Diagnosis and Evaluation of Hypersensitivity Pneumonitis

CHEST Guideline and Expert Panel Report

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BACKGROUND: The purpose of this analysis is to provide 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, 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. A diagnostic algorithm is provided, using supporting data from the recommendations where possible, along with expert consensus to help physicians gauge the probability of HP.

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. Criteria are presented to facilitate diagnosis of HP. 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: evidence-based medicine; guidelines; hypersensitivity pneumonitis; interstitial lung disease

ABBREVIATIONS: ALAT = Asociación Latinoamericana del Tórax; APC = antigen-presenting cells; BHP = bird-related hypersensitivity pneumonitis; CHEST = American College of Chest Physicians; COI = conflict of interest; CTD-ILD = connective tissue disease-associated interstitial lung disease; D_{LCO} = diffusing capacity of lung for carbon monoxide; GGO = ground-glass opacity; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HP = hypersensitivity pneumonitis; HR = hazard ratio; HRCT = high-resolution CT; IA = inciting antigen; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; JRS = Japanese Respiratory Society; K = Cohen's kappa statistic; LPT = lymphocyte proliferation test; MDD = multidisciplinary discussion; MDTM = multidisciplinary team meeting; MHC = major histocompatibility complex; NPV = negative predictive value; NSIP = nonspecific interstitial pneumonia; P(A-a)O_2 = alveolar-arterial oxygen pressure difference; PBMC = peripheral blood mononuclear cell; PICO = Population, Intervention, Comparator, Outcome; PPV = positive predictive value; ROC = receiver-operating characteristic; SIC = specific inhalation challenge; SLB = surgical lung biopsy; TBB = transbronchial biopsy; TBC = transbronchial cryobiopsy; UIP = usual interstitial pneumonia; VATS = video-assisted thoracoscopic surgery

AFFILIATIONS: From the Department of Medicine (E. R. Fernández Pérez and K. K. Brown), Division of Pulmonary, Critical Care and

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).

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2. **In patients with suspected HP, if the inciting antigen (IA) is thought to be related to an 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 facilitate 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 (eg, 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 (eg, 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 CT (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

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abnormality or ground-glass opacity associated with traction bronchiectasis or bronchiolectasis; 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 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 radiologic features may be seen only in patients with nonfibrotic 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 immunoassay 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 are 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 worldwide 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).

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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 nonfibrotic 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

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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.[1-3] 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, and avian), and less often, nonorganic inciting antigens (IAs). HP is a complex lung disease that occurs in genetically susceptible individuals previously sensitized to the inhaled IA.

HP can occur at any age, with most patients presenting after the fourth decade of life.[4] Conservatively, the prevalence of HP is estimated to range from one to two cases per 100,000 per year in North America and Europe.[4-6] Both the incidence and prevalence increase with advancing age and are highly variable worldwide reflecting the complex interplay among host risk factors, the IA, and environmental factors.[4,7-9] More than one-half of subjects present with chronic respiratory symptoms and resultant pulmonary fibrosis.[4,8,10,11]

While early diagnostic criteria required the presence of an identifiable IA,[12-14] it is now widely acknowledged that the IA often goes unrecognized or has ceased prior to diagnosis.[15] Within this context, the elusiveness of the IA together with the array of clinically heterogeneous HP phenotypes in terms of presentation, imaging and pathologic patterns, outcome, and response to therapy frequently leads to misdiagnosis.[16-19]

HP has traditionally been classified based on clinical features and disease duration as acute, subacute, or chronic.[12] Reliance on this classification framework has led to biased estimates of diagnostic test performance across these three broad categories hindering the impact of relevant HP subgroups on diagnostic test accuracy. Statements on the predictive value of specific HP diagnostic tests in the medical literature are often misleading when derived from highly selected individuals meeting these criteria for classification. Over the years, this HP diagnostic classification coupled with the requirement of strict traditional criteria has been unhelpful, even when accurate, when separated from a probabilistic diagnostic reasoning approach and multidisciplinary consensus.

Diagnostic variability in HP is attributed to multiple factors. However, a central source of practice variation and diagnostic disagreement across multidisciplinary teams and among clinicians has been the absence of a comprehensive clinical practice guideline to optimize diagnostic consistency and decision-making in HP. Recently published guidelines offer clinical practice guidance in this area.[20] Publication of these guidelines highlights the need for comprehensive guidance in HP diagnosis, and important distinctions between the guidance provided in that manuscript and in the present guidelines will be discussed further. The rationale for the development of this international evidence-based guideline and expert panel report is to provide rigorously developed contemporary guidance to clinicians on the HP diagnostic process to improve disease recognition, diagnostic accuracy, and individual care and outcomes of HP patients. A provisional HP diagnostic approach and criteria are provided, and a patient-centered and teamwork-oriented approach is emphasized.

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Methods

Expert Panel Composition

The Chair of the panel (E. R. F. P.) was reviewed for potential conflicts of interest (COIs) and approved by CHEST's Professional Standards Committee. An international panel was nominated by the Chair based on their expertise relative to potential guideline questions. The panel consisted of the guideline chair, 13 panelists (A. V., A. U. W., C. A. C. P., D. A. L., J. H. R., K. A. J., K. K. B., M. B. S., M. S., N. I., R. B. E., W. D. T., and Y. C. T. H), representing seven countries, a methodologist (L. F. G), and an additional panelist (S. A. M.) serving as a liaison to CHEST's Guidelines Oversight Committee. This multidisciplinary panel includes experts in interstitial lung diseases (ILDs), occupational and environmental medicine, chest radiology, and pulmonary pathology. A literature search for qualitative research on patients' views regarding the acceptability of diagnostic procedures for HP was conducted to incorporate the patient perspective.

Conflicts of Interest

All panel nominees were reviewed for potential COIs by the Professional Standards Committee. Nominees who were found to have no substantial COIs were approved, whereas nominees with potential intellectual and financial COIs that were manageable were "approved with management." Panelists approved with management were prohibited from voting on recommendations in which they had substantial COIs. A grid used to track COIs was created for each key clinical question and used during voting to ensure management terms were observed (e-Appendix 1).

Key Question Development and Systematic Literature Searches

The expert panel drafted 14 key clinical questions using the Population, Intervention, Comparator, Outcome (PICO) format. With the help of the methodologist, the panel reviewed the PICO questions to identify and finalize search terms, inclusion and exclusion criteria, and databases to be searched.

The methodologist performed an initial systematic search of the literature for all PICO questions in March 2018 using MEDLINE (via PubMed) and the Cochrane Library. A combination of the National Library of Medicine's medical subject headings and key words specific to the PICO elements of the key questions were used to identify studies. MEDLINE (via PubMed) search strategies are available (e-Appendix 2). A pragmatic search update was conducted in May 2020 using MEDLINE (via PubMed) to identify relevant studies published after the original literature search. All relevant studies identified were incorporated into the evidence base.

Reference lists of retrieved studies were also reviewed and additional studies were manually added to the search results. Searches were limited to English and Spanish language results but were not limited by study design or publication date. However, the inclusion criteria limited study designs to systematic reviews, randomized controlled trials, prospective and retrospective cohort studies, and case-control studies. Case reports, case series with a sample < 10, and conference abstracts were excluded. Study selection is detailed in e-Figure 1 (PRISMA diagram).

Study Selection and Data Extraction

Results from the completed literature searches were reviewed for relevance over two rounds of study selection. Panelists screened the identified studies using predefined inclusion and exclusion criteria based on the PICO components of the key questions. During the first round, panelists reviewed the titles and abstracts of identified studies. References deemed potentially relevant then underwent a second round of full-text screening, during which a final inclusion decision was made. For both rounds of screening, inclusion decisions were made independently and in parallel by two panelists. Disagreements were resolved through discussion by the original pair of reviewers to reach consensus.

Structured data tables were used to extract relevant data from all studies included after the second round of screening. Working in pairs, one panelist independently performed data extraction and the other panelist independently reviewed the extracted data. Discrepancies were resolved through discussion by the original pair of panelists.

Risk of Bias Assessment

The methodologist assessed the risk of bias in all included studies using the following assessment tools, as appropriate, based on study design: Cochrane Risk of Bias tool for randomized controlled trials, the Cochrane Bias Methods Group Tool to Assess Risk of Bias in Cohort Studies, and the Documentation and Appraisal Review Tool for systematic reviews.[21,22]

Meta-analysis

After completion of the quality assessment and data extraction, the computer program OpenMeta[analyst][23] was used to run meta-analyses when data were homogeneous and poolable. A random-effects model and the method of DerSimonian and Laird were used to pool the individual estimates.[24] Risk ratios were used to report the results for dichotomous outcomes and mean difference for continuous outcomes with accompanying 95% CIs. Statistical heterogeneity was assessed using the Higgins I^2 value and the χ^2

TABLE 1] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Wording of definitions from Balshem et al.[26]

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TABLE 2] CHEST Grading System

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong Recommendation, High-Quality Evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of the effect
Strong Recommendation, Moderate-Quality Evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of the effect and may change the estimate
Strong Recommendation, Low-Quality Evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of the effect and may well change the estimate
Strong Recommendation, Very Low-Quality Evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of the effect and may well change the estimate
Weak (Conditional) Recommendation, High-Quality Evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of the effect
Weak (Conditional) Recommendation, Moderate-Quality Evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of the effect and may change the estimate
Weak (Conditional) Recommendation, Low-Quality Evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of the effect and may well change the estimate
Weak (Conditional) Recommendation, Very Low-Quality Evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of the effect and may well change the estimate
Ungraded Consensus-based Suggestions			
Ungraded Consensus-Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of the effect and may change the estimate

test. [25] A Higgins' I^2 value ≥ 50% and P values < .05 were considered to represent significant heterogeneity.

Assessing the Overall Quality of the Body of Evidence

The overall certainty (quality) of the evidence was assessed for each outcome of interest using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[26] Evidence profiles were created using the GRADEPro Guideline Development Tool, which categorized the overall quality of the evidence for each outcome as either high, moderate, low, or very low. Each quality rating represents the confidence in the estimated effects for an outcome (Table 1).

Recommendation Drafting

The panel drafted recommendations based on the evidence that addressed the key clinical questions. Recommendations were graded using the CHEST grading system based on the GRADE approach (Table 2).[27] In instances in which there was insufficient evidence, but guidance was still warranted, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.[28]

It is important to highlight that the strength of some recommendations, such as numbers 10, 11, and 14, may seem incongruent with clinical knowledge as the evidence supporting the statements that may be considered best practices is indirect and of low or very low-quality precluding the development of strong recommendations.

Consensus Development

All drafted recommendations and suggestions were presented to the panel in an anonymous online voting survey to achieve consensus via a modified Delphi technique. Panelists were requested to indicate their level of agreement with each statement using a five-point Likert scale derived from the GRADE grid.[29] Additionally, panelists had the option to provide open-ended feedback on each statement. COI grids were included with the voting survey, and panelists with COIs related to individual recommendations were not permitted to vote on those statements in accordance with their management terms. Per CHEST policy, each statement required a 75% voting participation rate and at least 80% consensus for approval. Any recommendation or suggestion that did not meet these criteria was revised by the panel based on the feedback provided, and a new voting survey that incorporated suggested changes was disseminated and completed.

Peer Review Process

Reviewers from the Guidelines Oversight Committee, the CHEST Board of Regents, and the *CHEST* journal reviewed the methods used and content of the manuscript for consistency, accuracy, and completeness. The manuscript was revised according to feedback from the reviewers.

Additional Guidance

Ahead of the publication of this CHEST Guideline and Expert Panel Report, the American Thoracic Society (ATS), Japanese Respiratory Society (JRS), and Asociación Latinoamericana del Tórax (ALAT) published a clinical practice guideline on the diagnosis of HP in adults.[20] This CHEST and the ATS/JRS/ALAT guidelines address several analogous diagnostic questions with the aim of providing guidance on the diagnosis of HP. Despite conceptual and organizational differences in the high-resolution CT (HRCT) images and histopathological pattern description in these guidance documents, both guidelines' diagnostic approaches share several similarities.

While these guidance documents share similar aims, this CHEST guideline addresses a number of key diagnostic questions not covered in the ATS/JRS/ALAT guideline and thus reviewed and analyzed an additional comprehensive body of corresponding evidence. Perhaps the most salient difference based on the extent of evidence reviewed and expert consensus is that the guidance in this analysis stresses probabilistic reasoning during the stepwise diagnostic process. Thus, leading to important differences between this analysis and the guidance provided by ATS/JRS/ALAT regarding IA characterization (eg, establishing the IA likelihood vs dichotomizing the exposure into "yes" or "no"), the use of a structured questionnaire to optimize exposure identification and pretest likelihood, when to perform serum antigen-specific antibody testing, specific inhalational challenge testing, and the determination of HP diagnostic confidence. Another important difference is when to pursue BAL fluid analysis. The guideline committee does not recommend BAL with lymphocyte cellular analysis in all subjects, particularly in those with a compelling exposure history within the appropriate clinical context and a chest HRCT pattern typical for HP (eg, BHP). In high prevalence settings, such as nonfibrotic HP, such a combination may be sufficiently predictive of histopathological HP to forgo BAL (or lung biopsy). BAL fluid analysis should be considered to evaluate for an additional reason according to the pretest estimate and/or if the pretest probability of HP is in the middle, above the test threshold and below the treatment threshold (see Recommendation 12 and *probabilistic diagnostic categories*).

Results

Clinical History Taking

Question 1: For patients with suspected HP, should a clinical history be taken to support (or rule out) the diagnosis of HP?

Recommendation 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).

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Voting Results: definitely agree, 14; probably agree, 1; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

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).

Summary of the Evidence: The systematic review identified two prospective studies and a retrospective study providing indirect evidence to address the PICO question (e-Table 1). HP cases were diagnosed based on prespecified criteria.[3,8,30] The first prospective, multicenter study developed a clinical prediction rule for HP from a derivation cohort of 400 patients (116 with HP, 284 control subjects).[3] Exposure to an identified IA was the strongest of six significant predictors of HP identified (OR, 38.8; 95% CI, 11.6-129.6). The prediction rule derived from the six factors had a sensitivity of 86% (95% CI, 79-92) and a specificity of 86% (95% CI, 81-90) with an HP prevalence of 45%. The receiver-operating characteristic (ROC) curve was 0.93 (95% CI, 0.90-0.95). The rule retained its accuracy when validated in a separate cohort of 261 patients (area under the ROC curve was 0.90; CI, 0.87-0.94).

The second study was a prospective registry created to characterize newly diagnosed ILDs (n = 1,084).[8] A multidisciplinary discussion (MDD) was used to validate all diagnoses. A detailed history including information on presenting symptoms, prior and coexisting medical conditions, occupation, exposures, family history, and medications was obtained from all patients. A total of 513 patients were diagnosed with HP, and 75% had an identifiable exposure captured by an environmental and occupational case report form.

The third study used retrospective data to develop a diagnostic model for chronic HP. A diagnostic predictive model that had a specificity of 91% and sensitivity of 48% for the diagnosis of chronic HP when including a history of down feather and/or bird exposure, age, and specific HRCT features was identified.[30] This study highlighted the importance of clinical history taking for identifying a relevant exposure during the diagnostic workup of HP, which is influenced by the local disease prevalence and the clinical practice setting (ie, pretest probability),[4,8,31-36] and combining exposure information with other variables to diagnose HP.

Panel Discussion: Evidence of the diagnostic utility of the clinical history provided by the observational studies included in this analysis is of very low quality and indirectly addresses the PICO question as clinical history-taking was not directly evaluated as a diagnostic criterion. Additionally, the included studies did not provide relevant data on the structure of the environmental and occupational interview or how the relationship between the exposure and the HP diagnosis was established among subjects with and without lung fibrosis.

To ensure consistency and optimize patient recall during the history-taking process, the guideline panel suggests using a clinically relevant environmental and occupational questionnaire to guide the interview and improve the sensitivity of detecting the IA exposure(s). Consider using a questionnaire adapted to regional and local geography and customs (Table 3).[37-40]

Despite the complexity of gathering, integrating, and interpreting a thorough environmental and occupational exposure history, this recommendation places a high value on the desirable consequences of establishing the pretest likelihood of the disease based on the environmental and occupational history, as well as minimizing the risk of misdiagnosing HP as an idiopathic interstitial pneumonia.

Specialist Consultation

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?

Recommendation 2. In patients with suspected HP, if the inciting antigen (IA) is thought to be related to an occupational exposure, we suggest considering the inclusion of an occupational medicine specialist and

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TABLE 3] Suggested Environmental Assessment Steps During the Evaluation of a Subject With or Suspected to Have HP[a]

Steps	Characteristics	Comments
• IA exposure assessment	• *Epidemiologic context* – disease frequency, geographic area, climate, season • *Structured questionnaire* – with regional and cultural components • *Comprehensive clinical history* – assess for features of association and lack of refutability	- As part of the exposure assessment, the history and the structured questionnaire ideally include open-ended questions adapted to the epidemiological context: regional and local geography, customs, climate, or season, all of which are associated with variations in the type of IA and HP prevalence[38] - When possible, the clinician should consider including family members or caregivers in the exposure history-taking process. Visual reconstruction such as web-based geographical maps, pictures and drawings of possible antigen sources can help reduce recall bias. Dedicating a separate clinic visit to delve further into the environmental and work history may be beneficial - 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 clinician
• Characterization of IA type and sources	• *Workplace(s)* – understand current/prior jobs and type and extent of exposure(s) • *Home(s)* – detailed indoor and surrounding space survey • *Vocational activities, travel/migration, all animal contact*	- For work-related cases, ask patient to bring lists of material/chemicals or materials safety data sheet for documentation and review
• Determine the IA likelihood	• *Identifiable* – causal relationship and absence of refutability or evidence against the suspected IA cause. Urge prevention and remediation • *Indeterminate* – evidence is suggestive of an association. Consider trial away from the likely IA containing-environment and serologic testing • *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)	- Search for inorganic or organic antigen type, sources, and geographic locations on Web-based engines such as www.nlm.nih.gov/toxnet/index.html, www.epa.gov/iris, www.hplung.com - Clinician and patient Web resource when indoor mold suspected: www.cdc.gov/mold/default.htm
• Team-based evaluation	• Consider referral to specialized center • Occupational medicine consultation – workplace related, disease progression and suspicion for ongoing indeterminate IA exposure or multiple IA sources • Determine if site environmental assessment is required	- 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 officer[b] - Websites providing a geographic search of certified professional: www.ioha.net, www.aiha.org

(Continued)

TABLE 3] (Continued)

Steps	Characteristics	Comments
• Determine the need for site environmental assessment	• Establish the goal and objectives of the exposure assessment • Evaluate the results and limitations of the qualitative assessment – establish IA likelihood for indeterminate exposures • Provide recommendations and specific actions	- Walkthrough or visual assessment: Building, mechanical systems, appliances, maintenance - Home inspection commonly includes three domains: 1) home exterior (eg, damage 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 and condensation)[39,40]

[a]See Recommendation #1, #2, #3, #8, and #10. HP = hypersensitivity pneumonitis; IA = inciting antigen.
[b]The term environmental hygienist is broadly used throughout this guide. However, other terms such as "industrial hygienist" or "occupational hygienist" are also used depending on the consultant specialization, indoor setting, and world geography.

an environmental hygienist during the multidisciplinary diagnostic workup, especially when the source of exposure is obscure or unverified (Ungraded Consensus-Based Statement).

Voting Results: definitely agree, 9; probably agree, 5; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 1.

Summary of the Evidence: The systematic review identified one longitudinal study that evaluated the effectiveness of interventions to address an HP outbreak at a metalworking facility (35/120 workers diagnosed with HP over 2 years based on prespecified criteria).[41] The investigators completed a qualitative and quantitative environmental hygiene assessment of the work environment and made intervention recommendations based on their findings and the patients' return-to-work experiences. Workers with HP were re-evaluated regularly. Forty-nine percent (17/35) of workers diagnosed with HP were removed from the plant when their disease recurred. Active collaboration between environmental hygienists, occupational physicians, the employer, and the patients allowed for an iterative approach to exposure assessment and the implementation of control strategies that led to 51% of workers with HP returning to work and no additional cases of HP after the interventions were enacted (e-Table 2).

Panel Discussion: Based on the indirect evidence cited above and consensus generation, the guideline panel reasoned that inclusion of an occupational medicine specialist (eg, at referral medical center or employer's occupational medicine specialist) and an environmental hygienist during the multidisciplinary diagnostic workup of suspected occupational HP cases is beneficial, as (Table 3):

- Specialists can help determine the likelihood of an occupational exposure as the cause of HP and assist in the removal of workers from further exposure to the agent, suggest changes to improve work conditions and remove contaminants, educate workers on the use of safe workplace practices, bring clinical expertise on the options of work restrictions, assist the patient with a workers' compensation claim when applicable, and monitor the patient in future work locations to ensure safe placement.
- The diagnosis of a sentinel HP case in a particular occupational environment may indicate a risk for other similarly situated workers. Consultation with an

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occupational medicine specialist and certified environmental hygienist may help determine the purpose, scope, level of detail, and approach of an occupational exposure assessment and how its results can be used in risk assessment. Specialists can also recommend or help institute medical-surveillance programs for at-risk workers.

In patients with non-occupational HP, consultation with a certified environmental hygienist for visual inspection of an indoor environment (eg, home) may be helpful in identifying an antigenic source if there is suspicion of mold (ie, musty smell but no visible mold growth)[39] or other concerning exposure.

This recommendation places a high value on determining the likelihood of occupational exposure and a relatively lower value on the environmental assessment cost, lack of validated quantitative environmental sampling methods and numeric standards for airborne concentrations of mold or mold spores, and the limitations of interpreting environmental sampling. However, the guideline panel recognizes the limitations of the feasibility of this recommendation as access to an environmental hygienist or occupational and environmental consultation is limited in many health-care settings. While an employer may cover the occupational exposure assessment cost, environmental home inspection for the early identification and elimination of the IA is not typically reimbursed by insurance companies, limiting routine implementation. There is a considerable need for cost-effectiveness research in this area to help set and guide reimbursement rates and improve the quality and efficiency of systematic indoor environmental assessment and sampling.

