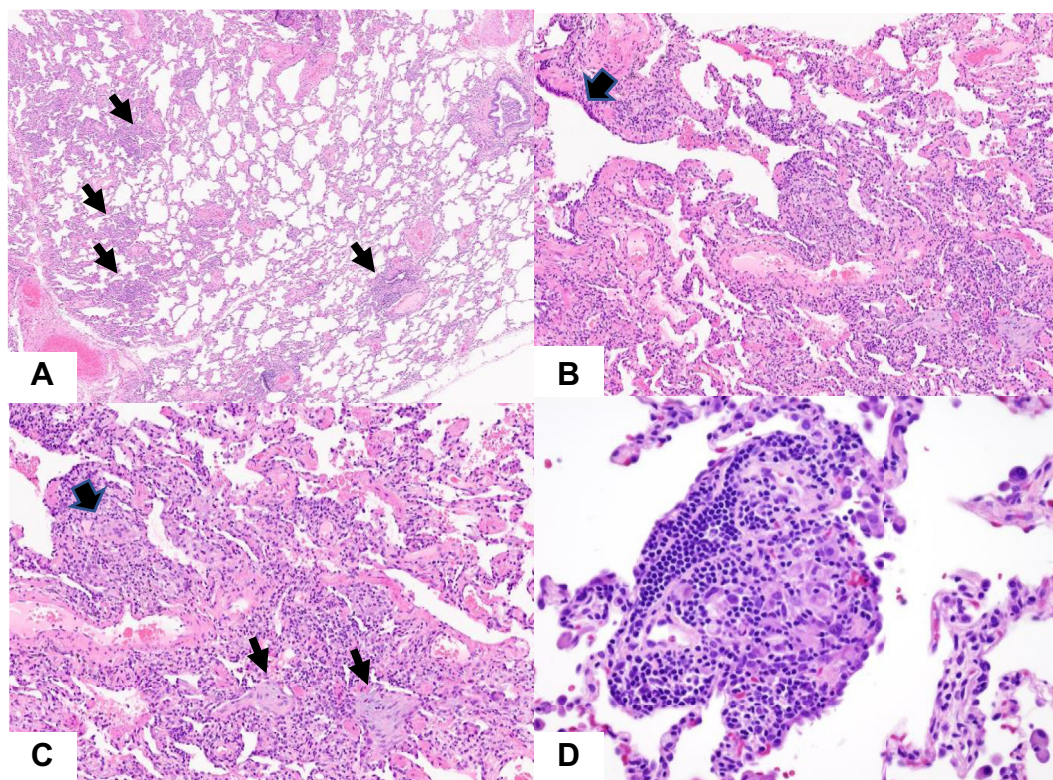


Figure 4 – **Typical nonfibrotic HP pathologic pattern.** A, Low power shows a bronchiocentric distribution. Low power shows patchy nodules of chronic inflammation centered on bronchioles (arrows). This bronchiole (arrowhead) is infiltrated by chronic inflammation which extends into the surrounding peribronchiolar interstitium. B, Higher power of the image in Figure B shows a poorly formed granuloma (arrowhead) and small foci of organizing pneumonia (arrows) are present. C, This poorly formed granuloma consists of a loose cluster of epithelioid histiocytes surrounded by lymphocytes. **Compatible with nonfibrotic HP.** D, Low power shows a bronchiocentric distribution (arrows).