Identification of Inciting Antigens

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

Recommendation 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).

Voting Results: definitely agree, 11; probably agree, 3; neutral (no recommendation for or against), 1; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

Remarks: Correct identification of the IA and the subsequent elimination of that exposure facilitate 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 (eg, 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 (eg, workplace inspection) may support the diagnosis and help guide management decisions.

Summary of the Evidence: The systematic review identified five observational studies that compared prognostic outcomes (eg, survival, disease progression) between HP subjects with and without an identifiable IA (e-Table 3). HP cases were diagnosed based on prespecified criteria.

Fernández Pérez et al[15] conducted a single-centered, observational cohort study of 142 patients with chronic HP, of whom 75 (53%) had an unidentified IA despite extensive evaluation. After adjusting for age, presence of fibrosis, mean FVC%, mean diffusing capacity of lung for carbon monoxide (DLCO%), and smoking history, an unidentified IA was associated with shortened survival (hazard ratio [HR], 1.76; 95% CI, 1.01-3.07). Similarly, in an observational cohort study of 202 subjects with HP where 41 (20%) had an unidentified IA, De Sadeleer et al[42] demonstrated a trend toward shorter survival for subjects with an unidentified IA compared to subjects with an identifiable IA (HR, 1.8; 95% CI, 0.99-3.29). After multivariate adjustment for age, sex, and baseline FVC%, unidentified IA was associated with shortened survival (HR, 2.08; 95% CI, 1.02-4.24). A smaller study

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described the outcome of 27 subjects with HP confirmed by open lung biopsy.[43] Compared to subjects with an unidentifiable exposure (17 [62%]), more subjects with an identified exposure were alive (10/10 vs 13/17) and without evidence of disease progression (0/10 vs 3/17) during the 2.7-year follow-up period.

In one study of 101 subjects with HP (72 with acute HP, 29 with chronic HP), 11 subjects (15%) in the acute HP group developed chronic HP, and an unidentified exposure was an independent risk factor for the progression of disease (OR, 0.08; 95% CI, 0.007-0.86; $P = .04$).[44] After adjustment for lung fibrosis on chest CT imaging, smoking history, and total lung capacity, an unidentified exposure was independently associated with survival (HR, 0.12; 95% CI, 0.02-0.68; $P = .02$).

In the study by De Sadeleer et al,[42] FVC% (mean decline 0.24% monthly vs mean 0.92% monthly increase; $P = .02$) and DLCO% (mean decline of 0.23% per month vs 0.37% monthly increase, $P = .04$) increased in nonfibrotic HP patients after exposure avoidance. A trend toward improved FVC% was seen after exposure avoidance in fibrotic HP patients (mean 0.06% monthly decline vs 0.28% monthly increase; $P = .15$). An observational study by Tsutsui et al[45] enrolled 196 subjects with chronic HP and 43 controls with non-HP lung diseases to undergo a 2-week hospital admission as an antigen avoidance test. They found that all clinical parameters significantly improved in the HP cohort (vital capacity, alveolar-arterial oxygen pressure difference, Krebs von den lungen-6, surfactant protein-D, WBC count, C-reactive protein, and body temperature) while none of the parameters changed significantly in the control group following the hospital admission (e-Table 3).

Two studies from the same institution excluded from the analysis (due to indirectness and inclusion of patient populations that overlap with those of studies included in our analysis) described the effect of an IA exposure on disease progression.[46,47] In these studies, higher levels of avian antigens from household dust at and after the diagnosis of bird-related hypersensitivity pneumonitis (BHP) was associated with more rapid annual FVC decline.

Panel Discussion: Outcome data from the studies included in this analysis were assessed to be very low-quality evidence. Synthesizing information from available studies is difficult due to the lack of comparable exposure assessment information across studies. For example, the available data were inadequate to establish a pooled estimate of the incidence of an unidentified IA in clinical practice today. This limitation affects not only the diagnosis but also the prognostic impact of classifying fibrotic and nonfibrotic HP subjects based on the likelihood of an occupational and/or environmental exposure(s). How the IA is ascertained and to what extent a potential IA is investigated during the diagnostic process requires additional study.

Although the prognostic value of classifying patients based on IA status may be less compelling in late-stage fibrotic disease,[48,49] the guideline panel weighed the desirable consequences (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 3) against the undesirable consequences of not attempting to characterize the IA (ie, potential early morbidity associated with an unidentified exposure before the recognition of disease progression). The panel determined that the balance favors classifying patients based on IA exposure likelihood.

Classification of HP

Question 4: In patients diagnosed with HP, should the disease be classified according to the presence or absence of fibrosis and the inciting antigen characterized?

Recommendation 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 CT of the chest (Weak Recommendation, Very Low-Quality Evidence).

Voting Results: definitely agree, 11; probably agree, 3; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 1.

Remarks: HRCT findings indicative of lung fibrosis include one or more of the following: reticular abnormality or ground-glass opacity associated with traction bronchiectasis or bronchiolectasis; 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 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,

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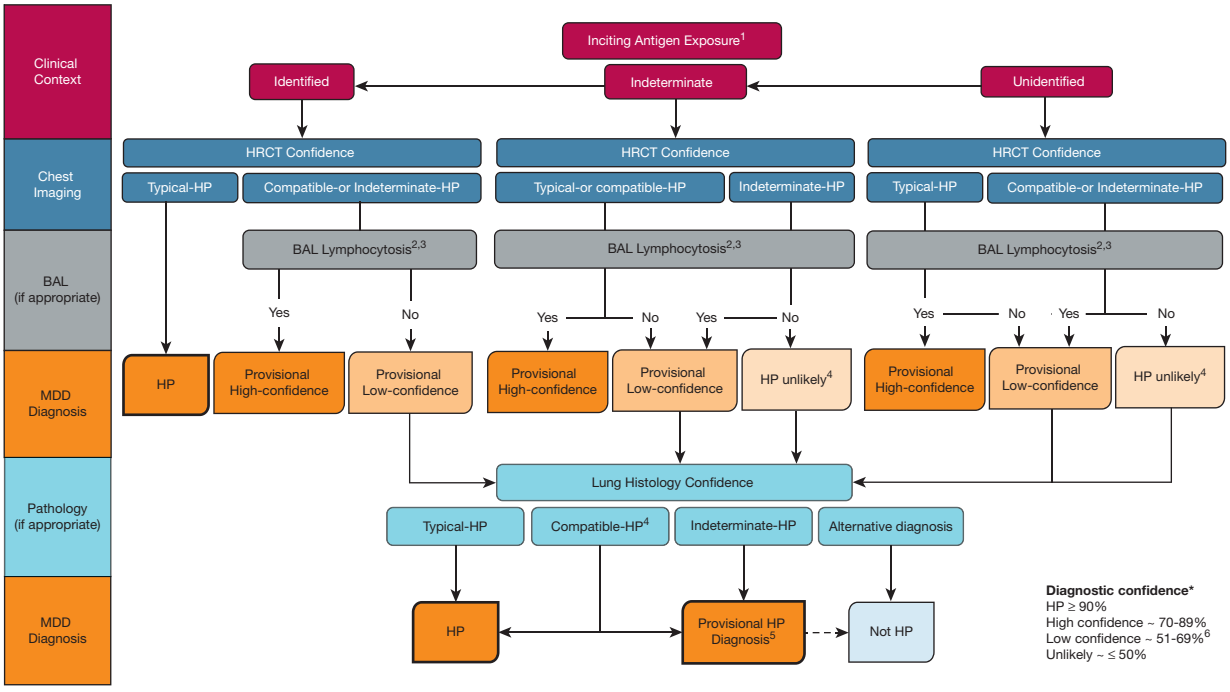

Figure 1 – ***Algorithm for the diagnosis of fibrotic and nonfibrotic hypersensitivity pneumonitis.*** **The diagnostic confidences are not intended to represent arbitrary estimates of the probability of HP diagnosis before and after testing but rather to provide a conceptual model for assessing discordant information and help optimize diagnostic clinical reasoning when evaluating patients with suspected HP. HRCT = high-resolution CT; MDD = multidisciplinary discussion.*

[1]See Table 3 and the exposure assessment section. The certainty of the IA cause and source may change over time after reevaluating additional exposure and clinical data. 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.

[2]The BAL in this algorithm does not imply that every suspected hypersensitivity pneumonitis (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, ≥ 20%) alone would not rule in HP and should be interpreted in the context of the entire cellular count differential, sampling site, and protocol as well as 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 interstitial lung disease (ILD). While 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 IA exposure is indeterminate or unidentified. Cutoffs that define abnormal increases in BAL lymphocyte counts to accurately distinguish HP from other ILDs remains to be determined (see Recommendation #14).

[3]Until further evidence becomes available, transbronchial biopsies may be considered (see Recommendation #12).

[4]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 may be lower if the exposure is unidentified and the chest CT is indeterminate for fibrotic HP in the absence of BAL lymphocytosis. The MDD consensus HP diagnosis may lead to a provisional HP 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.

[5]This scenario is more likely in cases of fibrotic HP than in cases of nonfibrotic HP. During serial multidisciplinary discussion evaluations, the diagnosis may change to "not HP" (dashed arrow), as more information becomes available.

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.

Summary of the Evidence: The systematic review did not identify any studies that directly address the PICO question focused on the combined effect of lung fibrosis and IA exposure status on HP-related mortality, adverse events, and disease progression. However, the systematic review did identify six observational studies that estimated survival over time or mortality rate between HP subjects (identified by predefined diagnostic criteria) with or without lung fibrosis on CT imaging of the chest and with or without an identified IA (e-Table 4). These studies were included in this analysis as they provide indirect evidence to address the PICO question.

In one study, the effect of lung fibrosis on the probability of survival over time was adjusted by the absence of an identified IA among 142 chronic HP patients (enrolled patients had respiratory symptoms and/or physical signs for > 1 year).[15] Fifty-three were classified as fibrotic and

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89 as nonfibrotic based on HRCT chest imaging and histopathological findings of fibrosis. The IA was identified in 24/53 (45%) fibrotic cases and in 43/89 (48%) nonfibrotic cases. Median survival time was 11.8 years (95% CI, 7.1-15.7) for nonfibrotic and unidentified IA cases, 14.5 years (95% CI, 12.3-not available) for nonfibrotic and identified IA cases, 4.88 years (95% CI, 2.82-12.3) for fibrotic and unidentified IA cases, and 8.75 years (95% CI, 5.83-15.7) for fibrotic and identified IA cases. After adjusting for age, unidentified IA, mean FVC%, mean DLCO%, and smoking history, pulmonary fibrosis was associated with increased risk of death (HR, 2.43; 95% CI, 1.36-4.35). A retrospective study from the same institution (n = 110) was excluded due to overlapping patient populations but analyzed the effect of lung fibrosis on different prognostic outcomes.[50] The IA was identified in 27/72 (38%) fibrotic cases and 22/58 (38%) nonfibrotic cases. Pulmonary fibrosis on CT imaging was associated with shortened survival (HR, 6.99; 95% CI, 1.34-61.92) after adjusting for age, unidentified IA, mean FVC%, smoking history, ground-glass opacity (GGO), mosaic perfusion/air-trapping, and axial diffuse disease distribution.

Three studies evaluated the effect of lung fibrosis on HRCT imaging, symptom duration before presentation, or symptom type as predictors of survival in HP. A study of 117 HP patients (diagnosed by predefined criteria, 79 with an identified IA exposure) grouped subjects based on HRCT pattern showing honeycombing (n = 12), non-honeycomb fibrosis (n = 45), or nonfibrotic HP (n = 60).[51] The combined effect of lung fibrosis and IA exposure status was not examined. Patients with nonfibrotic HP survived longer than those with non-honeycomb fibrosis (HR, 0.22; 95% CI, 0.10-0.51) or honeycombing (HR, 0.06; 95% CI, 0.02-0.15). HP patients with non-honeycomb fibrosis survived longer than those with honeycombing (HR, 0.26; 95% CI, 0.12-0.54). Symptom duration was not associated with unadjusted survival time (HR 1.0 per additional month of symptoms; 95% CI, 0.99-1.01). Further, symptom duration was similar across radiologic groups.

Similarly, in a cohort of 202 chronic HP patients, based on presence or absence of extensive reticulation, and/or traction bronchiectasis, and/or honeycombing on HRCT imaging, 93 cases were classified as nonfibrotic HP and 109 were classified as fibrotic HP.[42] The IA was identified in 83/93 (89%) nonfibrotic HP cases and 78/109 (72%) fibrotic HP cases. Throughout the entire cohort (both nonfibrotic and fibrotic HP patients), there was a trend toward worse survival in patients with an unidentified IA (HR, 2.07; 95% CI, 1.02-4.24). Fibrotic HP patients had an increased risk of death compared to patients with nonfibrotic HP (HR, 4.35; 95% CI, 2.22-8.33). Neither symptom chronicity (ie, > 6 months for chronic HP) nor symptom type (ie, systemic symptoms or temporal relation of symptoms with exposure, or both for acute HP) were associated with decreased survival, FVC%, or DLCO% in nonfibrotic HP subjects.

A study of 112 patients with BHP evaluated the prognostic value of serial HRCT findings in 17 subjects with acute HP (eg, diagnostic criteria included current exposure to avian antigen together with consistent signs and symptoms such as dyspnea, cough, and fever) and 95 with chronic HP (eg, diagnostic criteria included duration of symptoms of more than 6 months).[52] Chronic cases were classified as recurrent (n = 33, recurrent acute episodes of mild exertional dyspnea, cough, and low-grade fever) or insidious (n = 62, no history of acute episode, chronic, slowly progressing respiratory disease). Twenty-one patients died: 0/17 acute, 2/33 (6%) recurrent, and 19/62 (31%) insidious. The extent of honeycombing on chest CT imaging increased substantially more from the time of diagnosis to follow-up (mean 49.9 ± 3.5 months) in insidious compared to recurrent cases.

Two studies that were excluded from this analysis due to the inclusion of patient populations that overlapped with those of studies included in our analysis or due to lack of a corresponding comparison group revealed no association between mortality and symptom duration.[53,54]

Two studies examined the relationship between the overall extent of lung fibrosis on HRCT imaging and mortality.[49,55] In both studies, an identified IA on univariate analysis was not associated with mortality or survival.

In a study that included 177 patients with HP (diagnosed via predefined criteria), 132/177 (74%) patients were assigned a fibrosis score (from 0 = no involvement to 4 = 76%-100% involvement) based on the mean extent of reticulation and honeycombing in six lung zones observed by two thoracic radiologists on HRCT scans.[55] Fibrosis score was a significant univariate predictor of time to death or lung transplantation (HR, 1.54; 95% CI, 1.25-1.88). After adjusting for the presence of auscultatory crackles on examination, oxygen therapy, and FEV_1/FVC, the fibrosis score was independently associated with death or lung transplantation (HR, 1.35;

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95% CI, 1.08-1.70). Further, patients were divided into quartiles by their fibrosis score. Patients in the highest quartile for fibrosis score had worse transplant-free survival than patients in the two lowest quartiles for fibrosis score.

Similarly, in a study of 69 HP patients (26 with lung fibrosis on CT imaging), the age-adjusted HR for mortality in patients with fibrosis was 4.6 (95% CI, 2.0-20.1).[49] Twenty of the 26 (77%) fibrotic patients and 32/43 (74%) nonfibrotic patients had an identified IA. Mortality was highest in patients with > 40% lung involvement (5/6 patients died [83%]) followed by those with 10% to 40% involvement (3/6 patients died [50%]) followed by those with < 10% involvement (3/14 patients died [21%]) and lowest in those with no lung fibrosis (1/43 patients died [2%]). Duration of symptoms was similar in subjects who were alive (median 11 [3-44] months) and dead (median, 24 [11-42] months) after the study follow-up period.

Panel Discussion: The evidence from the studies included in this analysis is of very low-quality. As a whole, this evidence suggests that the extent of HRCT fibrotic change in HP has prognostic value. The guideline panel placed a high value on the prognostic benefits of classifying HP cases on the presence or absence of fibrosis considering HRCT imaging of the chest is noninvasive.

Indeed, compared to nonfibrotic HP, fibrotic HP is the leading cause of morbidity and death from HP.[7,15,51,55] The present analysis indicates that the classification of HP cases should also include a designation of IA likelihood (Fig 1) since the evidence suggests that IA status has implications for management and prognosis.

Although a time-based classification (ie, acute, subacute, chronic) has widely been used in the medical and patient community, the guideline panel's certainty in the utility of this practice is diminished by the data available from observational studies. Of note, definitions of HP classification categories are not uniform among the studies included in this analysis. Additionally, the data suggest that a time-based classification alone does not provide information on an individual patient's prognosis or longitudinal disease behavior (eg, whether acute disease is self-limited or chronic disease is inexorably progressive or fibrotic) and does not aid in appropriate treatment planning (eg, IA avoidance) or assist in enhancing diagnostic accuracy (eg, IA exposure status). The suggestive interpretation of symptom type and duration and inclusion of phenotypically similar conditions under a broad category (eg, designating a diverse group of HP subjects as "chronic," symptoms > 6 months, or as "acute," symptoms < 6 months) have been reported to lead to clinical uncertainty and diagnostic confusion.[56] Therefore, the guideline panel suggests that for clinical purposes and the design of future research, patients should be classified based on recognized prognostic indicators such as the presence or absence of pulmonary fibrosis.

Clinical Improvement With Antigen Avoidance

Question 5: In patients with suspected HP, does clinical improvement with antigen avoidance support (or rule out) the diagnosis of HP?

Recommendation 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).

Voting Results: definitely agree, 9; probably agree, 6; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

Remarks: Clinically appreciable improvement in symptomatic, physiologic, and radiologic features may be seen only in patients with nonfibrotic 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.

Summary of the Evidence: The systematic review did not identify any studies that evaluated the diagnostic yield of a patient's response to antigen avoidance to facilitate a working HP diagnosis. Alternatively, seven retrospective studies that assessed clinical response to antigen avoidance in subjects already diagnosed with HP based on prespecified criteria were identified and provided indirect evidence of the diagnostic utility of antigen avoidance (e-Table 5).

Four studies analyzed lung function trajectory in response to antigen avoidance.[42,45,57,58] As previously

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described, nonfibrotic HP subjects in the observational cohort study by De Sadeleer et al[42] and HP cases compared to controls in the study by Tsutsui et al44 were reported to have an increase in FVC% (or VC%) and DLCO% following antigen avoidance. Tsutsui et al[45] also reported clinical improvement following antigen avoidance for 2 weeks had a sensitivity of 51% and a specificity of 81% among patients with chronic HP.

Similarly, a study of 41 patients with nonfibrotic HP compared changes in lung function between those who avoided the IA for at least 2 years (n = 15) and those with continued exposure (n = 26).[57] The mean number of years between the first acute episode and follow-up lung function testing was similar in the two groups (7 years). The antigen avoidance cohort showed significant improvement in all lung function parameters (total lung capacity %, FVC%, and DLCO%, $P < .01$), while the continued exposure cohort showed no significant improvement in lung function. In a cohort study by Gimenez et al[58] that included 112 patients with fibrotic HP, antigen avoidance was reported by 61 (54%) patients, 45 patients remained exposed, while antigen avoidance was uncertain in six patients. The authors report no difference in FVC% decline between these three groups ($P = .12$).

In an additional study not included in this analysis for failure to meet all inclusion criteria, spirometric values were sequentially evaluated in 18 patients with acute BHP and abnormal baseline lung function.[59] Improvement (5/18 [28%]) or normalization (9/18 [50%]) of FVC occurred an average of 3.4 ± 2.4 months after the avian contact ceased. Patients who received corticosteroids compared to those who did not showed no substantial difference in FVC at the end of the study. Similarly, in another study of 14 patients with chronic HP, antigen avoidance by relocation or remediation of domestic environments kept 10/14 patients stable without a decline in VC% at 12 months (0.8 ± 3.6%).[60] However, three of the four patients with ongoing exposure (mean change in vital capacity within 12 months, -17.6 ± 11.0%) died of respiratory failure due to disease progression.

Four studies included in this analysis reported on the impact of antigen avoidance on symptomatic improvement and collectively included 149 HP patients.[58,61-63] In a cohort study of 61 patients with fibrotic HP who reported antigen avoidance, 25 (41%) experienced a sustained decrease in dyspnea and cough in two consecutive visits after antigen removal or avoidance.[58] In a study of 50 factory employees, 26 had a history of flu-like symptoms suggestive of acute HP.[61] During 1-year following removal of the suspected antigen source from the workplace, these symptoms did not recur. A study of 21 patients with hot tub lung followed up for a median of 5 months reported improvement in all patients and complete resolution of respiratory symptoms and radiologic abnormalities in 11 (52%) following hot tub avoidance (16/21 were additionally treated with steroids and/or antibiotics).[62] Similarly, a study that included 17 BHP subjects reported complete recovery based on clinical, physiologic, and radiological data in 9/17 (53%) over 2 years of following antigen avoidance (one subject was treated with corticosteroids).[63]

In a study of 161 HP patients with an identified IA, 116 (72%) terminated the exposure.[42] No survival benefit was observed with exposure avoidance after multivariate correction for age, sex, and baseline FVC% (HR, 1.29; 95% CI, 0.57-2.93). However, in a study by Gimenez et al,[58] clinical improvement after antigen avoidance was associated with decreased mortality (HR, 0.14; 95% CI, 0.03-0.60). On multivariate analysis, after adjusting for a decline in FVC by ≥ 10% during follow-up and baseline FVC%, clinical improvement with antigen avoidance remained associated with decreased mortality (HR, 0.18; 95% CI, 0.04-0.77).

Panel Discussion: Despite the absence of diagnostic process studies evaluating patients' responses to antigen avoidance, using it as an investigative tool is useful, as the response may have both diagnostic and prognostic implications. For example, the benefit of supporting the diagnosis and "treating" nonfibrotic HP cases with antigen avoidance can greatly exceed the potential harm of immunosuppressive treatment in a patient with continued exposure. Although prospective studies are needed to directly ascertain the diagnostic utility of antigen avoidance (the evidence provided by the observational studies included in this analysis is indirect and of very low-quality), the guideline panel concluded that the threshold for using a patient's response to immediate antigen avoidance as a diagnostic test is low, as complete resolution of early detected nonfibrotic HP may be observed with the timely elimination of the IA exposure. When remediation or complete avoidance is not possible or if the source of exposure is unclear, removing the patient from the suspected environment should be considered.[40] However, the absence of clinical improvement with antigen avoidance does not exclude the diagnosis of HP, as many fibrotic HP patients fail to improve with antigen avoidance.

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Clinical Improvement With Medical Therapy

Question 6: In patients with suspected HP, does clinical improvement with medical therapy support the diagnosis of HP?

Recommendation 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).

Voting Results: definitely agree, 11; probably agree, 4; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

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 more 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 ILDs with similar presentations, such as idiopathic nonspecific interstitial pneumonia (NSIP), may also improve with immunosuppressive treatment.

Summary of the Evidence: The systematic review identified one randomized trial[64] and nine observational studies[42,62,65-71] that evaluated HP patients' responses to medical therapy but not directly the diagnostic utility of clinical improvement with medical therapy (e-Tables 6a, 6b).

A double-blind, placebo-controlled study of 35 patients (per-protocol analysis) with acute nonfibrotic HP randomized 19 to prednisone (starting at 40 mg/daily) and 16 to placebo for 8 weeks. The study reported a difference in mean DLCO between treatment groups following 1 month of treatment ($P = .03$).[64] At 5 years after treatment, there were no significant between-group differences for any lung function measure studied (e-Table 6a).

A study of 19 children with nonfibrotic HP (mean age of 9 years) treated with monthly high-dose pulse methylprednisolone as monotherapy or in combination with other immunosuppressants (median of 15 monthly courses) reported a significant increase from baseline in all lung function measures tested after both 3 and 6 months of treatment ($P < .05$).[68] On follow-up HRCT imaging, 80% of patients had normal scans. In a study of 23 children with HP (mean age of 10 years), 20 treated with systemic corticosteroids (mean treatment duration of 34 ± 22 weeks), at a mean follow-up time of 1.1 ± 1.0 years, 17/23 were healthy, 5/23 were improved, and 1/23 was in worse clinical condition. The number of children with lung fibrosis was not reported.[65]

Three retrospective studies described the longitudinal trend in lung function in response to immunosuppressive therapy among subjects with nonfibrotic or fibrotic HP.[42,66,67] In a study of 202 patients with HP, 149 (74%) received corticosteroid therapy for a median of 6.5 months.[42] In nonfibrotic HP subjects, corticosteroid treatment (67/93 [79%]) resulted in a reversal from a monthly FVC% decline of 0.35% to an FVC% increase of 0.84% ($P < .01$). No difference in DLCO% was observed after corticosteroid initiation ($P = .43$). In contrast, no significant changes were observed for fibrotic HP (82/109 [80%]; FVC%, $P = .96$; DLCO%, $P = .59$). In a study of 131 patients with fibrotic HP, 93 (71%) were treated with immunosuppressive therapy (41 treated with prednisone only, 24 were also treated with azathioprine, and 28 with mycophenolate mofetil).[66] Patients who received prednisone, when compared to those who did not, had worse FVC% decline over 36 months (−10.0% vs −1.3%; $P = .04$). In patients previously receiving prednisone, mycophenolate mofetil or azathioprine (prednisone-sparing therapy) significantly altered the slope of monthly FVC decline (−0.7% vs −0.2%; $P = 0.001$) such that the overall FVC % decline over 36 months in the prednisone-sparing therapy subgroup remained similar to that of the prednisone subgroup (−9.4 ± 4.3% vs −11.5 ± 3.6%; $P = .58$).

A study of 70 subjects with chronic HP (51 treated with mycophenolate mofetil; 19 treated with azathioprine; 84% also on corticosteroids) reported that in contrast to no change in FVC%, DLCO% increased following 1 year of treatment (mean increase, 4.2%; 95% CI, 2.6-5.9; $P < .01$).[67] Similarly, a study of 30 subjects with chronic HP (22 treated with mycophenolate mofetil; eight treated with azathioprine; 100% also on corticosteroids) reported that in contrast to a nonsignificant reduction of the rate of FVC% decline 12 months after initiation of prednisone-sparing therapy, treatment with prednisone-sparing agents significantly improved DLCO % (from −0.55 ± 0.96 to +0.31 ± 0.58).[71] However, in

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both studies, data were not adjusted for the presence of lung fibrosis, and it is unclear if the possible treatment effect on DLCO% was driven by the nonfibrotic HP subjects.

A study of 21 patients with hot tub lung all treated with antigen avoidance and 16/21 additionally treated with steroids and/or antibiotics reported that 11 (52%) patients had complete resolution of symptoms and radiologic abnormalities at a median follow-up of 5 months.[62] A study of 86 patients with HP, of whom 57 were treated with prednisone for 4 to 12 weeks, reported that during a follow-up over 60 months, 6/86 (7%) patients had new radiologic fibrosis appear (5/6 were from the prednisone group).[69] A study of 18 patients with HP (one treated with antigen avoidance; 14 treated with antigen avoidance and prednisone, three treated with prednisone [1/3 also on cyclophosphamide]) reported that of 16 patients with chest imaging data, 8/16 (50%) showed HRCT normalization and 8/16 (50%) demonstrated improvement (no follow-up time specified).[70]

Panel Discussion: The evidence from the studies included in this analysis is of very low-quality. The outcome data differ from the clinical question of interest as the diagnostic utility of medical treatment for HP was not directly assessed.

Collectively the data suggest that clinical improvement with medical therapy is much more common in nonfibrotic HP than in fibrotic HP. However, the guideline panel's confidence in using a patient's response to treatment as an informative step when investigating potential HP, even in patients with nonfibrotic disease, 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 due to chance or patient selection bias). Lastly, treatment initiation may coincide with the patient's clinical improvement but may not be causative. For these reasons, the guideline panel elected to suggest not making a clinical diagnosis of HP based on clinical improvement with medical therapy alone.

Antigen-specific Antibody Testing

Question 7: In patients with suspected HP, should antigen-specific IgA and/or IgG testing be performed?

Recommendation 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).

Voting Results: definitely agree, 11; probably agree, 4; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

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 immunoassay 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.

Summary of the Evidence: Three observational studies evaluating the diagnostic value of antigen-specific antibody testing in HP (e-Table 7a) and nine observational studies providing data on the diagnostic yield of serum antigen-specific IgG/IgA testing were identified (e-Table 7b). Three of these observational studies enrolled subjects with different causes of HP,[3,72,73] while nine of the studies selected BHP cases.[73-82]

A study of 108 patients with suspected ILD evaluated the accuracy of serum antigen-specific IgG testing (serum precipitins) using HRCT imaging plus history of exposure or MDD as the reference standard.[72] The HRCT imaging and exposure history led to an MDD diagnosis of chronic HP in 16/18 (89%) patients regardless of precipitins. Serum precipitins had a sensitivity and specificity that ranged from 39% to 72% and 61% to 68% when using MDD, high confidence HRCT HP findings and positive exposure history, or either a confident HP HRCT finding and positive exposure history as the reference standard. Among these three reference standards, the positive predictive value (PPV) and negative predictive value (NPV) ranged from

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31% to 66% and 33% to 92%, respectively. Sixty percent of subjects with positive precipitins reported no exposure, whereas 32% of subjects with negative precipitins had an identifiable exposure.

In another single-center, observational study that enrolled 31 HP (with an identified exposure and/or compatible clinical, radiological, and histopathological findings) and 91 non-HP ILD cases (HP prevalence 25%), serum precipitins had a sensitivity of 76%, specificity 82%, PPV 69%, and NPV 86%.[73] Twenty percent of subjects with positive precipitins had no identifiable exposure, whereas 25% of subjects with negative precipitins had an identifiable exposure.

A third study, with a much larger cohort of 400 patients (116 with HP and 284 controls), assessed the diagnostic yield of serum-precipitating antibodies or enzyme-linked immunosorbent assay against a panel of antigens most likely to be encountered in a patient's environment based on center-specific predefined threshold values (tests conducted at seven centers across seven countries).[3] The diagnosis of HP was based on clinical, radiological, and histopathological findings and reviewed by an adjudication committee. Serum precipitins had a sensitivity of 78% and a specificity of 69%. The odds of positive serum antigen-specific IgG testing were 2.7- to 10.4-fold higher in HP than in non-HP controls. However, 114/116 (98%) HP patients had an identified exposure.

Nine observational studies evaluated the diagnostic yield of serum antigen-specific antibody testing among patients with BHP (range of n = 14-90, HP cases diagnosed based on predefined criteria).[73-82] The sensitivity of serum antigen-specific antibody testing in these studies ranged from 25% to 96% and specificity ranged from 60% to 100%. Heterogeneity in reported diagnostic utility is likely due to inter-study differences in patient populations, serological methods, type of antigen tested, and test cutoff values used (e-Table 7b). This heterogeneity precluded pooled estimation of the diagnostic yield of serum antigen-specific testing in HP.

Panel Discussion: The diagnostic yield data from these studies were assessed to be very low-quality evidence. Among identified studies, there are diagnostic applicability concerns due to study design (eg, case-control studies), biased subject recruiting (eg, testing subjects with a high pretest probability of disease), small sample sizes (eg, increased risk of random variation of test results), limited information about the clinical context (eg, unclear active exposure status and severity of disease), inappropriate reference standards (eg, diagnosis at the discretion of the referring physician), lack of information on negative tests (eg, true negatives vs false negatives), lack of information on when testing occurred during the diagnostic workup, and lack of test independence (eg, incorporation bias [the results of the test were part of the information used to establish the diagnosis of HP]). The results may also not be generalizable to the many facilities that do not perform serologic evaluation or utilize locally prevalent antigens and only have access to specific panels of antigens available at an outside laboratory.[73,83]

Due to these limitations, the panel concluded there is insufficient evidence at this time to support the utility of serum antigen-specific antibody test 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.

In addition to the limitations of the evidence base, there are noted limitations to the use of serum antigen-specific tests, including cross-reactivity among ubiquitous fungal species and among avian antigens (increasing the risk of false positives), and poorly standardized techniques and antigen preparations (increasing the risk of false negatives).[80,84-89] Studies are emerging on the use of immunoreactive proteins to circumvent the limitations of standard antigen extract preparation. Presently, such preparations are not yet commercially available or representative of all potential causative antigens of individual HP cases (eg, farmer's lung).[77,90,91]

Since the performance characteristics and interpretation of the serum antigen-specific antibody test are often site-specific and influenced by the prevalence of HP in the population being tested (ie, predictive value), the clinician ordering serum antigen-specific antibody testing should understand the validity and reliability of the test and the population sample type and size used to determine its diagnostic performance characteristics.

The utility of serum antigen-specific antibody testing as an exposure assessment tool is a viable topic for further research. Well-designed diagnostic studies focused on demonstrating whether or not serum antigen-specific antibody testing using a standard commercial or center-specific panel routinely identifies an IA that was not suspected by a thorough environmental and occupational exposure history and questionnaire (eg, feather duvet or pillow)[92] are needed. Of note, center-specific panels do not always correlate with the antigen

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preparation of collected samples from the patient environment.[93] This should also be considered in the design of diagnostic studies. Such studies may support the utility of testing to prompt further investigations into IA sources.

Antigen-specific Inhalation Challenge Testing

Question 8: In patients with suspected HP, should antigen-specific inhalation challenge testing be performed?

Recommendation 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).

Voting Results: definitely agree, 10; probably agree, 2; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 3.

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.

Summary of the Evidence: Six observational studies evaluating the diagnostic yield of antigen-specific inhalation challenge (SIC) in a laboratory met inclusion criteria (e-Table 8), including one that enrolled subjects with different causes of HP[94] and five studies that selected BHP cases (BHP cases diagnosed based on predefined study criteria).[79,80,95-97] The studies in this analysis were conducted in three countries: Japan, Spain, and Mexico.

The largest retrospective study (n = 113) evaluated the performance of SIC for diagnosing HP due to a variety of causal agents.[94] According to the diagnostic criteria used (established by chart review; not by MDD), enrolled HP subjects (88 diagnosed with HP, 25 with other lung conditions including four subjects with idiopathic pulmonary fibrosis [IPF]) had high disease likelihood (eg, evidence for exposure to an IA by history, temporal association between a specific exposure and symptoms, characteristic imaging, and/or histopathological findings).[13,79] On chest CT imaging, less than 1/3 of HP subjects had evidence of fibrosis (18% [16/88] had a usual interstitial pneumonia [UIP] pattern). In 32 patients, the antigens used were not soluble so the SIC was conducted by directly exposing the patient to the suspected causal IA in a challenge chamber. Nine patients (8%) experienced transient severe reactions related to SIC testing. Three patients required administration of oral corticosteroids. Twenty-seven percent (24/88) had a false-negative test result, 58% [14/24] had non-avian or fungi causes, and 32% had a UIP pattern on chest CT imaging. The sensitivity, specificity, PPV, and NPV of SIC were 73%, 84%, 94%, and 47%, respectively.

A second retrospective study from the same institution in Spain analyzed the diagnostic yield of SIC (avian sera and pigeon bloom extracts) in 59 of 86 (69%) subjects with BHP, 20 asymptomatic pigeon breeders, and 20 non-HP ILD cases.[79] All HP subjects had a history of current or prior exposure to birds. The sensitivity, specificity, PPV, and NPV of SIC were 92%, 100%, 100%, and 80%, respectively. However, patients with both negative serum antigen-specific antibodies and immediate hypersensitivity skin testing were excluded. Also, if either test was negative (or positive with the lack of clinical or physiologic improvement to antigen avoidance), the SIC test result (and/or BAL, and transbronchial biopsies [TBBs], and/or chest CT findings) was part of the criteria used to confirm the diagnosis of HP. None of the patients had a severe reaction to the test. However, adverse reactions were not described.

Three retrospective studies from the same institution in Japan (which included overlapping patient populations) also analyzed the diagnostic yield of SIC (avian dropping extracts) in BHP but assessed different diagnostic outcomes. In the first study,[95] the degree to which the SIC correlated with a prespecified diagnostic criterion of HP[98] was evaluated in 11 patients with fibrotic BHP and six control subjects (four asymptomatic bird owners and two IPF patients). SIC was part of the HP diagnostic criteria. Eight of 11 (73%) BHP patients exhibited a positive response (including fever, cough, dyspnea), while the remaining three (27%) exhibited a probable response to SIC. None of the control subjects showed a positive or probable response.

The second study sought to identify the most accurate SIC variables (change in WBC% and PA-aO_2 mm Hg) in

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the diagnosis of 28 subjects with BHP (diagnosed by surgical lung biopsy [SLB]) and 19 control subjects, including six HP cases associated with other IA, 12 connective tissue disease cases, and one drug-induced ILD case. In this study, the use of a SIC prediction score (ΔWBC [%] + 2× ΔP [A – a] O_2 [mm Hg]) showed a sensitivity and specificity of 93% and 95%, respectively.[96] Twelve of 28 (43%) in the BHP group and three of 19 (16%) in the control group developed respiratory symptoms (cough and dyspnea) after the SIC. This study was derived from a cohort of 130 subjects with SIC. Two (1.5%) required oxygen and steroid pulse therapies without intubation or an ICU stay.

The third study, with a much larger cohort, aimed to identify clinical variables associated with positive SIC results in subjects with fibrotic BHP.[80] Of 962 hospitalized patients with ILD, 107 (11%) with SIC test results and suspected BHP based on a history of avian antigen exposure, findings on chest CT imaging, findings in lung biopsy, or the results of immunological examinations were analyzed. When performed, the SIC was preceded by BAL and, in the majority of patients, SLB (n = 8) or TBB (n = 68). A history of raising birds (OR, 3.1; 95% CI, 1.2-8.0; $P = .02$) and exposure to birds from the surrounding environment (OR, 7.3; 95% CI, 2.6-20.9; $P = .0001$) were the strongest positive predictors of positive SIC results in patients with chronic BHP. Adverse reactions were not described.

A study of 17 patients with chronic BHP (unclear number with pulmonary fibrosis), 17 with other ILDs (including 13 subjects with IPF), and five healthy bird-exposed control subjects who underwent SIC with pigeon serum reported ROC curves showing that for FVC, the optimal cutoff point was a drop of 16% displaying a sensitivity of 76% and specificity of 81%. For either a drop of 3 mm Hg in PaO_2 or 3% SaO_2 the sensitivity was 88%, while the specificity of these findings was 82% and 86%, respectively.[97] An increase in body temperature > 0.5°C had a sensitivity of 100% and specificity of 82%. The diagnoses of BHP and other ILD were made independently of the results of the SIC. All patients displaying a positive response (17 BHP and three control subjects) had fever and at least one systemic symptom such as headache, shivers, arthralgia, or malaise. Two patients vomited.

In a study of 46 patients (excluded due to inclusion of patient populations that overlap with those of studies included in our analysis) initially diagnosed with IPF, 43% (20/46) were subsequently diagnosed with HP after clinical re-evaluation.[19] Ten subjects with an unidentifiable IA had histopathological features on SLB that were consistent HP (5 had a positive SIC). Of the remaining 10 patients (four had a positive SIC, including one with indicative SLB findings), all had an identifiable IA and six had histopathological features on SLB consistent with HP. Adverse reactions to SIC were not described.

Panel Discussion: Evidence for the diagnostic yield of SIC provided by the observational studies included in this analysis is of very low quality. The potential for diagnostic incorporation bias in several of the included studies further lowers certainty in the evidence. Based on the currently available evidence and documented limitations of the diagnostic utility of SIC for HP, the guideline panel suggests 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. Specifically, evidence is lacking on the utility of SIC findings to provide diagnostic refinement of a working diagnosis above and beyond a thorough environmental and occupational exposure history and questionnaire and preventing the need for a lung biopsy when the clinical context is indeterminate for HP or the CT pattern is not indicative of typical HP. Evidence is also lacking regarding the utility of SIC findings to establish a working diagnosis of HP when histopathologic data are unavailable or where a biopsy has been performed but is nondiagnostic upon multidisciplinary evaluation. The lack of evidence addressing the diagnostic utility of SIC for HP in this context may represent a practice-specific and geographically restricted research opportunity for select centers. It is also unclear what additive discriminative value SIC provides beyond a positive exposure history.

In addition to a lack of standardized techniques, protocols, and test interpretation, validated data on test precision and accuracy in subjects with a provisional multidisciplinary consensus diagnosis, cost (eg, trained personnel and laboratory resources), and safety requirements, adverse reactions can occur following SICs. All these factors may limit widespread implementation. Lastly, efforts to assess the effects of SIC on patient important outcomes (eg, obviate the need for further invasive diagnostic procedures) are warranted.

Specific Lymphocyte Proliferation Testing

Question 9: In patients with suspected HP, should antigen-specific lymphocyte proliferation testing be performed?

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Recommendation 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).

Voting Results: definitely agree, 9; probably agree, 2; neutral (no recommendation for or against), 1; probably disagree, 1; definitely disagree, 0; abstained from voting, 2.

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.

Summary of the Evidence: Four observational studies assessing the utility of antigen-specific lymphocyte proliferation test (LPT) in subjects with BHP (BHP cases diagnosed based on predefined criteria) were identified by the systematic review and met inclusion criteria (e-Table 9).[75,80,95,99]

The challenge of identifying the correct pigeon serum antigen among several proteins of different molecular weights contributing to a distinguishing polyclonal T-cell response was shown in a study of LPT in response to 15 antigenic fractions obtained from pigeon serum in the peripheral blood mononuclear cells (PBMCs) of 11 patients with BHP and 10 non-pigeon exposed healthy volunteers.[99] The study found a wide variety of responses across study groups with no distinctive pattern of reaction in either group. Responses were assessed via the stimulation index, calculated as the mean response to antigen stimulation divided by the mean response of unstimulated cells grown under the same conditions. Nine of the 10 healthy controls responded to some of the fractions, with 50% of controls displaying a significant stimulation index response to at least one antigen fraction. Most BHP patients responded to more fractions and had a higher stimulation index score than control subjects. Despite the heterogeneity of responses, a high molecular weight antigenic fraction (220 kd) was recognized by 73% of BHP patients but only 20% of control subjects.

One study evaluated the clinical factors associated with a positive SIC test result in 107 subjects with fibrotic BHP.[80] The LPT was not found to be a predictor of positive SIC response. Sixteen of 49 (33%) subjects diagnosed with BHP via SIC had a positive LPT, and 14/43 (33%) SIC negative subjects had a positive LPT.

Two additional studies[75,95] from the same medical center evaluated the diagnostic value of LPT in BHP cases in response to pigeon or budgerigar serum. The first study evaluated 10 patients with acute BHP, 14 patients with acute summer-type HP, 35 patients with chronic BHP, and 76 patients with non-HP ILD (not defined).[75] The sensitivity and specificity of LPT in acute BHP and acute summer-type HP from PBMC were 50% and 100%, respectively, and in BAL were 100% for both conditions. In chronic BHP and other chronic non-HP ILDs, the sensitivity and specificity of LPT in PBMC were 46% and 91%, respectively (BAL findings not reported). In the second study, 11/11 BHP patients had positive LPTs and 6/6 control subjects (four asymptomatic bird owners, two IPF cases) had negative LPTs. The LPT was part of the HP diagnostic criteria. All of the patients with chronic BHP had positive LPT responses of PBMC and/or BAL lymphocytes, whereas the four asymptomatic bird owners had negative LPT results.

Panel Discussion: Evidence of the diagnostic yield of LPT provided by the observational studies included in this analysis is of very low quality. In addition to the diagnostic limitations of LPT outlined in the recommendation remark, the panel's 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. For example, among all potential non-bird-related causes, choosing the suspected antigen in subjects with an indeterminate IA exposure history may increase the test's false-negative rate. Moreover, the panel was concerned that the performance characteristics of LPT are misleadingly high in the identified evidence as they were derived from a very select population and limited only to responses to avian antigens.