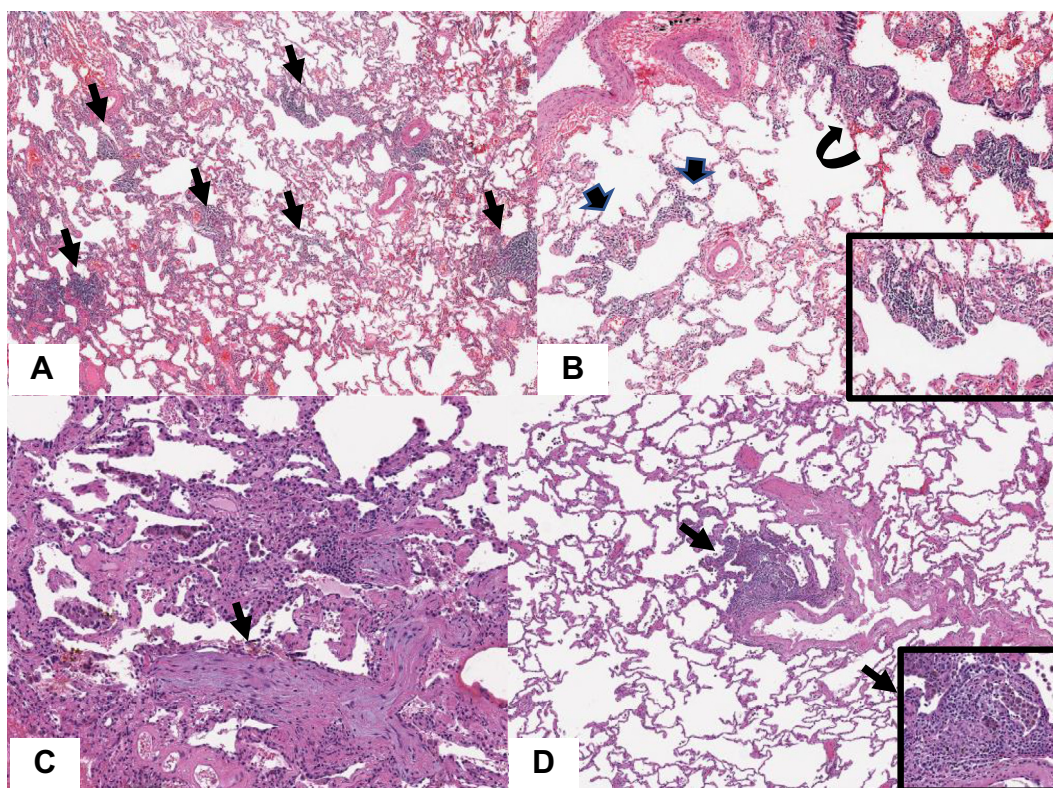


Figure 5 – A, This bronchiole (curved arrow) and alveolar duct (arrowheads and insert) are infiltrated by chronic inflammation which extends into the surrounding peribronchiolar interstitium. No granulomas were seen. Indeterminate for nonfibrotic HP. B, This biopsy showed minimal histologic changes and was initially regarded as nonspecific with very focal, patchy foci of interstitial chronic inflammation and organizing pneumonia (arrow). C, After review of the CT which showed features of typical nonfibrotic HP, the biopsy was re-reviewed and vague collections of epithelioid histiocytes were reinterpreted as a poorly formed granuloma (arrows and insert) and could be reclassified as compatible with nonfibrotic HP.

diagnosis accuracy (eg, prognostic outcome measures among concordant and discordant MDD and pre-MDD HP cases according to the clinical context).

Based on this evidence and given the few proven strategies to address HP misdiagnosis, particularly among those with an unidentified IA, we suggest that MDD be used for diagnostic decision-making in HP. This recommendation places a low value on the potential challenges of running an MDD panel and a high value on preventing misdiagnosis and the potential impact of MDD on appropriate management change for a concordant or discordant pre-MDD HP diagnosis.