The LPT requires freshly collected lymphocytes for in vitro culture, exposes workers performing the test to radiation, requires at least a week for results, and suffers from technical variability that limits robust inferences. Furthermore, as an exposure assessment tool, high-quality evidence is lacking on the value of LPT in determining whether the IA is a marker of exposure or an indication that the antigen is involved in the disease process.

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High-Resolution CT Pattern

Question 10: Should patients be clinically diagnosed with HP on the basis of 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?

Recommendation 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).

Voting Results: definitely agree, 15; probably agree, 0; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

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.

Summary of the Evidence: The systematic review identified nine studies evaluating the performance characteristics of HRCT imaging of the chest for establishing the diagnosis of HP in patients with ILD that met inclusion criteria (e-Table 10).[30,100-107]

Early in the course of nonfibrotic HP, a minority of chest HRCT scans may be normal, indicating that a normal chest CT scan does not entirely exclude the diagnosis of HP. In a study of 31 symptomatic pool employees, 11 were clinically diagnosed with nonfibrotic HP and 5/11 (45%) had abnormal HRCT findings (sensitivity of 45%). Of the 20 subjects without HP, all had negative HRCT findings (specificity of 100%).[104] In each HP case, the abnormality consisted of fine (2- to 3-mm), ill-defined centrilobular nodules ranging from subtle to moderately profuse in extent. No lobar predominance was seen.

The evaluation of specific CT features of HP is essential for establishing the level of radiological confidence. A retrospective study evaluated the causes of widespread GGO and the utility of associated findings in distinguishing between causes of diffuse GGO on chest CT imaging in 234 consecutive inpatient and outpatient subjects with diffuse lung diseases.[100] CT scan protocols were varied. Three radiologists blinded to the diagnosis independently reviewed the CT examinations. Twelve (5.1%) study subjects had HP based on prespecified diagnostic criteria, all with diffuse GGO on chest CT imaging. Air trapping was seen in 10/12 (83%) cases resulting in a PPV and NPV of 83% and 99%, respectively. Centrilobular nodules were observed in 8/12 (67%) resulting in a PPV and NPV of 53% and 98%, respectively. The combination of centrilobular nodules and air-trapping had a PPV and NPV of 100% and 98%, respectively.

A retrospective study evaluated the performance of HRCT imaging alone and in combination with clinical data to differentiate chronic ILDs with a predominant ground-glass pattern in 162 subjects (18 [11%] had HP based on prespecified criteria and all had an identified IA).[101] Two radiologists blinded to the diagnosis independently reviewed the CT examinations. A model for HP based on HRCT data that included the presence of centrilobular GGO, lucent lobules, the extent of GGO $>$ 70%, and absence of lower zone predominance had a PPV and NPV of 66% and 97%, respectively. Combining clinical data (exposure to birds and lack of clinical features of connective tissue disease or smoking) with HRCT imaging in the analysis resulted in a PPV and NPV of 84% and 100%, respectively.

Similarly, in a multinational study that included 66 patients (18 with a diagnosis of fibrotic HP, 23 with IPF, and 25 with NSIP based on prespecified criteria), the CT features that best differentiated fibrotic HP from IPF and NSIP were lobular areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower zone predominance of abnormalities.[102] Two independent radiologists, blinded to the diagnoses, assessed the CT images. Interobserver agreement for a confident first-choice diagnosis (70 [53%] of 132 readings) was good to excellent (k = 0.77-0.96).

A second study by the same group that included 63 non-overlapping patients (27 with a diagnosis of fibrotic HP or nonfibrotic HP and 36 with IPF based on prespecified criteria) investigated whether CT scans can distinguish IPF from HP.[103] A CT diagnosis was made with a high level of confidence in 39 (62%) of the 63 patients. In these patients, the CT diagnosis was correct in 35 cases (90%): 23 (88%) of 26 patients with a CT diagnosis of

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IPF and 12 (92%) of 13 patients with a CT diagnosis of HP. Patients with HP were less likely to have honeycombing, traction bronchiectasis, and peripheral or lower zone predominance of disease and more likely to have micronodules than were patients with IPF.

Three studies developed a diagnostic predictive model according to a set of CT images and patient characteristics. In a study that included a derivation cohort of 124 subjects (44 [35%] with HP based on prespecified criteria) and a validation cohort comprising 66 subjects (22 [33%] of whom had HP), a diagnostic predictive model that included patient age, a history of down feather and/or bird exposure, the presence of diffuse craniocaudal GGO, and mosaic perfusion on HRCT imaging had a specificity of 91% and sensitivity of 48% for the diagnosis of chronic HP.[30]

In patients with pulmonary fibrosis, the greater the extent of mosaicism and air-trapping the higher the likelihood of fibrotic HP as opposed to IPF. In a study that analyzed a derivation cohort of 356 subjects (121 [34%] with HP) when CT mosaic attenuation or air-trapping was more extensive than reticulation and the disease had a diffuse and axial distribution, the specificity and sensitivity for diagnosing HP was 90% and 55%, respectively.[105] The same diagnostic model had a specificity of 96% and a sensitivity of 18% in a validation cohort of 424 patients with ILD (66 [16%] with HP).

In a study of 111 subjects with ILD, 38 (34%) with mostly nonfibrotic HP based on prespecified criteria, five independent CT predictors were identified and weighted according to their regression coefficient: ground-glass attenuation nodules (4 points), homogeneous GGO (3 points), patchy GGO (2 points), absence of adenopathy (2 points), and absence of linear/reticular patterns (2 points). A total score of 5 points offered the best trade-off between sensitivity, specificity, and likelihood ratio: 74%, 90%, and 7.7.[106]

In HP, the combination and sharp demarcation of areas of lobules of decreased attenuation reflecting air-trapping, normal lung, and areas of increased ground-glass lung opacification on HRCT imaging form the three-density sign (previously known as the "headcheese" sign),[20,108] which is highly specific for distinguishing fibrotic HP from IPF. In a study by Barnett et al[107] of 102 patients with MDD diagnoses of IPF (n = 57) and fibrotic HP (n = 45), inspiratory and expiratory CTs were evaluated by two readers. Findings were validated in an external cohort from a secondary referral institution (34 with IPF; 28 with fibrotic HP). The three-density sign, when present in three or more lobes, was found to have a specificity of 93% and a sensitivity of 49% for a high confidence diagnosis of fibrotic HP. When the three-density sign was present in five or more lobules and in three or more lobes bilaterally, it had a specificity of 96% and sensitivity of 42%. The same study showed that the presence of three or more lobules of lobular air-trapping in three or more lobes also had high specificity for HP, but the specificity of this finding dropped in the validation cohort. Thus, it is reasonable to regard the three-density sign as being most typical of fibrotic HP. The specificity of mosaic attenuation and lobular air-trapping may vary depending on the observer and on the presence of associated signs of HP.

Panel Discussion: Evidence of the diagnostic utility of the pattern and distribution of CT features provided by the observational studies included in this analysis is of very low quality. 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 IPF can be challenging. In this context, the guideline panel's confidence in the estimated performance characteristic of CT imaging was low for three reasons. First, several studies enrolled neither subjects with true diagnostic uncertainty nor employed 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, the panel suggests 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. The diagnostic performance characteristics of combined findings, such as HRCT features plus the likelihood of an occupational or environmental IA exposure, represent a research opportunity.

Multidisciplinary Discussion

Question 11: For patients with suspected HP, should MDD compared to clinical judgment alone be employed for diagnostic decision-making?

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

Voting Results: definitely agree, 12; probably agree, 0; neutral (no recommendation for or against), 2; probably disagree, 0; definitely disagree, 0; abstained from voting, 1.

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 antigen 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.

Summary of the Evidence: The systematic review identified six observational studies that described the use of MDD for the diagnosis of HP (e-Table 11).[109-114] Five of the included studies compared referral ILD diagnoses based on clinical information and/or histology to subsequent MDD diagnoses and one study compared the agreement on individual diagnoses across seven MDD panels. In the largest retrospective cohort of 938 patients with suspected ILD referred to a tertiary care center for evaluation, 34/938 (4%) had a referral diagnosis of HP. Upon MDD (including a pulmonologist, radiologist, pathologist, and additional consulting specialists as needed) in only 16/34 (47%) was the diagnosis of HP confirmed. An additional 61 patients referred with a non-HP ILD diagnosis received a post-MDD diagnosis of HP.[110] Similarly, in a study of 90 patients referred to two tertiary care centers for suspected ILD, 3/90 (3%) had a referral diagnosis of HP. An additional 11 patients referred with non-HP ILD diagnoses received a post-MDD diagnosis of HP (14/90 [16%]).[111]

In an observational, single-center study of 150 cases discussed during a multidisciplinary team meeting (MDTM), MDD led to a significant increase in the number of HP diagnoses from 11 to 20 cases.[114] The pre-MDD diagnosis of the additional nine HP cases was unclassifiable ILD.

Two studies compared ILD diagnoses from lung biopsy material made by pathologists with interdisciplinary case evaluations. In a study of 88 patients with suspected ILD who underwent SLB, HP was not suspected based on histopathology alone. However, HP was subsequently diagnosed in 3/88 (3%) patients based on the combination of clinical information and histological features and in another 10/88 (11%) following interdisciplinary case evaluation.[112] In another study of 71 patients with suspected ILD who underwent SLB, 8/71 (11%) received an MDD diagnosis of HP. The corresponding pathologists' diagnoses were nonspecific in 3/8 (38%) and included HP in the differential diagnoses for 4/8 (50%). The MDD made a specific diagnosis in one patient whose biopsy was reported as nonspecific fibrosis and in two in whom the original report was resolving pneumonia.[109]

The adverse impact of the lack of standardized, widely used HP diagnostic criteria was noted by a case-control study that assessed MDD agreement on 70 cases of suspected ILD evaluated by multidisciplinary teams at seven international institutions.[113] The study reported inter-MDTM agreement on confident diagnoses of HP ($K = 0.24$), and agreement on diagnostic likelihood (weighted $K = 0.29$; 95% CI, 0.24-0.40) were fair. The MDD diagnosis of HP is influenced by the composition of the multidisciplinary team, the clinical data provided (eg, comprehensive or limited environmental and occupational history), the team's governance and processes, the care setting, and advances in the diagnostic understanding of ILD over time. Some of these challenges were illustrated by a retrospective study of 93 MDD-diagnosed IPF patients, between 1992 and 2010, from eight medical centers who had a pathological diagnosis of UIP by SLB.[115] After a step-wise clinical-radiological re-evaluation, 40/93 (43%) cases were deemed to have HP (11/40, 27% with high probability).

An individual clinician's or MDD consensus working diagnosis of HP may evolve as new information emerges during the longitudinal evaluation (eg, previously unrecognized IA exposure). In a retrospective single-center study of 56 ILD patients initially evaluated over an average of 7 months, reevaluation after additional clinical data and a second HRCT scan became available altered the original HP diagnosis in 7/22 (32%) and increased the interobserver agreement between the pulmonologist and radiologist (k from 0.17 to 0.44).[116] The relevance of the follow-up re-evaluation in changing the initial HP MDD diagnosis is also highlighted by others.[117]

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Panel Discussion: The ILD MDD is a formally organized team meeting of pulmonologists, chest radiologists, and pathologists with experience in ILD and sometimes includes other specialists (eg, rheumatologist, occupational medicine). The MDD aims to enhance the accuracy and confidence of diagnosis through consensus and may also provide recommendations on additional testing and/or a management plan for each patient. Evidence supporting MDD for the diagnosis of HP provided by the observational studies included in this analysis is of low to very low-quality. The evidence suggests that MDD provided a new or altered the preexisting HP diagnosis in a significant proportion of patients and that it may be associated with improved accuracy over individual clinician diagnoses. However, improved accuracy may be attributed to re-evaluation at regular intervals in the context of the MDD. Also, the included study designs did not provide conclusive supportive evidence of the HP MDD diagnosis accuracy, such as prognostic outcome measures among concordant and discordant MDD and pre-MDD HP cases according to the clinical context.

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

BAL Cellular Analysis

Question 12: In patients with suspected HP, should BAL cellular analysis be performed?

Recommendation 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).

Voting Results: definitely agree, 10; probably agree, 3; neutral (no recommendation for or against), 1; probably disagree, 0; definitely disagree, 1; abstained from voting, 0.

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%).

Summary of the Evidence: Following a review of 566 studies, three single-centered retrospective studies describing the diagnostic yield of BAL cellular analysis in HP were identified by the systematic review and met inclusion criteria (e-Table 12).[118-120]

A cohort study of 710 patients with clinical and/or histopathologically diagnosed ILDs (66 with clinically diagnosed HP) evaluated how the likelihood for a given ILD diagnosis changed with the knowledge of BAL cell differentials. All subjects were without immunomodulatory therapy and had a recovery of $\geq$ 25 mL, viability of $\geq$ 75%, and $\geq$ 15% epithelial cells in BAL fluid. When the BAL showed a high granulocytes count ($>$ 4% neutrophils) and a lymphocyte count of $<$ 30%, 30% to 50%, or $>$ 50% the likelihood of HP changed from 9.3% to 3.2%, 35.7%, or 43%, respectively.[118] However, the study presented no data on the HP diagnostic criteria applied, the pretest diagnostic confidence, or the diagnostic accuracy of BAL cellular analysis according to the presence or absence of lung fibrosis.

In a cohort of 77 patients with an MDD diagnosis of HP, 53 (69%) patients underwent BAL (14 with nonfibrotic HP, 39 with fibrotic HP).[119] The median BAL lymphocyte count was higher in nonfibrotic HP (46%; range, 20%-80%) compared to fibrotic HP (19%; range, 11%-41%). No difference was observed in the proportion of nonfibrotic HP and fibrotic HP subjects with a BAL lymphocyte percentage cutoff of $>$ 20%, $>$ 30%, or $>$ 40%.

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In subjects with an MDD consensus diagnosis of HP, the diagnostic performance characteristics of BAL cellular analysis are unclear, and this warrants further study. However, in individuals with fibrotic ILD of unknown cause who are clinically suspected of having IPF and have UIP-like HRCT findings, the cellular analysis of BAL fluid may help separate IPF from other ILDs such as fibrotic HP.[120,121] A retrospective study evaluated the clinical utility of BAL among 95 subjects with undiagnosed fibrotic ILDs and an indeterminate UIP pattern on HRCT imaging.[120] The mean BAL lymphocyte percentage was higher in subjects ultimately diagnosed with fibrotic HP compared to IPF (24.1 ± 15.4 vs 11.4 ± 6.2). Reevaluation of patients driven by BAL fluid results led to a change in diagnosis in 14 patients (15%). However, incorporation bias could not be adequately addressed in this study. In the majority of these cases (11/14 [79%]), the initial diagnosis was changed from IPF to fibrotic HP.

A recent meta-analysis evaluated the performance characteristics of BAL at different lymphocyte % thresholds to discriminate chronic HP from non-chronic HP ILDs or IPF/idiopathic interstitial pneumonia, using individual patient data.[122] If the cutoff level of BAL lymphocyte percentage was set low at 20%, the trade-off is a PPV of 41% (95% CI, 37-44) and 57% (95% CI, 52-62) in suggesting chronic HP vs non-chronic HP ILD and IPF/idiopathic interstitial pneumonia, respectively. On the other hand, if the cutoff level was set high at 50%, more subjects with chronic HP would be captured minimizing false-positives (PPV increases to 60% [95% CI, 51-68] and 78% [95% CI, 68-85], respectively).

Panel Discussion: Evidence of the diagnostic utility of BAL fluid analysis in HP by the observational studies included in this analysis is of very low quality. The BAL fluid analysis varies according to the burden of fibrosis in the lung. Collectively, studies both excluded from and included in this analysis consistently report a higher mean or median lymphocyte count in nonfibrotic HP cases, or likely overestimate the lymphocyte count due to selection bias when combining fibrotic HP and nonfibrotic HP subjects compared to research subjects with fibrotic HP or IPF.

In this body of literature the strength of conclusions that can be drawn is limited by study design issues, such as lack of adequate diagnostic designs, inherent limitations of retrospective studies and the employed patient selection criteria for BAL, and methodological heterogeneity and deficiencies (eg, variable or unreported BAL techniques, fluid collection processing, and quality, when the test was done in the diagnostic process, or incorporation bias, small sample sizes, insufficient adjustment for confounding variables). Specifically, the identified literature does not allow specification of cutoffs that define abnormal increases in BAL cell differential counts or mean difference estimates in lymphocyte counts to accurately distinguish fibrotic HP from other fibrotic ILDs or in modifying the pretest probability of fibrotic HP.

Due to the high risk of bias and absence of appropriate diagnostic accuracy measures in all studies (eg, not establishing the relationship between BAL results and final diagnosis, BAL findings reported without the a priori MDD probability of HP), 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). In this context, 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 (VATS) or transbronchial cryobiopsy (TBC) (eg, fibrotic HP vs IPF). However, the diagnostic value of BAL lymphocytosis is tethered to the integration and quality of the clinical and radiological assessment (eg, fibrotic HP vs NSIP), the BAL protocol, including the BAL cutoff lymphocyte thresholds and confidence intervals according to disease pretest likelihood and confounding factors (eg, age, smoking, systemic corticosteroid therapy, disease severity).

Despite having very low confidence in the reported estimated diagnostic yield of BAL fluid analysis in the HP literature to date, this recommendation places a high value on the importance of establishing the HP diagnosis in a stepwise approach according to the overall

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probability of disease using first the test that is less risky, less invasive, easier to perform, and less expensive in contrast to VATS or TBC. 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.

Lung Biopsy

Question 13: In patients with suspected HP, should lung biopsy be performed?

Recommendation 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).

Voting Results: definitely agree, 10; probably agree, 5; neutral (no recommendation for or against), 0; probably disagree, 0; definitely disagree, 0; abstained from voting, 0.

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 nonfibrotic 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.

Summary of the Evidence: Seven single-center observational studies evaluating the diagnostic yield of lung biopsy in HP were identified during the systematic review and met inclusion criteria (e-Table 13).[19,48,112,119,123-125]

A study of VATS-guided SLBs in 66 patients with suspected ILD reported 16/66 (24%) patients were given a differential diagnosis of HP based on CT findings alone and 21/66 (32%) patients were diagnosed with HP based on biopsy findings alone.[124] Fourteen of the 66 patients (21%) were ultimately given a consensus diagnosis (based on chest CT imaging, lung biopsy findings, and overall clinical findings) of HP. Additionally, 15% (2/13) and 17% (1/6) of patients who received a differential diagnosis of probable or possible UIP, respectively, based on chest CT findings had their diagnosis changed to HP after consensus diagnosis informed by VATS findings.

A study of VATS biopsies in 64 patients with suspected ILDs reported that 3/5 (60%) patients with clinically unclassifiable ILD were subsequently diagnosed with chronic HP following biopsy. Additionally, 4/10 (40%) patients with a pre-biopsy diagnosis of chronic HP were diagnosed with UIP and 2/8 (25%) patients with a preoperative diagnosis of UIP were diagnosed with chronic HP post-biopsy.[125] However, the study did not specify how the ILD diagnosis was made or identify histological features used in the diagnosis.

A study of 46 patients initially diagnosed with IPF found that 20/46 (43%) had a subsequent diagnosis of HP based on additional environmental investigations and clinical testing.[19] Sixteen of the 20 patients (80%) diagnosed with HP had histopathological features on SLB consistent with the diagnosis based on predefined criteria.

In a small (n = 15) retrospective study evaluating the role of SLB in separating chronic HP (diagnosed via predefined criteria) from IPF, most patients (10/15 [67%]) showed diagnostic features of HP in all specimens (ie, bronchiolocentric chronic interstitial pneumonia and/or chronic bronchiolitis and poorly formed non-necrotizing granulomatous inflammation confined to peribronchiolar interstitium), 2/15 (13%) patients showed HP features in one specimen but UIP or nonspecific changes in others, and 3/15 (20%) patients showed non-HP features (UIP or NSIP) in all specimens.[48]

In a proportion of subjects with suspected ILDs, TBC is used as an alternative to SLB for histopathological confirmation at specialized centers with established experience. A recently published prospective multicenter study evaluated the diagnostic accuracy of TBC compared to SLB performed sequentially in 65 subjects requiring lung biopsy to support their ILD diagnosis.[126] Although the initial clinical-radiological confidence before TBC and SLB was not described, the initial consensus histopathological diagnosis and the post-MDD-based final

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diagnosis showed that 15% (10/65) and 23% (15/65) vs 23% (15/65) and 28% (18/65) of cases were diagnosed as chronic HP after incorporating the findings by TBC compared with findings by SLB, respectively. In those with high confidence or definite TBC-supported MDD diagnoses, there was concordance with the SLB-supported MDD diagnosis in 37 (95%) of 39 cases. In 26 unclassifiable or low-confidence TBC-supported MDD diagnoses, six (23%) were reclassified into high confidence or definite diagnoses by SLB-supported MDD diagnosis. Within these six cases, TBC-supported MDD favored IPF in three cases but SLB-supported MDD favored HP with high confidence as the diagnosis. Of the other three cases, HP was favored with TBC-supported MDD but SLB-supported MDD favored IPF in one case.

Compared to SLB or TBC, the yield from smaller TBB specimens in suspected cases is limited. In a retrospective study of 105 TBBs with adequate material from 55 patients with acute HP and 50 controls with non-HP lung diseases evaluated by two pathologists with a fair level of agreement (weighted K = 0.29), 49% of specimens were read by the first pathologist as nonspecific, while 22% of the specimens were read by the second pathologist as nonspecific.[123] A study of the diagnostic utility of TBB in 155 patients with an MDD diagnosis of HP reported TBB findings that were characteristic of HP in 29/72 (40%) of patients who underwent the procedure.[119] TBBs revealed features suggestive of HP (granulomas or giant cells, inflammatory bronchiolitis, cellular interstitial infiltrate) in 26 of 57 (46%) patients with fibrotic HP and in 8 of 15 (53%) patients with nonfibrotic HP. The addition of TBB significantly increased the yield of the procedure regardless of the BAL lymphocyte cutoff used (> 20%, > 30% or 40%).

The importance of the histologic interpretation within a specific clinical and chest imaging context was highlighted by a retrospective study of open lung biopsies in 88 patients with ILDs (10 with HP and 78 with non-HP ILDs).[112] None of the 88 patients was diagnosed with HP based on histology alone. However, three patients were diagnosed based on histology and clinical information, and 10 patients were diagnosed based on interdisciplinary case evaluation.

Panel Discussion: Evidence of the diagnostic utility of lung biopsy in HP from the observational studies included in this analysis is of very low quality.

Based on preliminary evidence, in the correct clinical context, the combination of TBB and BAL might provide a higher diagnostic yield than either technique alone and obviate the need for more invasive testing, such as SLB or TBC. However, further research is needed to validate this observation and to clarify the number of TBBs required for optimal diagnostic yield according to the pretest likelihood and CT confidence. If validated, the combination of TBB and BAL findings may obviate the need for more invasive testing, such as SLB or TBC.

Also, the guideline panel suggests that the yield of TBC may be similar to that of SLB, that a confident diagnosis of HP can be made when high confidence or definite TBC diagnoses of HP are supported by MDD, and that appropriate patient selection is required to optimize the safety and diagnostic yield of this procedure.[126,127] Thus, assessment of the HP pretest probability is essential before considering SLB or TBC, and explicit clinical reasoning in the context of a consensus MDD is recommended to assess the appropriateness of SLB or TBC as the next step of the diagnostic process.

Biopsy interpretation needs to be patient-specific and to consider all the relevant information from the comprehensive exposure history and clinical evaluation. When the pathology interpretation is indeterminate or suggests an alternative diagnosis distinct to the clinical context and/or HRCT findings, re-review of the tissue specimens by a thoracic pathologist in consultation with an ILD team at expert centers is suggested.

The goal of obtaining histological lung biopsy sampling in the diagnostic process is to reduce diagnostic uncertainty and to make optimal decisions for subsequent care. Therefore, considering the disease severity, behavior and patient-related factors (eg, comorbidities, views and preferences), refining the working diagnosis by histological lung biopsy sampling is unnecessary if a definite HP diagnosis is unlikely to change management.

In subjects with an intermediate or low pretest probability of HP, no clinical measures or imaging predictors of HP are currently available that diagnostically distinguish individuals with fibrotic HP from other fibrotic ILDs. Prospective studies are urgently needed that evaluate the clinical utility and validity of molecular markers (eg, peripheral blood, airway brushing, or BAL/TBB as a safe and accessible alternative to SLB or TBC) for the discrimination of fibrotic HP from other fibrotic ILDs among heterogeneous HP patients and for the potential

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enhanced diagnostic accuracy compared to clinical variables alone.

Lung Biopsy Pattern

Question 14: In patients with suspected HP who underwent biopsy, does the presence of non-necrotizing 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?

Recommendation 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).

Voting Results: definitely agree, 13; probably agree, 1; neutral (no recommendation for or against), 0; probably disagree, 1; definitely disagree, 0; abstained from voting, 0.

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.

Summary of the Evidence: Three single-center observational studies reporting on the diagnostic utility of prespecified histological features of HP were identified by the systematic review and met inclusion criteria (e-Table 14).[19,119,123]

Two of the studies evaluated the diagnostic utility of TBB specimens in HP. In the first study of 155 subjects with an MDD diagnosis of HP, TBB was performed in 72 (46%) patients and was found to be characteristic of HP (ie, granulomas or giant cells and inflammatory bronchiolitis or a predominantly mononuclear cellular interstitial infiltrate) in 29 of the 72 (40%) patients.[119] Additionally in this cohort, in 12/26 (46%) patients with < 20% lymphocytes on BAL, TBB specimens were suggestive of HP. There was no difference between nonfibrotic and fibrotic patients (categorized based on chest CT imaging) in the suggestive HP histopathological yield of TBB. The addition of TBB to BAL substantially increased diagnostic yield regardless of the BAL lymphocyte cutoff (20%, 30%, or 40%) used, particularly among subjects with fibrotic HP.

In the second study, an analysis of 105 TBBs from 55 cases of acute HP (based on prespecified diagnostic criteria including the presence of > 22% lymphocytes on

TABLE 4] Diagnostic CT Categories of Nonfibrotic HP Based on CT Patterns

HRCT	Typical Nonfibrotic HP	Compatible With Nonfibrotic HP
Features	Any of the following: • Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones • Inspiratory mosaic attenuation with three-density sign • Inspiratory mosaic attenuation and air-trapping associated with centrilobular nodules ***And*** • Lack of features suggesting an alternative diagnosis	Any of the following: • Centrilobular nodules of ground-glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air-trapping • Patchy or diffuse ground-glass opacity • Mosaic attenuation and lobular air-trapping without centrilobular nodules or ground-glass abnormality ***And*** • Lack of features suggesting an alternative diagnosis

In a nonsmoker, the presence of diffuse, profuse, poorly defined ground-glass centrilobular nodules is highly suggestive of the diagnosis of hypersensitivity pneumonitis (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. HRCT = high-resolution CT.

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TABLE 5] Diagnostic CT Categories of Fibrotic HP Based on CT Patterns

HRCT	Typical Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP
Features	CT signs of fibrosis with either of the following: • Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones • Inspiratory mosaic attenuation with three-density sign ***And*** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis with any of the following: • Patchy or diffuse ground-glass opacity • Patchy, nonprofuse centrilobular nodules of ground-glass attenuation • Mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP ***And*** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis without other features suggestive of HP

CT signs of fibrosis include any of the following: reticular or ground-glass abnormality with traction bronchiectasis or bronchiolectasis; lobar volume loss; honeycombing. The distribution of fibrotic hypersensitivity pneumonitis (HP) is quite variable and often not diagnostically helpful. However, a mid-lung 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. HRCT = high-resolution CT.

BAL cell analysis) and 50 matched control samples was performed by two independent pathologists.[123] As many as 49% of the TBB findings were read as nonspecific. Diffuse lymphocytic infiltration was better than loosely formed granuloma to discriminate acute HP from control samples (likelihood ratio, 9.1 [CI, 2.2-37.0] vs 1.8 [CI, 0.5-6.9]). On the overall assessment of the TBB findings, 11/105 (10%) specimens were considered probable acute HP by the first observer (likelihood ratio, 1.1; CI, 0.35-3.35), as opposed to 39/105 (37%) biopsy specimens identified as probable acute HP by the second observer (likelihood ratio, 2.64; CI, 1.44-4.84).

In contrast to the first study that found that TBB specimens increased the diagnostic likelihood of HP, particularly when combined with BAL results, TBB specimens in the second study were of limited usefulness for diagnosis despite assessing cases with a much higher pretest likelihood for HP. This discrepancy may be explained by selection bias and random variation in the sampling of patients and not controlling for the independent effects of the number and small sample size of TBBs.

In a study of 46 patients initially diagnosed with IPF based on 2011 guidelines,[128] a subsequent diagnosis of chronic HP was made using bronchial challenge testing results, IgG antibody testing results, and/or lung tissue obtained by SLB or explants in 20 (43%).[19] Two pathologists re-examined the biopsy specimens. Sixteen of the 20 subjects subsequently diagnosed as having chronic HP had evidence of HP, based on prespecified histopathological criteria, on SLB. This indicates that SLB specimens help separate HP from other forms of diffuse lung disease and highlights the importance of multidisciplinary review.

Lastly, in addition to the qualitative tissue characterization, quantification of HP features can help separate HP from other types of ILD. For example, in a series of 28 SLB cases originally diagnosed as HP or connective tissue disease-associated interstitial lung disease (CTD-ILD) that were subsequently reviewed blind without knowledge of the original diagnosis, a diagnosis of HP was more common in the presence of peribronchiolar metaplasia (12/16 HP vs 4/12 CTD; OR, 6.00; 95% CI, 1.15-31.2) and in patients with a greater

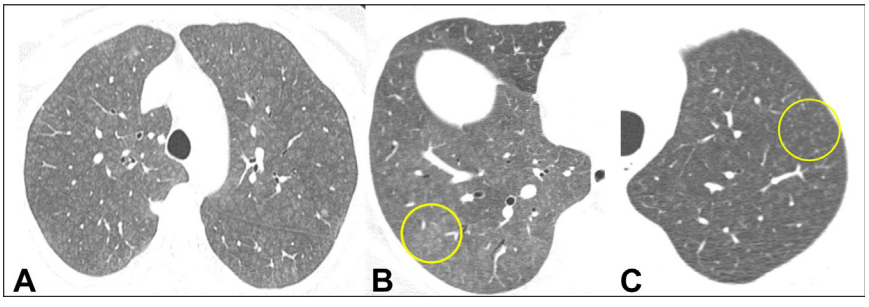

Figure 2 – *Poorly defined centrilobular nodules of ground-glass attenuation in three different patients with nonfibrotic hypersensitivity pneumonitis (HP), selected to show the range of CT appearances for this finding. A,* ***Typical nonfibrotic HP*** *with profuse centrilobular nodules in the upper 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****.*

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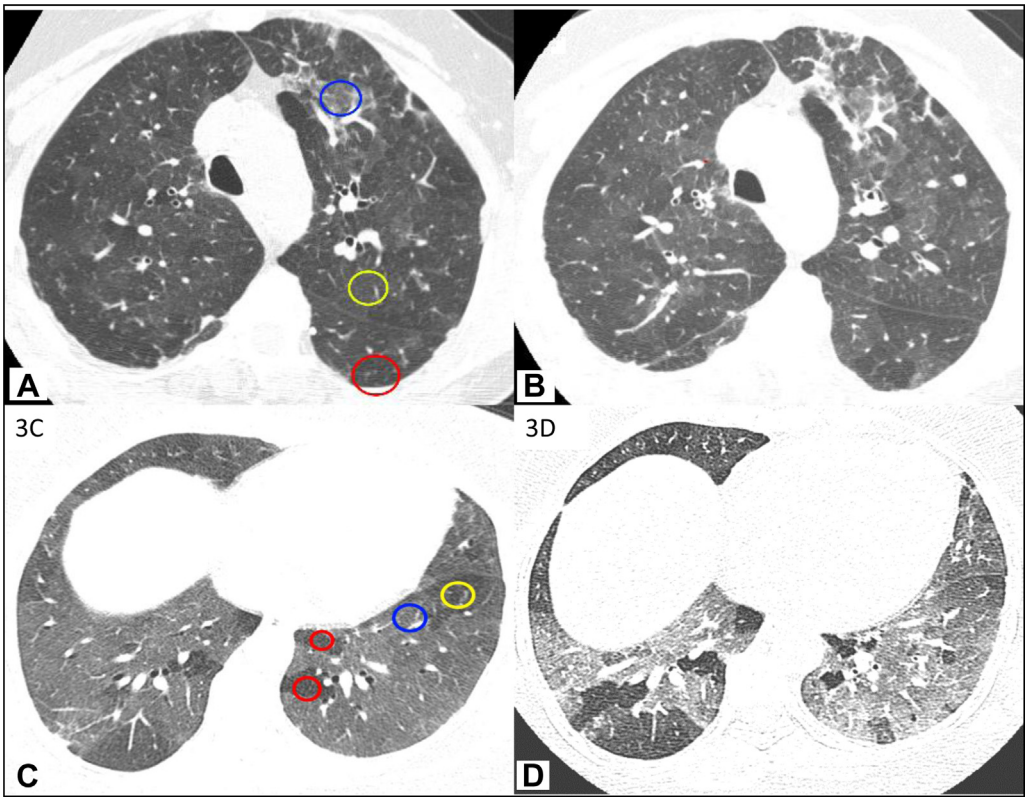

Figure 3 – ***Two examples of three-density sign in patients with nonfibrotic hypersensitivity pneumonitis.*** *A, Inspiratory CT imaging shows patchy ground-glass attenuation in the anterior left upper lobe (blue circle). Other lobules are of preserved (normal) attenuation (yellow circle), and there is lobular decreased attenuation in the posterior left lung (red circle). No signs of fibrosis are present. B, Expiratory CT imaging accentuates numerous lobules of decreased attenuation representing air-trapping. C, Inspiratory CT imaging in a different patient 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. D, Expiratory CT imaging accentuates numerous lobules of decreased attenuation representing air-trapping.*

fraction of bronchioles showing peribronchiolar metaplasia (0.41 ± 0.33 vs 0.16 ± 0.27).[129] All biopsies showed interstitial fibrosis in various patterns. Similarly, a recent cohort study that included 23 SLB, including 10 with fibrotic HP and 13 with UIP/IPF also reviewed blind without knowledge of the original clinical-radiological-pathological diagnosis, pathologic variables associated with a higher MDD-based confidence of fibrotic HP, included an increased fraction of bronchioles with peribronchiolar metaplasia, increased foci of peribronchiolar metaplasia/cm^2, and presence of giant cells/granulomas.[130] Again, in these two studies, a final confident diagnosis required multidisciplinary correlation with imaging and clinical findings.

Panel Discussion: Evidence of the diagnostic utility of histological features provided by the observational studies included in this analysis is of very low quality. The guideline panel does not suggest performing lung biopsy in subjects with a high level of pre-biopsy diagnostic certainty. In this subgroup of subjects with a high level of diagnostic certainty, the data suggest that the finding of HP histopathological features by TBB is possibly much less than 50%, suggesting that negative TBB specimens should not be used to rule out HP (eg, sampling error, inadequate or nondiagnostic specimens[131]). However, in the context of MDD, the clinician should consider that pathological TBB findings supportive of HP together with BAL lymphocytosis may preclude the need for more invasive testing such as SLB or TBC (see Recommendation 12). A question that remains unanswered is the minimum number of TBB or TBC specimens required to provide the optimal balance between diagnostic yield and complication rate. Additionally, research is needed on the additive value of BAL fluid analysis coupled with either biopsy method in patients with intermediate pretest probability of HP of varying severity.

In contrast to the aforementioned studies evaluating the diagnostic utility of TBB, findings from cohort studies reporting on histopathological findings by SLB in subjects with HP, excluded from this analysis due to indirectness, describe a higher prevalence of

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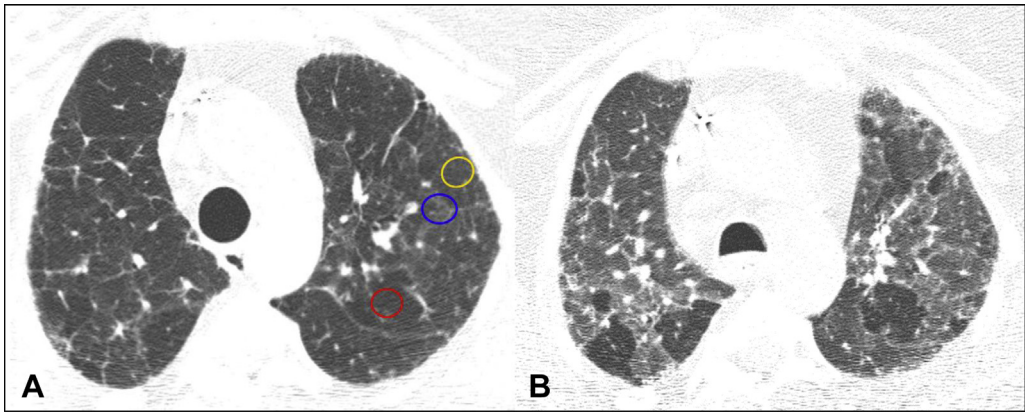

Figure 4 – ***Typical fibrotic hypersensitivity pneumonitis*** *(HP) with three-density sign. A, CT scan shows patchy ground-glass attenuation (blue circle). Other lobules are of normal attenuation (yellow circle), and there are several lobules of decreased attenuation (red circle). Mild subpleural reticulation is present. B, Expiratory CT scan accentuates numerous lobules of decreased attenuation representing air-trapping.*

lymphohistiocytic inflammatory changes (eg, histiocytes often loosely clustered, forming poorly formed granulomas and occasionally fusing into multinucleated giant cells, cellular infiltration that involves the walls of the small airways with extension into the lung parenchyma surrounding the airways) in HP. However, these features were found with less consistency and were replaced by fibrosis in advanced cases of HP.[48,132-137] These studies suggest that the biopsy at this point may show a UIP-like pattern and that the presence of any bronchiolocentricity or significant peribronchiolar metaplasia (ie, replacement of alveolar pneumocyte epithelium by airway epithelium commonly found directly adjacent to small bronchioles) may indicate fibrotic HP. However, these findings are nonspecific and often subtle, suggesting clinicians should not rely only on the histopathological findings for diagnosis but may need to integrate biopsy results with clinical variables for individual cases considered by consensus-based MDD.[138,139]

No studies evaluating the diagnostic performance characteristics of TBC in modifying the pretest likelihood of HP have been reported. However, results of a recent prospective multicenter study that evaluated the diagnostic accuracy of TBC in 65 patients with ILD and an indication for SLB suggests a confident diagnosis of an ILD, such as HP, made by TBC can be given similar weight in the context of MDD as a diagnosis made by SLB (see Recommendation 12).[126] In patients with suspected HP, the decision to obtain TBC or SLB for tissue diagnosis should be individualized for every patient. One crucial factor with regard to TBC, is the experience and confidence of individual pathologists

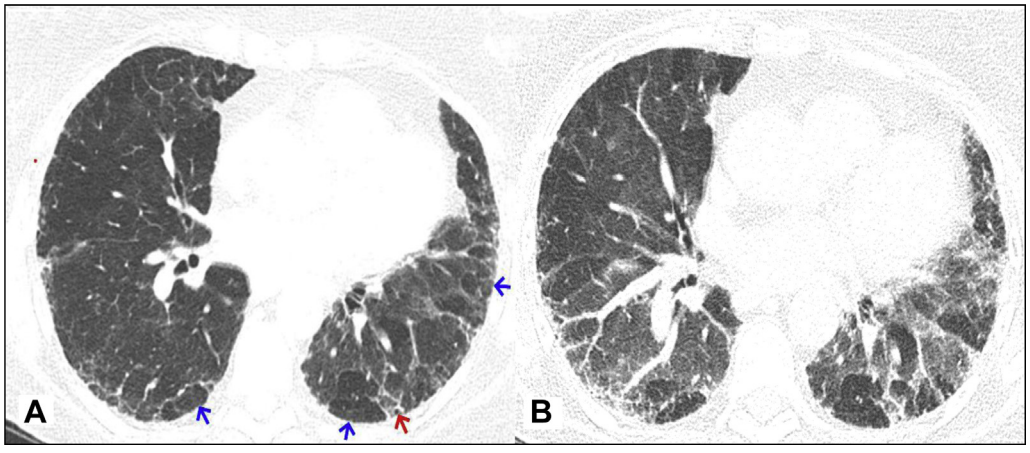

Figure 5 – *Mosaic attenuation and air-trapping compatible with fibrotic hypersensitivity pneumonitis. A, CT imaging shows reticular abnormality with architectural distortion and mild traction bronchiolectasis (red arrow) indicating fibrosis. Multifocal lobular mosaic attenuation is present (blue arrows). B, Expiratory CT imaging confirms multifocal air-trapping.*

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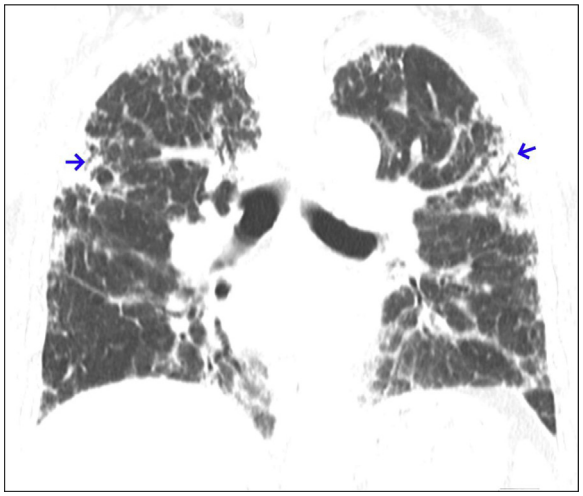

Figure 6 – ***Fibrotic hypersensitivity pneumonitis***. *Coronal CT imaging shows upper lung predominant reticular abnormality with architectural distortion and traction bronchiectasis (arrows).*

(generally trained in evaluating larger SLB samples), as this may impact the diagnostic performance of TBC. TBC performed at expert centers may be used to provide histopathologic findings for MDD diagnosis, as an alternative to SLB, if tissue with diagnostic histologic lesions is sampled.[127]

Pathogenesis and Diagnostic Evaluation

Antigen Recognition and Sensitization

The identification of lymphocytes comprising the majority of infiltrating effector cells in the alveolar walls, interstitium, and peribronchiolar parenchyma place the adaptive immune response at the center of early pathogenesis in HP.[140,141] Following inhalation, the IA recognition by antigen-presenting cells (APC), such as dendritic cells and macrophages, initiates an adaptive immune response that is specific and has memory. While B cells recognize IA determinants via surface immunoglobulin receptors, CD4+ and CD8+ T cells recognize IA determinants by the T-cell receptor coupled with class II or I major histocompatibility complex (MHC) molecules on the cell surface of APCs, respectively. Primed antigen-specific T- and B-cells lung homing is then followed by clonal expansion and differentiation into memory and effector subsets.[142,143] These processes are directed by the expression of specific cytokine and chemokine receptors and their activation by cytokines/chemokines released by infiltrating and tissue-resident cells.

The resulting alveolitis is commonly self-limited and transient. Elimination of the IA terminates activation signals for B cells. Likewise, the lack of IA/MHC activation signals for T cells causes them to lose their cytokine receptors, stopping cytokine production. The adaptive immunity then recedes to a resting state. However, after IA sensitization, if exposure continues, a subgroup of subjects will develop HP. The antibody repertoire driven by antigen-specific clones of memory B cells is large enough to ensure that there will be an antigen-biding site to fit almost any potential antigenic determinant.[140,143] However, the current narrow set of serum IgG laboratory tests does not capture the formidable diversity of antigen-antibody complexes (sensitization; see Recommendation #7).