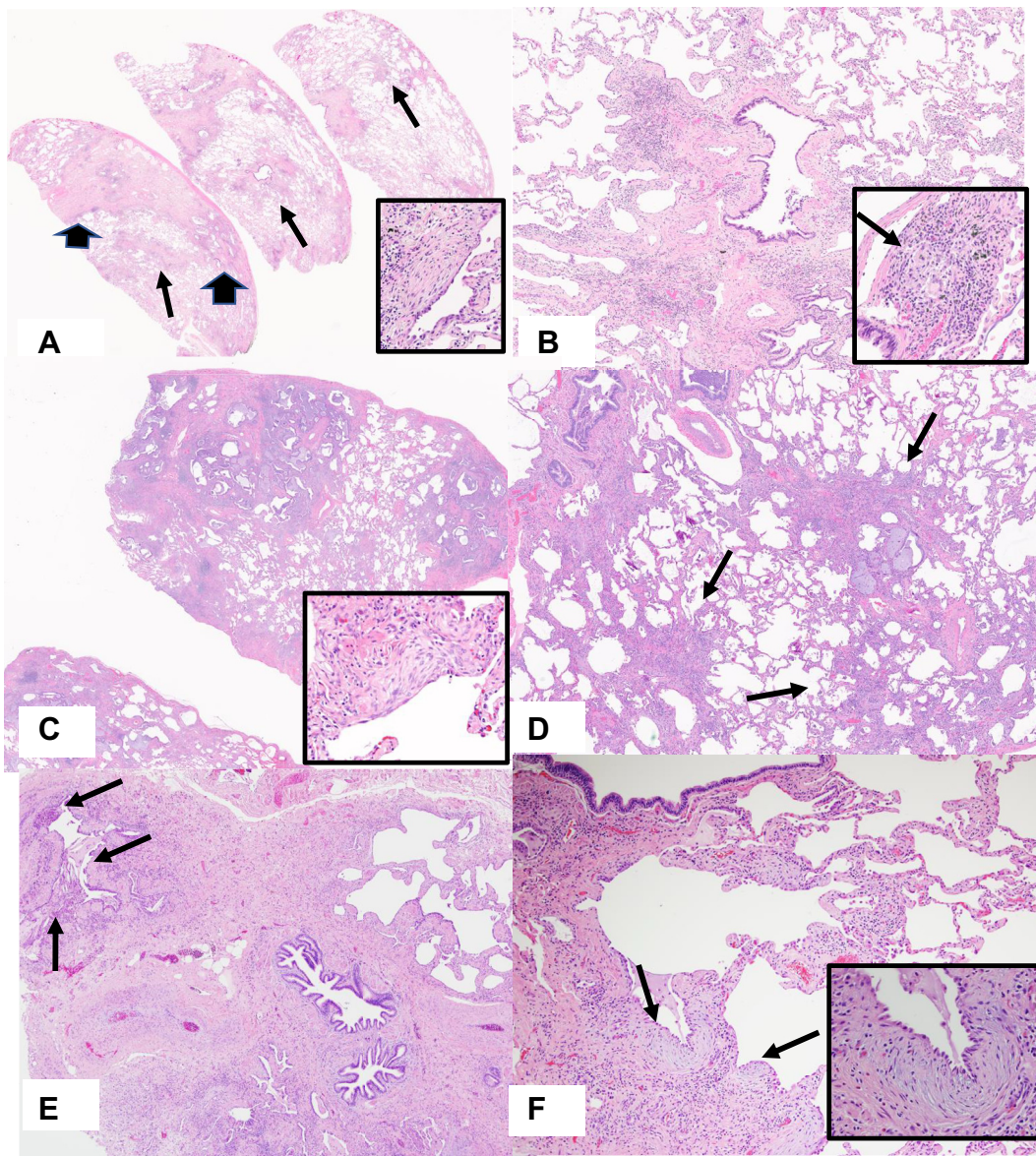
### BAL Cellular Analysis

**PICO Question 12: In patients with suspected HP, should BAL cellular analysis be performed?:** Three single-centered retrospective studies and one meta-analysis describing the diagnostic yield of BAL cellular analysis in HP were identified by the systematic review (see e-Table 12 from Fernández Pérez et al<sup>4, 77-80</sup>). Because of the high risk of bias and absence of

appropriate diagnostic accuracy measures in the literature on BAL, analysis of subgroups or meta-analysis of the discriminative ability of BAL fluid cellular analysis to distinguish fibrotic HP from other fibrotic ILDs was not possible. The literature suggests that the diagnostic accuracy of BAL fluid analysis in HP lies in the positive predictive value of lymphocytosis in supporting the diagnosis of nonfibrotic HP and in separating IPF from fibrotic HP. In the latter, the BAL fluid analysis may be appropriate in subjects with an MDD consensus working diagnosis of fibrotic HP as seen in cases of indeterminate exposure history and typical HP CT pattern (Fig 1).

Although no study exists in which BAL findings are combined with the pretest MDD probability of disease, based on the panel's clinical experience, the presence of a high BAL lymphocyte count provides an important addition to clinical practice by potentially adjusting the MDD consensus estimate of the probability of the presence of HP enough to alter management or the decision to proceed with video-assisted thoracoscopic surgery or transbronchial cryobiopsy.





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Figure 6 – A-B, **Typical fibrotic hypersensitivity pneumonitis (HP)**. A, This fibrotic HP case shows a bronchiolocentric pattern of fibrosis (long arrows) in addition to extensive areas of subpleural fibrosis (wide arrows) reminiscent of usual interstitial pneumonia (UIP) pattern. B, This bronchiole is surrounded by fibrosis and mild chronic inflammation. Scattered poorly formed granulomas were also identified (inset and arrow). The low power bronchiolocentricity and subtle granulomas are key features in suspecting fibrotic HP. C-D, **Compatible with fibrotic HP**. C, This biopsy showed a UIP pattern in one area of the biopsy with patchy subpleural fibrosis with remodeling of the lung architecture with foci of honeycombing. Fibroblastic foci were seen at the edges of the fibrotic scars (inset). D, This separate lobe of the same biopsy showed a bronchiolocentric pattern (arrows) of fibrosis, but no granulomas were seen. The CT scan showed features of typical HP. These features exclude the diagnosis of idiopathic pulmonary fibrosis. E-F, **Indeterminate for fibrotic HP by surgical lung biopsy**. E, This biopsy showed a pure fibrotic pattern that showed a UIP pattern with extensive fibrosis causing remodeling of the lung parenchyma, and areas of honeycombing (arrows). No bronchiolocentricity or granulomas were seen. F, Adjacent to areas of preserved lung parenchyma, the fibrosis shows fibroblastic foci with loose myxoid connective tissue in contrast to the dense eosinophilic collagen (arrows and inset). The CT scan showed the typical HP pattern.