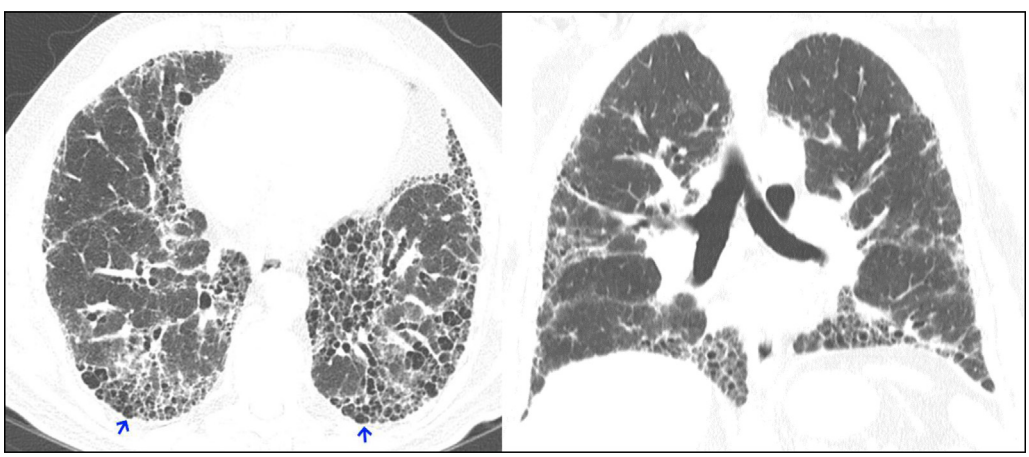

Figure 7 – *Usual interstitial pneumonia pattern,* ***indeterminate for fibrotic HP****. Axial and coronal CT images show lower lung predominant, subpleural predominant reticular abnormality with traction bronchiectasis and subpleural honeycombing (arrows). There are no imaging features to suggest hypersensitivity pneumonitis; the diagnosis was based on exposure and surgical biopsy.*

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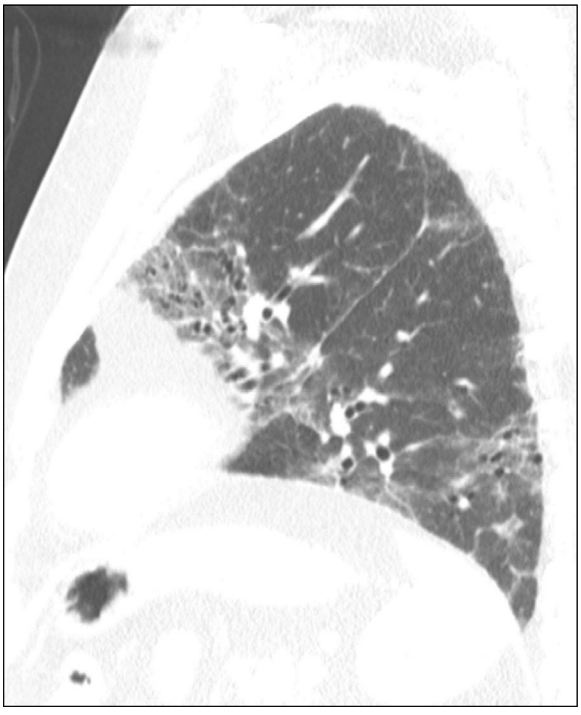

Figure 8 – ***Fibrotic hypersensitivity pneumonitis with mid-lung predominance***. *Sagittal CT section shows reticular abnormality and traction bronchiectasis with peribronchovascular extension and mid-lung predominance.*

Environmental and Host Factors

The presence of additional host and environmental risk factors[15,144,145] and genetic susceptibility, usually associated with the MHC, have been linked to the development of HP. Polymorphisms in the MHC genes involved in antigen recognition/processing and immune responses, including HLA-DR and HLA-DQ,[146-148] transporter-associated antigen processing,[149] tissue inhibitors of matrix metalloproteinases,[150] immunoproteasome catalytic subunit β type 8,[151] and the TNF-α promoter,[146,152] are associated with increase susceptibility to HP. Also, familial clustering of patients with HP exposed to a variety of IAs, including among related family members living in different environments, has been reported.[146,153,154] Additional genetic factors have been associated with a UIP pattern on histology and CT imaging. The MUC5B promoter variant rs35705950 and mutations in genes associated with telomere biology have been correlated with an increased risk of pulmonary fibrosis development.[155,156]

In sensitized and susceptible individuals, the presence of primed antigen-specific, long-lived memory T and B cells helps orchestrate a robust secondary dysfunctional immune response upon re-encountering the IA. During the disease course, CD4+ T cells (Th0) can differentiate into several functional subclasses. Th1 cells and their related cytokines (IFN-γ, TNF-α, and IL-2), which characterize HP, promote granuloma or formation of multinucleated giant cells. Also, the recognition of IAs by Toll-like receptors on APCs can enhance antigen-specific adaptive immune responses, facilitating granulomatous lung inflammation induced by inhaled IAs.[157,158]

Fibroinflammatory Lung Injury and Development of Fibrosis

As the disease progresses to fibrosing interstitial pneumonia, mononuclear cell recruitment is enabled by endothelial activation with the expression of adhesion molecules and the release of chemokines by inflammatory/immune cells. This compromises the epithelial-endothelial barrier integrity and accentuates the IA-mediated inflammatory response.[159,160] Likewise, fibroblast and fibrocyte migration and epithelial to mesenchymal transition provoke the expansion of the fibroblasts/myofibroblasts population and ultimately the accumulation of extracellular matrix and abnormal lung remodeling.[160,161] Progression to fibrosis is at least partially associated with changes of cytokine patterns, which may shift over time. Changing from a Th1 to Th2 or Th17 environment in the context of impaired regulatory T cells and a decrease of γδT-cell activity can promote a proinflammatory milieu, contribute to fibroblast growth, differentiation, and extracellular matrix synthesis leading to fibrosis.[162-165] However, the molecular mechanisms that sustain disease progression are not understood.

In HP, gene expression is enriched with adaptive immune responses and B-cell receptor signaling.[156,166,167] However, fibrotic HP pathway analyses also exhibit developmental pathways such as those involved in epithelial cell development and extracellular matrix-receptor interaction. In a subset of HP cases, despite complete IA avoidance, alveolar epithelial injury and subsequent aberrant repair, abnormal fibroblast proliferation, extracellular matrix remodeling, excessive collagen deposition, and destruction of the lung architecture occur as a direct consequence of chronic inflammation or by the independent or mutually interacting mechanisms of lung inflammation and fibrosis.[156,168]

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TABLE 6] 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	Figure 2
Ground-glass opacification	Ground-glass opacification is increased lung attenuation through which normal pulmonary structures can still be identified. In HP, ground-glass opacifications have a patchy or diffuse distribution in the axial plane and are often associated with mosaic attenuation and/or evidence of lung fibrosis	Figure 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 imaging[173]	Figures 3, 4, 5
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).[20,108] 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 decrease vessel size due to air-trapping, occurring within the same lobe. The lobules of decreased attenuation are accentuated on expiration	Figures 3, 4
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	Figure 5
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 imaging	Figures 3, 4, 5
Fibrosis	Fibrosis is identified by the presence of any or all of the following: reticular pattern or ground-glass opacification with traction bronchiectasis or bronchiolectasis, lobar volume loss; and honeycombing. The diagnosis of fibrosis should not be made when reticular abnormality is present without other confirmatory signs	Figures 6, 7, 8

HP = hypersensitivity pneumonitis.

Exposure Assessment

A detailed medical history that includes a comprehensive environmental and occupational exposure history is critical to establishing the IA source. IA identification provides the best pretest estimate of HP likelihood and will influence the predictive value of any subsequent test and the diagnostic accuracy of the initial multidisciplinary assessment (see Recommendation #1).

A structured questionnaire incorporated during the initial information-gathering process can prevent the premature conclusion that the exposure history is negative, aid patient recall, save time when completed prior to a scheduled clinic visit, and ensure consistency (Table 3).[169-172] A questionnaire also facilitates clinician-patient communication by enabling a structured review of exposure details that may require further clarification.

Inciting antigen characterization is iterative, and as information gathering continues, the goal is to develop a more precise and complete understanding of the environmental and/or occupational exposure and integrate the generated pretest likelihood (eg, mostly informed by the exposure history) with the overall clinical context. Therefore, as opposed to dichotomizing the exposure into "yes" or "no," we suggest as depicted in Table 3 the categorization of the IA exposure based on the degree of certainty: identified, indeterminate, unidentified.

An IA is *identified* when there is sufficient evidence of an association between the IA and the lung disease. This association can be informed by causal inference such as the strength of association, reversibility, temporality, dose-response, and consistency of the association between the IA and symptoms or progression of lung disease. An IA is *indeterminate* if evidence is suggestive but not sufficiently conclusive of an association. For example, a likely IA source may be identified but a temporal relationship with symptoms is not clear. Over time the strength of the effect of an IA on the occurrence

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TABLE 7] Histologic Diagnostic Criteria for Nonfibrotic HP Pattern

Typical Nonfibrotic HP	Compatible With Nonfibrotic HP	Indeterminate for Nonfibrotic HP	Alternative Diagnosis
Major Features Presence of all four major features in at least one of the sampled lobes of lung: 1) Small airway distribution (bronchioles and/or alveolar ducts) 2) Uniform cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis); may include regions with a cellular NSIP pattern 3) Inflammation consisting of mostly lymphocytes 4) Interstitial scattered, usually single, poorly formed non-necrotizing granulomas and/or multinucleated giant cells **Minor Features** a) Organizing pneumonia, small foci b) Foamy macrophages c) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals (Fig 10) ***And*** **Lack of** Features suggesting an alternative diagnosis (see column 4)	**Major Features** Presence of these three major features in at least one of the sampled lobes of lung: 1) Small airway distribution 2) Cellular interstitial inflammation causing cellular bronchiolitis and/or interstitial pneumonia (including a cellular NSIP pattern) 3) Inflammation consisting mostly of lymphocytes **Minor Features** a) Organizing pneumonia, small foci b) Foamy macrophages c) Cholesterol clefts, Schaumann bodies, calcium oxalate crystals (Fig 10) ***And*** **Lack of** 1) Poorly formed non-necrotizing granulomas 2) Features of an alternative diagnosis (see column 4)	Biopsies that show an interstitial lung disease pattern that does not meet criteria for ***Nonfibrotic HP, Compatible with Nonfibrotic HP***, or an ***Alternative Diagnosis*** **Comment:** There is uncertainty about the histologic features in these cases that raise the consideration of nonfibrotic HP as well as other differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not Note: Cellular NSIP pattern is in this category	A biopsy favoring other processes such as: Primary small airway disease (ie bronchiolitis from a variety of causes) is usually distinguishable since the findings are restricted to the small airways and there is a lack of appreciable involvement of the surrounding alveoli ***Other Interstitial Lung Diseases*** • Sarcoidosis (well-formed granulomas that may coalesce in a lymphatic distribution) • Aspiration (bronchiolocentric inflammation frequently with foreign material and giant cell or histiocytic reaction). Tends not to be as uniform and diffuse as HP • Connective tissue disease, drug induced lung disease, immunodeficiency (increased plasma cells, prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, pleuritis, granulomas) • Respiratory bronchiolitis or other smoking-related lesions (bronchiolocentric pigmented alveolar macrophages) • Granulomatous infection (robust, frequent necrotizing granulomas, especially mycobacterial, and fungal infections) • Pneumoconiosis/occupational exposures (flock workers-lymphocytic bronchiolitis and lymphoid hyperplasia; berylliosis – well-formed granulomas, BADE[a]) • Langerhans cell histiocytosis (peribronchiolar cellular infiltrates of Langerhans cells with or without cavitation and/or fibrosis)

HP = hypersensitivity pneumonitis; NSIP = nonspecific interstitial pneumonia.
[a]Lymphocytic bronchiolitis, alveolar ductitis, and emphysema in industrial machine manufacturing workers.

TABLE 8] Histologic Diagnostic Criteria for Fibrotic HP Pattern

Typical Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP	Alternative Diagnosis
Major Features Presence of all three major features in at least one of the sampled lobe(s) of lung: 1) Regions where small airway-centered fibrosis is clearly present with or without peribronchiolar metaplasia 2) Fibrosing interstitial pneumonia affecting at least one sampled area/lobe of lung parenchyma with regions showing one or more of the following patterns a) NSIP-fibrosing pattern b) UIP-pattern c) Fibrosing pattern that is difficult to classify d) Fibrosis that is solely peribronchiolar 3) Poorly formed noncaseating granulomas ***Or*** Fibrosing interstitial pneumonia meeting only major feature #2 in at least one lobe, as well as all criteria for ***Typical Nonfibrotic HP*** in a separate lobe(s) **Minor Features** a) Organizing pneumonia, small foci b) Focal peribronchiolar metaplasia c) Foamy macrophages d) Cholesterol clefts ***Lack of*** Features of an alternative diagnosis (see column 4)	**Major Features** Presence of these two major features in at least one of the sampled lobe(s) of lung: 1) Regions where small airway-centered fibrosis is clearly present with or without widespread peribronchiolar metaplasia[a] 2) Fibrosing interstitial pneumonia affecting at least one sampled area of lung parenchyma with one or more of the following patterns a) NSIP-fibrosing pattern b) UIP-pattern c) Fibrosing pattern that is difficult to classify d) Fibrosis that is solely peribronchiolar e) Depending on the morphology this category could include some bronchiolocentric interstitial pneumonias. See Table 9. ***Or*** Fibrosing interstitial pneumonia meeting only major feature #2 in at least one lobe, as well as criteria for ***Compatible with Nonfibrotic HP*** in a separate lobe(s) **Minor Features** a) Organizing pneumonia, small foci b) Focal peribronchiolar metaplasia c) Foam cells d) Cholesterol clefts, Schaumann bodies or calcium oxalate crystals (Fig 10) ***Lack of*** a) Poorly formed non-necrotizing granulomas b) Features of an alternative diagnosis (see column 4)	Cases that show a pattern of fibrosing interstitial lung disease that does not meet the criteria for the pattern of ***Fibrotic HP, Compatible with Fibrotic HP*** or an ***Alternative Diagnosis*** **Comment:** There is uncertainty about the histologic features in these cases that raise the consideration of ***Fibrotic HP*** as well as other differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not Note: Fibrotic NSIP and UIP patterns are in this category. Depending on the morphology, this category could include some bronchiolocentric interstitial pneumonias. See Table 9.	A biopsy that shows definitive features of other interstitial lung diseases such as: • Fibrosing sarcoidosis (well-formed granulomas in a lymphatic distribution, perigranulomatous fibrosis is common,[192] inflammation is inconspicuous) • 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[193,194]) • Fibrosing interstitial pneumonia in connective tissue disease,[129,195] drug-induced lung disease, or immunodeficiency[196] (prominent lymphoid hyperplasia and/or cellular interstitial lymphoid infiltrates, marked pleuritis, with or without granulomas) • Smoking-related patterns (airspace enlargement with fibrosis—which overlaps with smoking related interstitial fibrosis—which is usually accompanied by respiratory bronchiolitis and emphysema[197,198]) • Pneumoconiosis/occupational exposures (asbestos, hard metal, BADE[b])[199-201] Fibrotic pulmonary Langerhans cell istiocytosis

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

[a]Widespread means peribronchiolar metaplasia affects > 50% of the bronchioles.[129]

[b]Lymphocytic bronchiolitis, alveolar ductitis, and emphysema in industrial machine manufacturing workers.

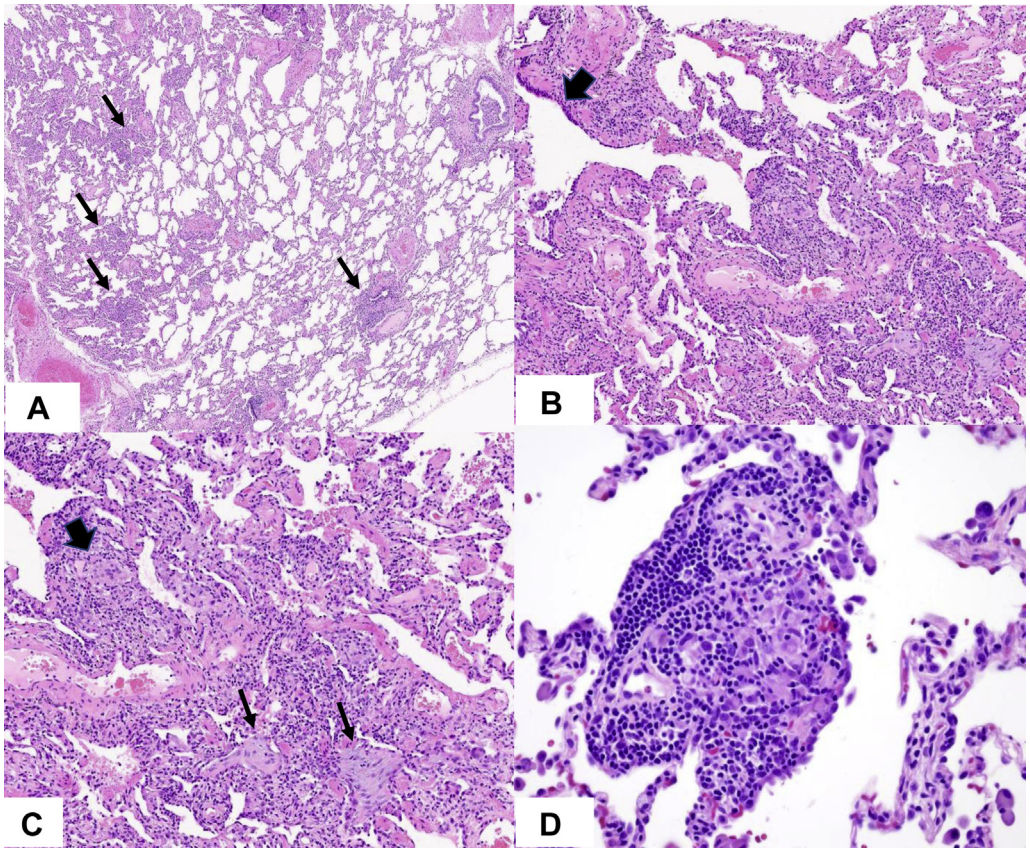

Figure 9 – ***Typical nonfibrotic hypersensitivity pneumonitis pathologic pattern.*** *A, Low power shows a bronchiolocentric distribution. Low power shows patchy nodules of chronic inflammation centered on bronchioles (arrows). B, This bronchiole (arrowhead) is infiltrated by chronic inflammation, which extends into the surrounding peribronchiolar interstitium. C, Higher power of the image in panel B shows a poorly formed granuloma (arrowhead), and small foci of organizing pneumonia (arrows) are present. D, This poorly formed granuloma consists of a loose cluster of epithelioid histiocytes surrounded by lymphocytes.*

of HP may change as the prevalence of other host factors such as lung fibrosis changes. In a sizable group of patients, the IA remains unrecognized for several reasons. Thus, the term *unidentified* IA. An antigen should only be considered unidentified after a thorough clinical assessment that includes a history and exposure questionnaire.

Subjects with an indeterminate IA, suspected occupational exposure, or identified IA requiring quantification of the severity, remediation, and monitoring may require additional evaluation beyond a standard occupational and environmental history. Under these circumstances, an occupational medicine specialist and/or certified environmental hygienist may be of help (see Recommendation #2). Under the guidance of a multispecialty expert team, on a case-by-case basis, qualitative home or worksite assessment (eg, systematic walkthrough investigation) may help inform the pretest likelihood of an indeterminate IA exposure (Table 3).

HRCT Evaluation

CT Image Quality and Diagnostic Categories

High-resolution CT imaging using standardized techniques including expiratory imaging is far more accurate than chest radiographs in assessing the extent, distribution, and pattern of disease and can be critical for making the diagnosis of HP. Images should be obtained on full inspiration and expiration and should be free of respiratory motion. Expiratory imaging is critical to show geographic air-trapping. Coronal reconstructions should be included to show the craniocaudal and axial distributions of abnormality. Examples of technical recommendations for performing high-resolution chest CT imaging may be found at https://www.acr.org/-/media/ACR/Files/Practice-Parameters/HRCT-Lungs.pdf).