Despite having very low confidence in the reported estimated diagnostic yield of BAL fluid analysis in the HP literature to date, recommendation 12 places a high value on the importance of establishing the HP diagnosis in a stepwise approach according to the overall probability of disease using first the test that is less risky, less invasive, easier to perform, and less

expensive in contrast to video-assisted thoracoscopic surgery or transbronchial cryobiopsy. The acceptability of the test and the potential of BAL fluid to affect clinical decisions in subjects with intermediate pretest probability when the lymphocyte count is high are also of high importance when evaluating testing approaches.

**TABLE 4 ]** Histologic Diagnostic Criteria for Nonfibrotic HP Pattern

Typical Nonfibrotic HP (Figs 4A-D)	Compatible With Nonfibrotic HP (Figs 5A, 5B)	Indeterminate for Nonfibrotic HP (Figs 5C, 5D)	Alternative Diagnosis
<p><b>Major Features</b> Presence of all four major features in at least one of the sampled lobes of lung:</p> <ol style="list-style-type: none"> <li>1) Small airway distribution (bronchioles and/or alveolar ducts)</li> <li>2) Uniform cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis); may include regions with a cellular NSIP pattern</li> <li>3) Inflammation consisting of mostly lymphocytes</li> <li>4) Interstitial scattered, usually single, poorly formed nonnecrotizing granulomas and/or multinucleated giant cells</li> </ol> <p><b>Minor Features</b></p> <ol style="list-style-type: none"> <li>1) Organizing pneumonia, small foci</li> <li>2) Foamy macrophages</li> <li>3) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals (e-Fig 1)</li> </ol> <p><b>And</b></p> <p><b>Lack of</b> Features suggesting an alternative diagnosis (see column 4)</p>	<p><b>Major Features</b> Presence of these three major features:</p> <ol style="list-style-type: none"> <li>1) Small airway distribution</li> <li>2) Cellular interstitial inflammation causing cellular bronchiolitis and/or interstitial pneumonia (including a cellular NSIP pattern)</li> <li>3) Inflammation consisting mostly of lymphocytes</li> </ol> <p><b>Minor Features</b></p> <ol style="list-style-type: none"> <li>1) Organizing pneumonia, small foci</li> <li>2) Foamy macrophages</li> <li>3) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals (e-Fig 1)</li> </ol> <p><b>And</b></p> <p><b>Lack of</b></p> <ol style="list-style-type: none"> <li>1) Poorly formed nonnecrotizing granulomas</li> <li>2) Features of an alternative diagnosis (see column 4)</li> </ol>	<p>Biopsies that show an interstitial lung disease pattern that does not meet criteria for nonfibrotic HP, compatible with nonfibrotic HP, or an alternative diagnosis</p> <p><b>Comment:</b> There is uncertainty about the histologic features in these cases that raise the consideration of nonfibrotic HP and other differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not</p> <p>Note: Cellular NSIP pattern is in this category</p>	<p>A biopsy favoring other processes such as the following: Primary small airway disease (ie, bronchiolitis from a variety of causes) is usually distinguishable because the findings are restricted to the small airways and there is a lack of appreciable involvement of the surrounding alveoli</p> <p><b>Other Interstitial Lung Diseases</b></p> <ul style="list-style-type: none"> <li>• Sarcoidosis (well-formed granulomas that may coalesce in a lymphatic distribution, e-Figs 2A, 2B)</li> <li>• Aspiration (bronchiolocentric inflammation frequently with foreign material and giant cell or histiocytic reaction). Tends not to be as uniform and diffuse as HP (e-Figs 2C, 2D).</li> <li>• Connective tissue disease (e-Fig 3), drug induced lung disease, immunodeficiency (e-Figs 4A, 4B) (increased plasma cells, prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, pleuritis, granulomas)</li> <li>• Respiratory bronchiolitis or other smoking-related lesions (bronchiolocentric pigmented alveolar macrophages)</li> <li>• Granulomatous infection (e-Figs 4C, 4D) (robust, frequent necrotizing granulomas, especially mycobacterial, and fungal infections)</li> <li>• Pneumoconiosis/occupational exposures (flock workers—lymphocytic bronchiolitis and lymphoid hyperplasia; berylliosis—well-formed granulomas, BADE)</li> <li>• Langerhans cell histiocytosis (peribronchiolar cellular infiltrates of Langerhans cells with or without cavitation and/or fibrosis)</li> </ul>

BADE = lymphocytic bronchiolitis, alveolar ductitis, and emphysema in industrial machine manufacturing workers; HP = hypersensitivity pneumonitis; NSIP = nonspecific interstitial pneumonia.

**TABLE 5 ] Histologic Diagnostic Criteria for Fibrotic HP Pattern**

Typical Fibrotic HP (Figs 6A, 6B; e-Figs 5A-D)	Compatible With Fibrotic HP (Figs 6C, 6D; e-Figs 5E, 5F)	Indeterminate for Fibrotic HP (Figs 6E, 6F; e-Fig 6)	Alternative Diagnosis
<p><b>Major Features</b> Presence of all three major features in at least one of the sampled lobe(s) of lung:</p> <ol style="list-style-type: none"> <li>Regions where small airway-centered fibrosis is clearly present with or without peribronchiolar metaplasia</li> <li>Fibrosing interstitial pneumonia affecting at least one sampled area/lobe of lung parenchyma with regions showing one or more of the following patterns:               <ol style="list-style-type: none"> <li>NSIP-fibrosing pattern</li> <li>UIP pattern</li> <li>Fibrosing pattern that is difficult to classify</li> <li>Fibrosis that is solely peribronchiolar</li> </ol> </li> <li>Poorly formed noncaseating granulomas</li> </ol> <p><b>Or</b> Fibrosing interstitial pneumonia meeting only major feature #2 in one lobe, as well as all criteria for <i>Typical Nonfibrotic HP</i> in a separate lobe(s)</p> <p><b>Minor Features</b></p> <ol style="list-style-type: none"> <li>Organizing pneumonia, small foci</li> <li>Focal peribronchiolar metaplasia</li> <li>Foamy macrophages</li> <li>Cholesterol clefts</li> </ol> <p><b>Lack of</b> Features of an alternative diagnosis (see column 4)</p>	<p><b>Major Features</b> Presence of these two major features in at least one of the sampled lobe(s) of lung:</p> <ol style="list-style-type: none"> <li>Regions where small airway-centered fibrosis is clearly present with or without widespread peribronchiolar metaplasia<sup>a</sup></li> <li>Fibrosing interstitial pneumonia affecting at least one sampled area of lung parenchyma with one or more of the following patterns:               <ol style="list-style-type: none"> <li>NSIP-fibrosing pattern</li> <li>UIP pattern</li> <li>Fibrosing pattern that is difficult to classify</li> <li>Fibrosis that is solely peribronchiolar</li> <li>Depending on the morphology, this category could include some bronchiolocentric interstitial pneumonias</li> </ol> </li> </ol> <p><b>Or</b> Fibrosing interstitial pneumonia meeting only major feature 2 in at least one lobe, and criteria for compatible with nonfibrotic HP in a separate lobe(s)</p> <p><b>Minor Features</b></p> <ol style="list-style-type: none"> <li>Organizing pneumonia, small foci</li> <li>Focal peribronchiolar metaplasia</li> <li>Foam cells</li> <li>Cholesterol clefts, Schaumann or calcium oxalate crystals (e-Fig 1)</li> </ol> <p><b>Lack of</b></p> <ol style="list-style-type: none"> <li>Poorly formed nonnecrotizing granulomas</li> <li>Features of an alternative diagnosis (see column 4)</li> </ol>	<p>Cases that show a pattern of fibrosing interstitial lung disease that do not meet the criteria for the pattern of fibrotic HP, compatible with fibrotic HP, or an alternative diagnosis</p> <p><b>Comment:</b> There is uncertainty about the histologic features in these cases that raise the consideration of fibrotic HP and other differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not</p> <p>Note: Fibrotic NSIP and UIP patterns are in this category. Depending on the morphology, this category could include some bronchiolocentric interstitial pneumonias.</p>	<p>A biopsy that shows definitive features of other interstitial lung diseases such as the following:</p> <ul style="list-style-type: none"> <li>Fibrosing sarcoidosis (well-formed granulomas in a lymphatic distribution, perigranulomatous fibrosis is common,<sup>86</sup> inflammation is inconspicuous)</li> <li>Aspiration with fibrosis (bronchiolocentric inflammation frequently with foreign material and giant cell or histiocytic reaction. However, aspiration with peribronchiolar interstitial lymphocytic infiltrates and/or fibrosis can closely resemble fibrotic HP, particularly when food or other particulate matter is not present<sup>87,88</sup>)</li> <li>Fibrosing interstitial pneumonia in connective tissue disease,<sup>89,90</sup> drug-induced lung disease, immunodeficiency<sup>91</sup> (prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, marked pleuritis, with or without granulomas)</li> <li>Smoking-related patterns (air space enlargement with fibrosis, which overlaps with smoking-related interstitial fibrosis, which is usually accompanied by respiratory bronchiolitis and emphysema<sup>92,93</sup>)</li> <li>Pneumoconiosis/occupational exposures (asbestos, hard metal, BADE)<sup>94-96</sup></li> <li>Fibrotic pulmonary Langerhans cell histiocytosis</li> </ul>