After assessing the image quality and the presence, distribution, and extent of CT features, we suggest classification of chest imaging patterns into nonfibrotic

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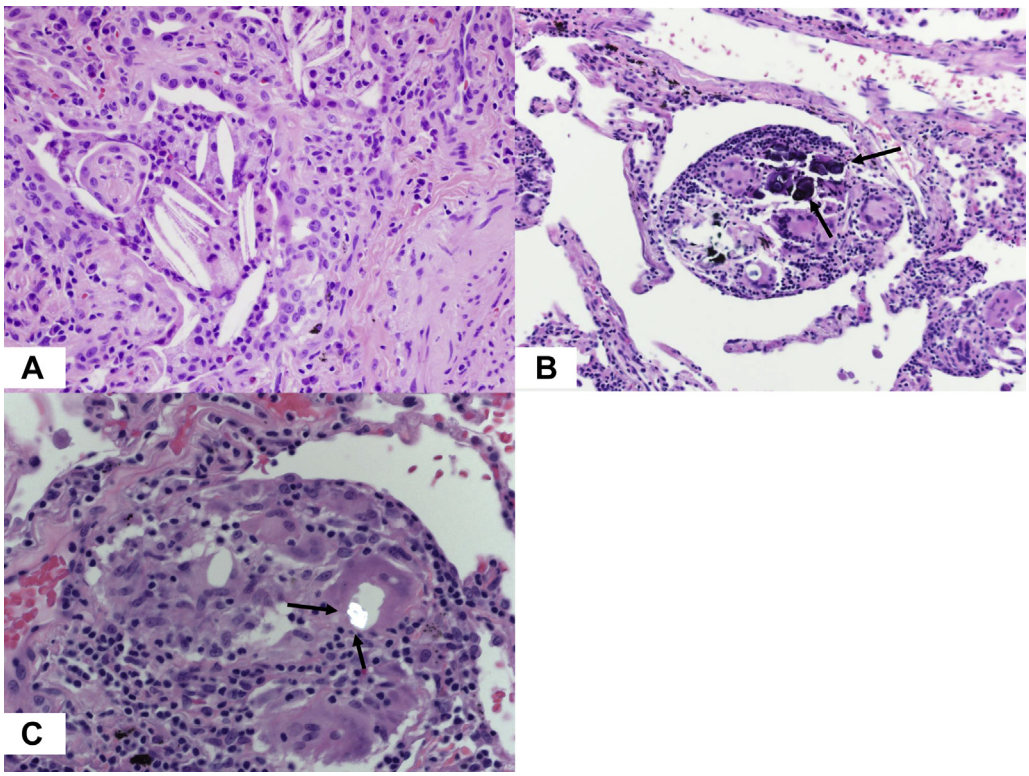

Figure 10 – ***Nonspecific inclusions.*** *A, Cholesterol clefts are surrounded by epithelioid histiocytes and giant cells. B, Schaumann bodies: This granuloma consists of multinucleated giants cells and epithelioid histiocytes. Laminated calcifications (arrows) represent Schaumann bodies. C, A birefringent calcium oxalate crystal is present within the cytoplasm of this giant cell in a poorly formed granuloma. This crystal appears bright white under polarized light (arrows).*

or fibrotic (Tables 4 and 5). Non-fibrotic abnormality is classified as *typical for HP* (Figs 2A, 2B, 3) or *compatible with HP* (Fig 2C). Fibrotic abnormality is classified as *typical for HP* (Fig 4), *compatible with HP* (Fig 5), *or indeterminate* (Figs 6, 7, 8). The indeterminate category is used when pulmonary fibrosis of any pattern is present without specific features of HP. The radiological confidence level should then be integrated with the patient's exposure likelihood and clinical information, with subsequent review in an MDD. Such a review should occur prior to considering and determining if invasive testing will significantly alter the posttest probability of HP and optimize decision-making (Fig 1).

Key HRCT Diagnostic Features and Differential Diagnosis

Evaluation of the CT scan begins with a precise description of the CT findings. Characteristic CT features of HP include centrilobular nodules, GGO, mosaic attenuation, and multilobular air-trapping. These features are usually more common and more extensive in nonfibrotic than in fibrotic HP. The features are defined in Table 6,[20,108,173] but some further comments and differential diagnosis are provided below.

Centrilobular Nodules: In HP, centrilobular nodules are often present diffusely in the axial plane, and in the craniocaudal plane may have an upper and mid-lung predominance, or may be diffuse.[174,175] The profusion of these nodules varies: diagnostic confidence is highest when the nodules are profuse (Fig 2A). When the nodules are relatively sparse, diagnostic confidence is correspondingly lower, and the appearance may be regarded as compatible with HP rather than typical HP (Fig 2C).

The centrilobular nodules of HP can be distinguished from the perilymphatic nodules of sarcoidosis, which predominate along the peribronchovascular, septal and subpleural interstitium, and from miliary nodules, which are randomly distributed.

In addition to HP, poorly defined centrilobular nodules of ground-glass attenuation may occur in patients with respiratory bronchiolitis due to cigarette smoking,[176,177] but are usually sparser and patchier than in typical HP.

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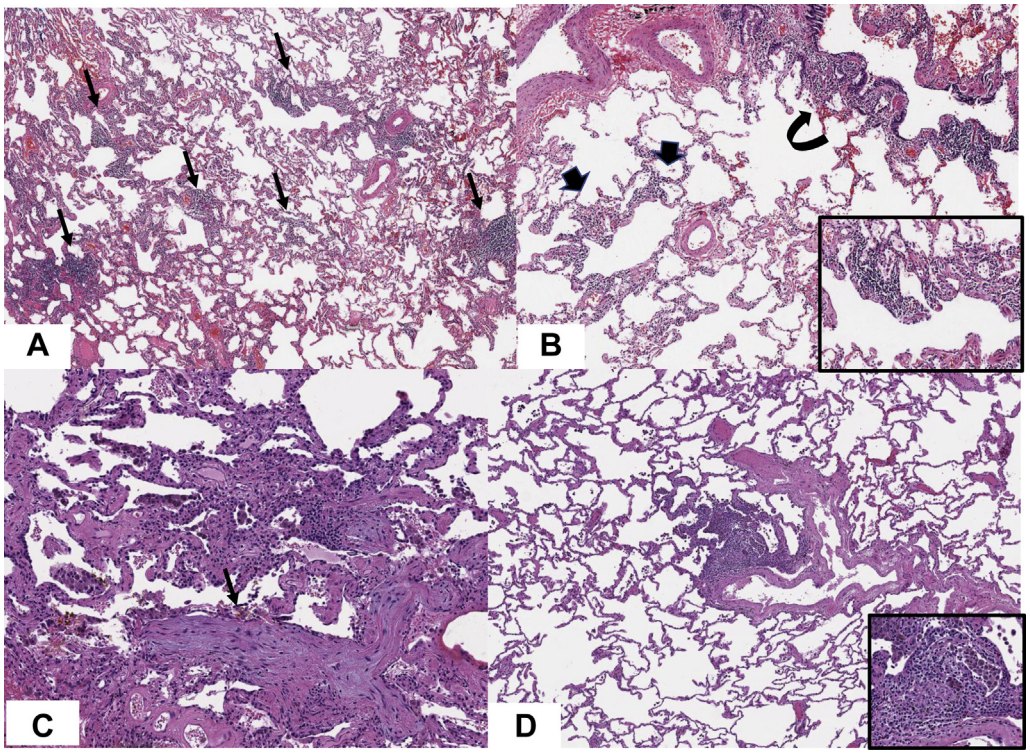

Figure 11 – ***Compatible with nonfibrotic hypersensitivity pneumonitis (HP).*** *A, Low power shows a bronchiolocentric distribution. B, This bronchiole is infiltrated by chronic inflammation (curved arrows) which extends into the surrounding peribronchiolar interstitium (arrowheads). No granulomas were seen.* ***Indeterminate for nonfibrotic HP.*** *C, 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). D, After review of the CT scan, 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 (center and insert) and could be reclassified as* Compatible with Nonfibrotic 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 in infections, pulmonary hemorrhage, metastatic pulmonary calcification, or severe Group 1 pulmonary hypertension, but the clinical context will usually identify these rare causes.[175]

Mosaic Attenuation: As discussed above, the category of mosaic attenuation that is most specific for HP is the three-density sign (previously referred to as the headcheese sign).[20,108] The specificity of mosaic attenuation and lobular air-trapping without the three-density sign may vary depending on the observer and on the presence of associated signs of HP.[110,111]

In patients who have mosaic attenuation without three-density sign or characteristic centrilobular nodules, obliterative bronchiolitis is an important consideration.[178] In patients with a combination of lung fibrosis and mosaic attenuation the possibility of a connective tissue disease should be considered (particularly rheumatoid arthritis).[179]

Air-trapping: Lobular air-trapping[173] is usually caused by obstruction of the supplying bronchioles and is usually indicative of small airways disease including HP and obliterative bronchiolitis. Areas of air-trapping can be seen in normal patients, and some degree of heterogeneity of lung attenuation is expected at expiratory imaging.[180]

Lung Fibrosis: IPF is a primary diagnostic consideration in any patient with pulmonary fibrosis. A diffuse distribution in the axial plane and upper or mid-lung predominant fibrosis in the craniocaudal plane supports the diagnosis of HP. However, at least 30% of HP cases have lower lung predominant fibrosis.[50,51,181] In patients with upper lung predominant fibrosis, differential diagnosis includes idiopathic pleuroparenchymal fibroelastosis,[182] familial pulmonary fibrosis,[183] drug toxicity,[184] sarcoidosis, and connective tissue disease.

Nontypical Features of HP: Consolidation has been occasionally described in patients presenting with nonfibrotic HP[52,185] but when present should suggest an alternative diagnosis such as infection or acute

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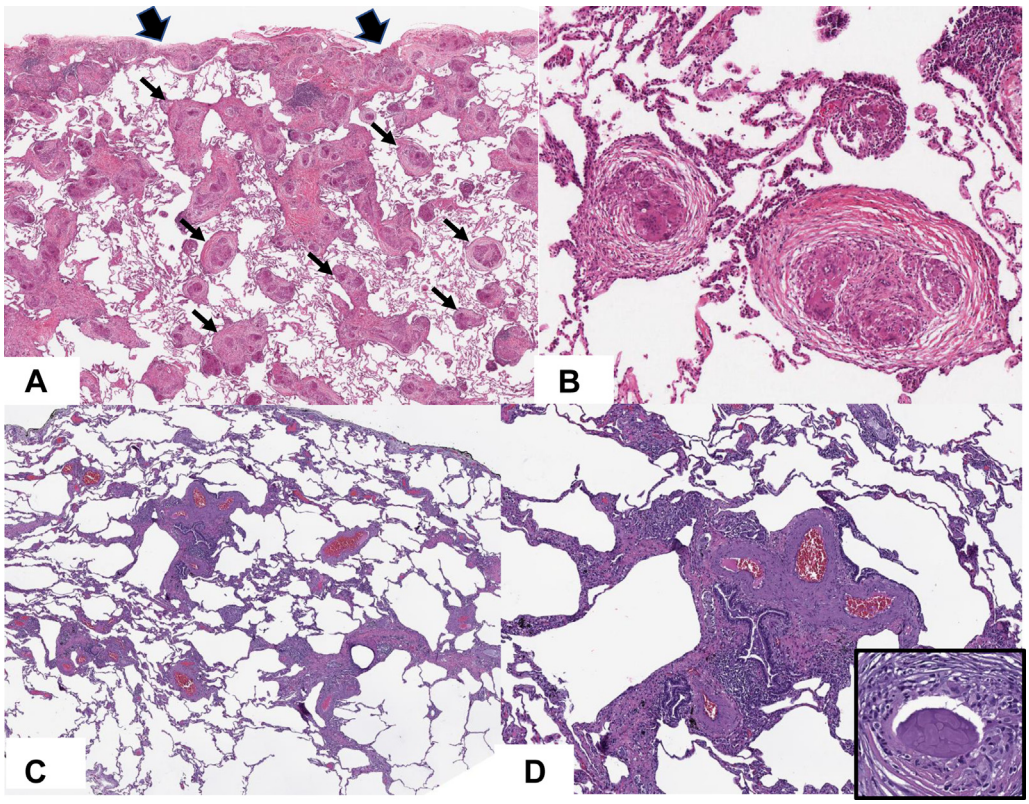

Figure 12 – ***Sarcoidosis.*** *A, This biopsy is infiltrated by numerous noncaseating granulomas distributed along lymphatic routes including the pleura (arrowheads) and bronchovascular bundles (arrows). B, These granulomas consist of multinucleated giant cells and epithelioid histiocytes. Fibrosis surrounds the granulomas. The number of granulomas, their lymphatic distribution and the associated fibrosis are all features against hypersensitivity pneumonitis.* ***Chronic aspiration.*** *C, This biopsy shows bronchiolocentric fibrosis and chronic inflammation. D, This bronchiole is surrounded by dense fibrosis and chronic inflammation. Associated with these bronchiolar changes were granulomas surrounding vegetable particles (insert).*

exacerbation.[186] Sparse thin-walled cysts may be seen in about 15% of HP cases and are usually accompanied by other more typical features.[178] On long-term follow-up of patients with HP, emphysema may be seen in 20% to 30% of never smokers.[187,188]

Distribution

The distribution of CT features is variable and often not diagnostically helpful, particularly in fibrotic HP. One exception is a mid-lung predominance of fibrosis, which is highly suggestive of HP since it is rarely found in other fibrotic lung diseases (Fig 8).[103,189] Upper lung predominance is seen in 10% to 20% of cases.[50,51,181] Upper or mid-lung predominance, when present, can help distinguish fibrotic HP from IPF.[102] Lower lung predominance occurs in about 30% of cases of fibrotic HP.[50,51,181] In the axial plane, findings may be diffuse or subpleural predominant.

Pathology

HP is a challenging pathological diagnosis as the histologic appearance of the disease can vary depending upon the disease stage and it may overlap with patterns seen in other forms of ILD.[48,132-134,137,138,190,191] Based on the presence or absence of an interstitial fibrotic pattern, lung biopsy findings are divided into "nonfibrotic HP" (cellular HP) and "fibrotic HP" patterns, with worse survival seen in the fibrosing cases (Tables 7 and 8).[129,192-201] Surgical lung biopsies obtained from multiple lobes will have a higher diagnostic yield compared to approaches using more limited sampling of lung tissue, such as TBB or TCB, as the likelihood of identifying diagnostic features of HP is related to the biopsy sampling size.[43,48,123,129,132,160,202-206]

We suggest the use of four pathologic categories that reflect the level of confidence that a histopathological specimen is likely to represent HP in the appropriate clinical context (Tables 7 and 8): 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 as they represent an attempt to categorize a complex continuum of histologic findings that may have

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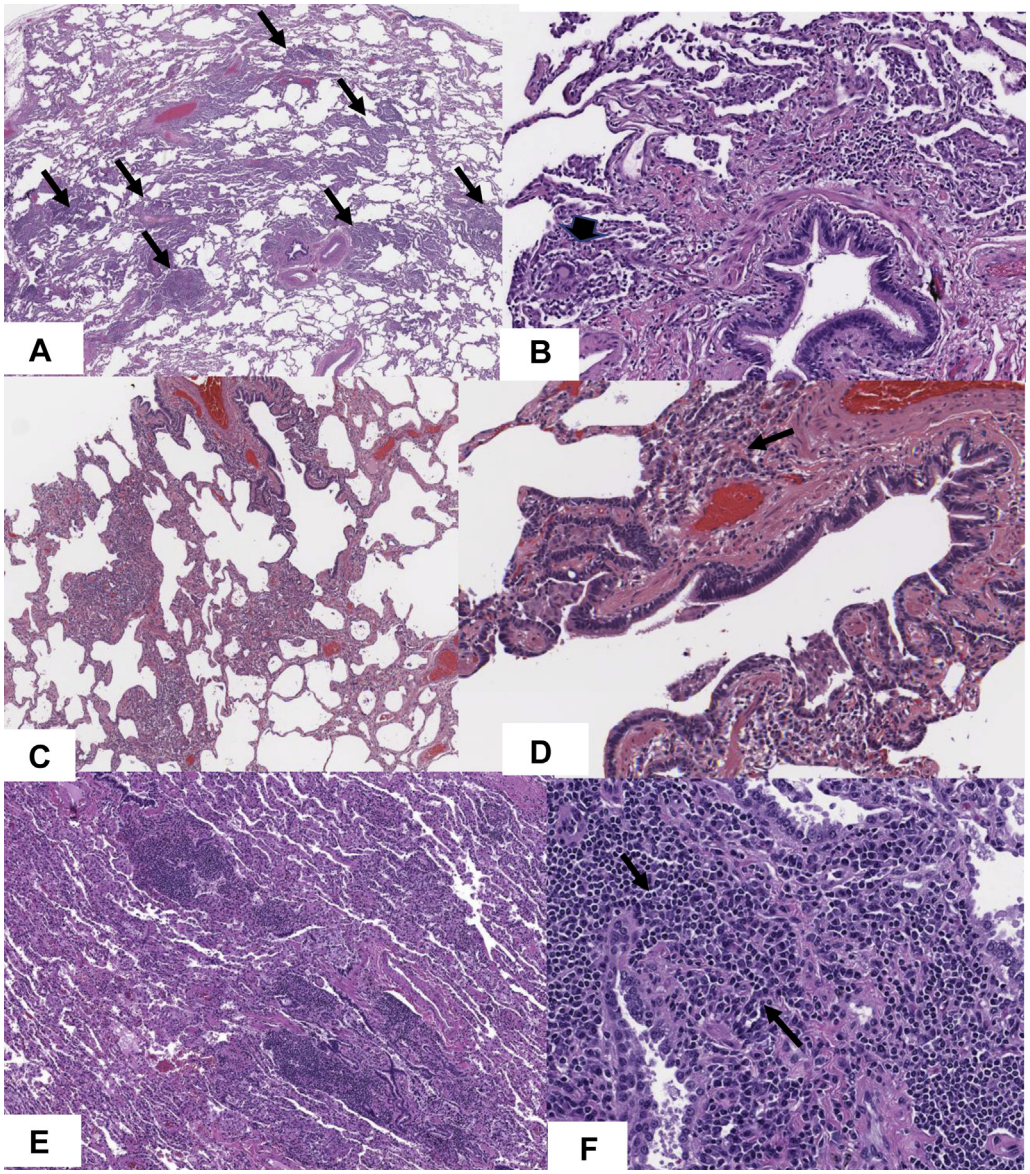

Figure 13 – ***Connective tissue disease: scleroderma patient with CREST syndrome and esophageal dysmotility.*** *A, This biopsy shows a bronchiolocentric pattern of cellular chronic inflammation (arrows). B, This bronchiole is surrounded by chronic inflammation including a poorly formed granuloma (arrowhead). In the absence of clinical history, it would be difficult to exclude hypersensitivity pneumonitis (HP) on such a biopsy.* ***Systemic lupus erythematosus. C,*** *This biopsy shows a bronchiolocentric cellular interstitial pneumonia. D, This wall of this bronchiole is infiltrated by lymphocytes and prominent plasma cells (arrow). The prominence of plasma cells is against a diagnosis of HP.* ***Mixed connective tissue disease with overlap of systemic lupus erythematosus and rheumatoid arthritis.*** *E, This biopsy shows bronchiolocentric cellular chronic inflammation and lymphoid aggregates. F, The inflammation in the wall of the bronchiole consists of lymphocytes with numerous plasma cells (arrows). The plasma cells and prominence of lymphoid follicles are against a diagnosis of HP.*

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

In routine practice, MDD may facilitate the integration of histologic findings into the clinical and radiologic context. The terminology and criteria for these patterns are suggested for use in the context of MDD for the diagnosis of HP rather than as diagnostic terms for pathologists to use in routine clinical work. For example, even "*typical nonfibrotic HP*" an appropriate pathology diagnosis would be more descriptive such as: "Bronchiolocentric cellular interstitial pneumonia with poorly formed granulomas" with a comment about the level of suspicion for HP and differential diagnostic considerations such as CTD, inhalational injury, or drug toxicity.

Nonfibrotic HP Patterns

To recognize the *typical nonfibrotic HP pattern,* four *major features* should be identified in at least one of the

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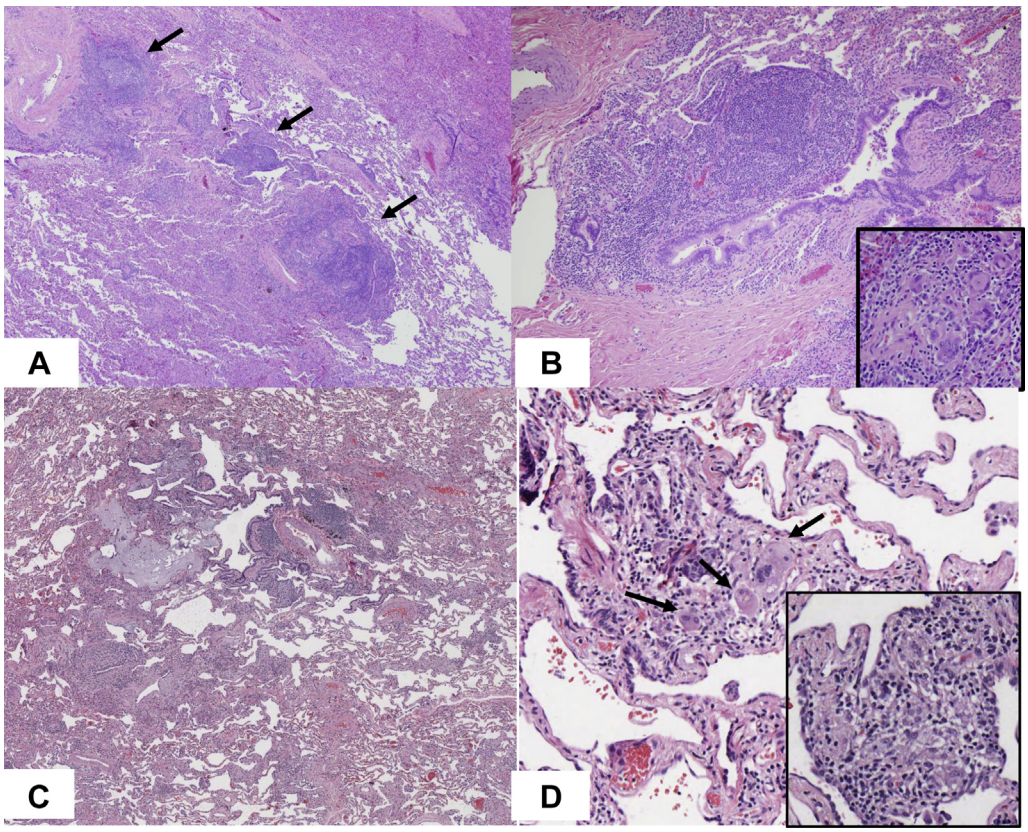

Figure 14 – ***Common variable immunodeficiency.*** *A, This biopsy shows bronchiolocentric cellular interstitial chronic inflammation with lymphoid aggregates. B, A closer view shows marked chronic inflammation surrounding this bronchiole with a lymphoid aggregate. Within the inflammatory infiltrate, there were a few poorly formed granulomas consisting of loose aggregates of multinucleated giant cells. The size and prominence of lymphoid follicles are against a diagnosis of hypersensitivity pneumonitis.* ***Atypical mycobacterial infection.*** *C, This biopsy cultured positive for atypical mycobacterial infection. Histologically the biopsy showed bronchiolocentric inflammation and fibrosis. D, The peribronchiolar interstitium showed giant cells (arrows) and small poorly formed granulomas (insert). Most commonly atypical mycobacterial-related chronic bronchiolitis shows more numerous and better formed granulomas than hypersensitivity pneumonitis.*

sampled lobes of lung (Figs 9A-D, Table 7).[43,134,205,207] These include:

1) Small airway-centered distribution involving bronchioles and/or alveolar ducts (often designated "bronchiolocentricity" [Fig 9A]).
2) Uniform cellular interstitial inflammation of alveolar walls and bronchioles (cellular bronchiolitis) (Fig 9B). This may include regions with a cellular NSIP pattern.[135,205]
3) Inflammation consisting mostly of lymphocytes with relatively fewer plasma cells (Fig 9C); and
4) Interstitial scattered poorly formed granulomas and/or multinucleated giant cells (Figs 9C, 9D). In addition, there can be *Minor Features* that are nonspecific and do not represent diagnostic criteria such as small foci of organizing pneumonia (Fig 9C), foamy macrophages, and cholesterol clefts. *Lack of features suggesting an alternative diagnosis* represents another requirement for the *typical nonfibrotic HP pattern.*

The granulomas of HP are usually small and poorly formed consisting of loose clusters of epithelioid cells and multinucleated histiocytes (Fig 9D) often in a peribronchiolar distribution. Granulomas are usually situated in the interstitium but they can be seen in airspaces as well.[137,160,208] Cholesterol clefts (Fig 10A), Schaumann bodies (Fig 10B) and birefringent oxalate crystals (Fig 10C) are nonspecific inclusions that can be seen within giant cells but both of the latter are more often found in sarcoidosis.[209] The inflammation consists predominantly of lymphocytes, with relatively few plasma cells.[129] Eosinophils are usually inconspicuous or absent. Alveolar macrophages may be extensive and foamy in character reflecting local distal airway obstruction.