BADE = lymphocytic bronchiolitis, alveolar ductitis, and emphysema in industrial machine manufacturing workers; HP = hypersensitivity pneumonitis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

<sup>a</sup>Widespread means peribronchiolar metaplasia affects > 50% of the bronchioles.<sup>89</sup>



## Lung Biopsy

**PICO Question 13: In patients with suspected HP, should lung biopsy be performed?:** Seven single-center observational studies evaluating the diagnostic yield of lung biopsy in HP were identified (see e-Table 13 from Fernández Pérez et al<sup>4</sup>).<sup>74,78,81-85</sup>

The goal of obtaining histologic lung biopsy sampling in the diagnostic process is to reduce diagnostic uncertainty and to make optimal decisions for subsequent care. Therefore, assessment of the HP pretest probability is essential before considering lung biopsy and explicit clinical reasoning in the context of a consensus MDD is suggested to assess the appropriateness of biopsy as the next step of the diagnostic process. Considering the available evidence, disease severity, behavior, and patient-related factors (eg, comorbidities, preferences), we suggest refining the working diagnosis by histologic lung biopsy sampling is unnecessary if a definite HP diagnosis is unlikely to change management.

## Lung Biopsy Pattern

**PICO Question 14: In patients with suspected HP who underwent biopsy, does the presence of nonnecrotizing granulomas and/or giant cells and/or organizing pneumonia and/or cellular interstitial inflammation and/or bronchiolocentric inflammation or disease distribution and/or fibrosis support (or rule out) the diagnosis of HP?:** Three single-center observational studies reporting on the diagnostic utility of prespecified histologic features of HP were identified by the systematic review and met inclusion criteria (see e-Table 14 from Fernández Pérez et al<sup>4</sup>).<sup>78,81,82</sup> Based on this limited, very low quality evidence, we suggest physicians not rely only on the histopathologic findings for diagnosis, but may need to integrate biopsy results with clinical variables for individual cases considered by MDD.

Also, we suggest the use of four pathologic categories that reflect the level of confidence that a histopathologic specimen is likely to represent HP in the appropriate clinical context (Tables 4, 5; e-Table 1, e-Fig 7)<sup>86-96</sup>: (1) typical nonfibrotic HP or fibrotic HP, (2) compatible with nonfibrotic HP or fibrotic HP, (3) indeterminate for nonfibrotic or fibrotic HP, and (4) alternative diagnosis. These patterns are not discrete because they represent an attempt to categorize a complex continuum of histologic findings that may have overlapping

features. Patterns 1 and 4 are clearly defined, whereas distinctions between patterns 2 and 3 may be more difficult.

## Summary

A systematic review of the literature based on 14 PICO questions resulted in 12 evidence-based, graded recommendations and two ungraded consensus-based statements. All evidence was of very low quality. In sum, the guidance in this document suggests the diagnosis of HP should use a patient-centered approach and include a multidisciplinary assessment that incorporates the environmental and occupational exposure history and CT pattern to establish diagnostic confidence before considering BAL and/or lung biopsy. Additional research is needed on the performance characteristics and generalizability of exposure assessment tools and traditional and new diagnostic tests in modifying clinical decision-making for HP, particularly among those with a provisional diagnosis.

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**Additional information:** The e-Appendix, e-Figures, and e-Table can be found in the Supplemental Materials section of the online article.

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