Biopsies can be classified as *compatible with nonfibrotic HP pattern* if the first three *Major Features* are identified but both granulomas and features of an alternative diagnosis are lacking (Figs 11A, 11B). Since this

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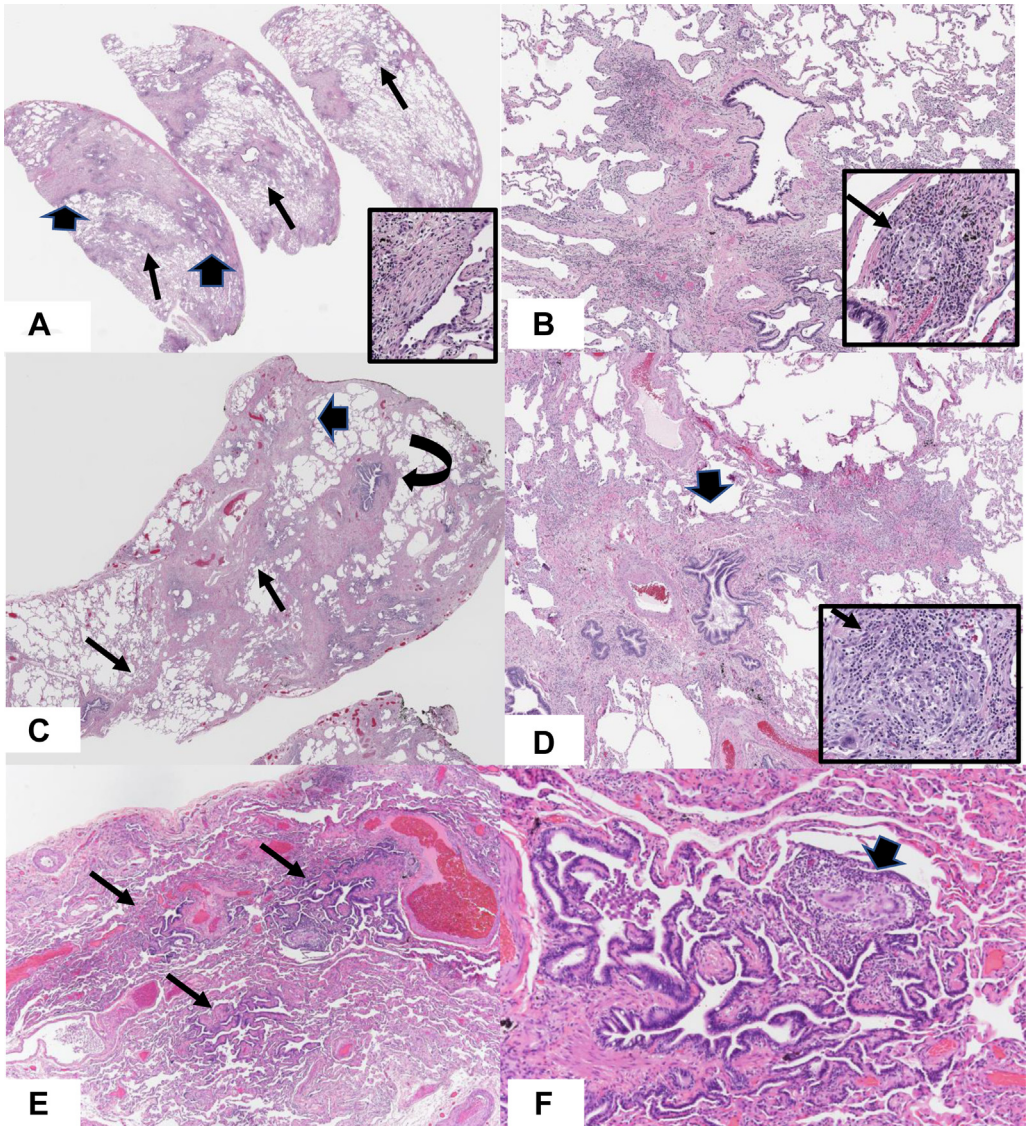

Figure 15 – ***Typical fibrotic hypersensitivity pneumonitis (HP).*** *A, This fibrotic HP case shows a bronchiolocentric pattern of fibrosis (arrows) in addition to extensive areas of subpleural fibrosis (arrowheads) reminiscent of usual interstitial pneumonia pattern. Fibroblastic foci were seen at the edge of dense fibrotic scars (insert). B, This bronchiole surrounded by fibrosis and mild chronic inflammation. Scattered poorly formed granulomas were also identified (insert and arrow). The low power bronchiolocentricity and subtle granulomas are key features in suspecting fibrotic HP. C, This biopsy shows patchy dense interstitial fibrosis with a bronchiolocentric distribution (curved arrow). Bands of fibrosis show bridging patterns between bronchioles (arrows) and the pleura (arrowhead). D, This bronchiole is surrounded by dense fibrosis with mild chronic interstitial inflammation (arrowhead). Rare poorly formed granulomas were identified (insert and arrow). E, The bronchiolar fibrosis in this case consisted of widespread peribronchiolar metaplasia affecting each of the bronchioles in this image (arrows). F, The peribronchiolar metaplasia consists of bronchiolar remodeling due to fibrosis extending beyond the bronchiolar lumens to the surrounding interstitium of alveolar walls. The thickened alveolar walls are lined by bronchiolar epithelium. A poorly formed noncaseating granuloma is present (arrowhead).*

histologic picture can also be seen in other conditions including connective tissue disease,[129,210] inhalational injuries,[211] other environmental exposures,[212,213] and drug toxicity,[214,215] the more general term "compatible with" was chosen rather than "probable HP". Because the histologic findings in these cases are relatively nonspecific, they do not necessarily imply that the diagnosis is probably HP.

The *indeterminate for nonfibrotic HP pattern* category is based primarily on radiologic and/or clinical features that suggest HP but a biopsy ILD pattern that by itself does not meet pathologic criteria for *typical nonfibrotic HP*, *compatible with nonfibrotic HP*, or an *alternative diagnosis* (Figs 11C, 11D). In these cases, there is uncertainty about the histologic features that raise the consideration of nonfibrotic HP, as well as other

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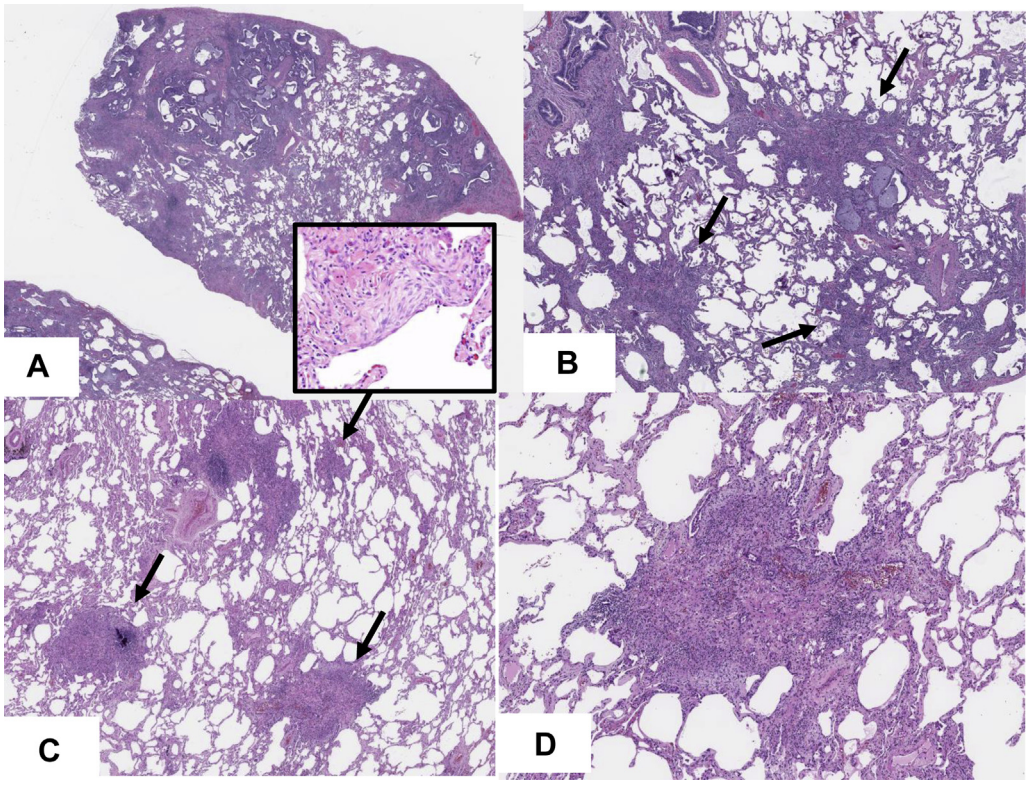

Figure 16 – ***Compatible with fibrotic hypersensitivity pneumonitis (HP)***. *A, This biopsy showed a usual interstitial pneumonia pattern in one area of the biopsy with patchy subpleural fibrosis with remodeling of the lung architecture with foci of honeycombing. Fibroblastic foci were seen at the edges of the fibrotic scars (insert). B, 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. C, This biopsy shows a pattern consisting of bronchiolar fibrosis. At low power this appears as evenly distributed nodules of fibrosis which are centered on bronchioles (arrows). D, This nodular fibrotic scar has completely replaced a bronchiole and has mild interstitial chronic inflammation. No granulomas were seen. The CT scan showed features of typical HP. Such cases might have been included in series of bronchiolocentric interstitial pneumonias.*

differential diagnoses that become part of the multidisciplinary discussion whether the case is HP or not. Examples of this would be biopsies that show a pure cellular NSIP pattern or examples of cellular interstitial pneumonia that only have a vague suggestion of bronchiolocentricity. Another scenario includes cases where on initial review the biopsy findings are regarded as indeterminate for the HP pattern but subsequent MDD, including review of the CT imaging, reveals findings that favor HP. Re-review of the biopsy findings prompted by the MDD identifies subtle findings that are reinterpreted, such as granulomas, as suggestive of HP (Figs 11C, 11D).

The category of *alternative diagnosis* includes a variety of disorders that can affect the lung interstitium and/or small airways in a manner that may overlap with histologic features of the HP pattern but which have diagnostic histologic features of another disorder (Table 6) such as sarcoidosis (Figs 12A, 12B),[192] aspiration (Figs 12C, 12D),[193,194] connective tissue disease (Figs 13A-F),[129,195] drug-induced lung disease,[216] immunodeficiency (Figs 14A, 14B),[196,217] or smoking-related lesions including respiratory bronchiolitis,[218] infection (Figs 14C, 14D),[219] environmental exposure or pneumoconiosis,[199,220] and Langerhans cell histiocytosis.[221]

Fibrotic HP Patterns

Three *major features* characterize a *typical fibrotic HP pattern* (Figs 15A-F, Table 9[16,62,129,130,135,138,139,210,212,213,222-226]) in at least one of the sampled lobe(s) of biopsied lung tissue including:

1) Regions where small airway-centered fibrosis is clearly present with or without widespread peribronchiolar metaplasia (defined as involving > 50% of the bronchioles[129]).
2) A chronic fibrosing interstitial pneumonia affecting at least one sampled area/lobe of lung parenchyma with regions showing one or more of the following

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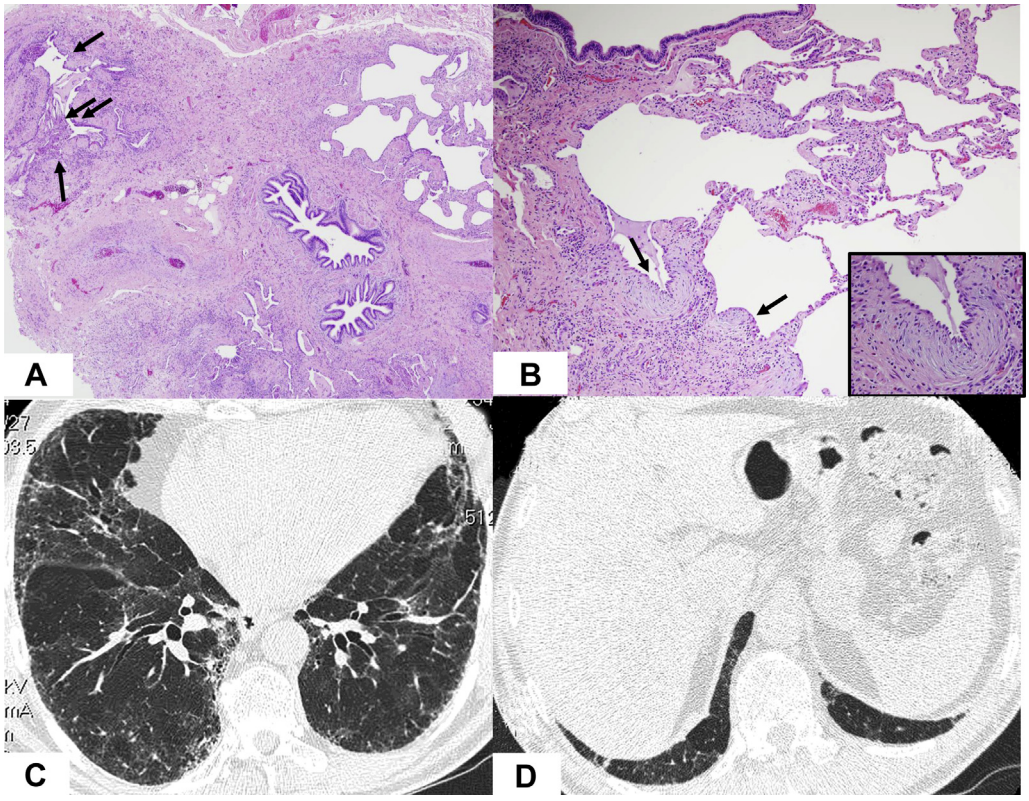

Figure 17 – ***Indeterminate for fibrotic hypersensitivity pneumonitis (HP) by surgical lung biopsy.*** *A, This biopsy showed a pure fibrotic pattern that showed a usual interstitial pneumonia pattern with extensive fibrosis causing remodeling of the lung parenchyma, and areas of honeycombing (arrows). No bronchiolocentricity or granulomas were seen. B, 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 insert). The CT scan (panels C and D) showed the typical HP pattern.* ***Typical HP by CT imaging.*** *This CT scan is from the patient whose biopsy in panels A and B showed a usual interstitial pneumonia pattern. C, The CT scan shows bilateral ground-glass, mild reticulation, traction bronchiectasis, and the three-density sign (scattered areas of ground-glass attenuation, interspersed with normal lung attenuation, and mosaic attenuation) typical of HP. D, There is relative sparing of the lung bases, which would be unusual in idiopathic pulmonary fibrosis, and further supports the diagnosis of HP.*

patterns: a) NSIP-fibrosing pattern,[132] b) UIP-pattern (Figs 15A, 15B),[132] c) A fibrosing pattern that is difficult to classify (Figs 15C, 15D); and d) Fibrosis that is solely peribronchiolar (Figs 15E, 15F)[132,212]; and

3) Poorly formed interstitial noncaseating granulomas and/or multinucleated giant cells (Figs 15B, 15D, 15F).[16,48,129,130,132,135,139,204-206,227-229]

In addition, *typical fibrotic HP* can be seen in patients where biopsies only show *major feature #2:* fibrosing interstitial pneumonia pattern in at least one lobe but *typical nonfibrotic HP* in a separate lobe. The bridging fibrosis pattern (Figs 15C, 15D) has historically been described as characteristic of fibrotic HP. It is characterized by a bridging pattern of fibrosis between centrilobular areas and an adjacent bronchiole, the pleura, or an interlobular septa.[16,130,134,205] However, recent data suggested this feature is not a significant feature for distinguishing fibrotic HP from UIP/IPF.[130] Fibroblast foci can be seen in subpleural, paraseptal, or peribronchiolar locations.[16,130,134,205] Peribronchiolar metaplasia is a nonspecific reaction to bronchiolar and peribronchiolar injury seen in many interstitial lung disorders, but when it is widespread (affecting > 50% of bronchioles) fibrotic HP should be considered (Figs 15E, 15F).[130,210,226]

The *compatible with fibrotic HP* pattern shows the *major features* #1 and #2 (Figs 16A-D, Table 8) in at least one of the sampled lobes, but both poorly formed noncaseating granulomas and features of an alternative diagnosis are absent. This category can also include cases with only *major feature* #2, such as UIP in at least one lobe and a separate lobe meeting criterion for *compatible with nonfibrotic HP*, such as bronchiolocentric fibrosis (Figs 16A, 16B). Some cases consist of a pure pattern of bronchiolar fibrosis with little peribronchiolar interstitial involvement (Figs 16C, 16D).

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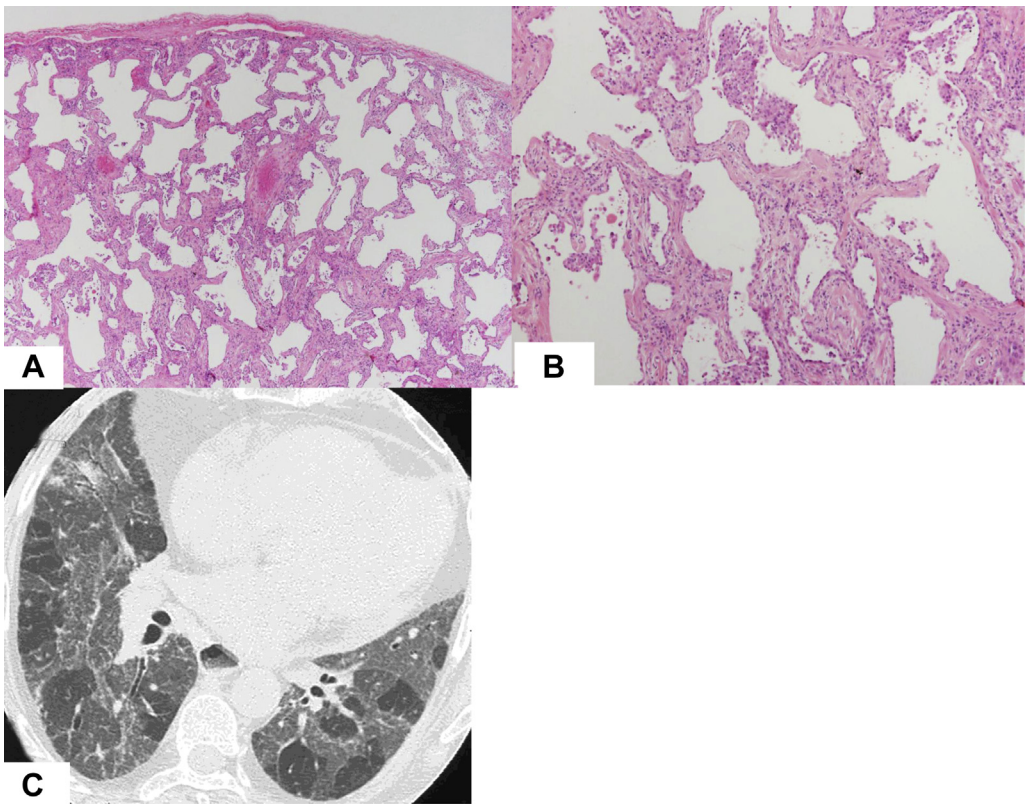

Figure 18 – ***Indeterminate for fibrotic hypersensitivity pneumonitis (HP) by surgical lung biopsy but typical fibrotic HP by CT imaging.*** *A, A fibrosing pattern of nonspecific interstitial pneumonia was seen in this biopsy with diffuse involvement of the alveolar parenchyma lacking any bronchiolocentric distribution. No granulomas or honeycombing are seen. B, The alveolar walls show uniform thickening by fibrosis with mild chronic inflammation. The CT scan showed the typical HP pattern.* ***Typical HP by CT imaging.*** *C, This CT scan is from the patient whose biopsy in panels A and B showed a fibrosing pattern of nonspecific interstitial pneumonia. It shows the three-density sign (predominant ground-glass attenuation with areas of normal attenuation and mosaic attenuation) with mild reticulation and traction bronchiectasis. This combination of findings provides strong support for the diagnosis of HP rather than idiopathic nonspecific interstitial pneumonia.*

Similar to nonfibrotic HP, the category of *indeterminate for fibrotic HP* pattern is based largely on a clinical finding or radiologic pattern suggesting fibrotic HP; however, a lung biopsy (Figs 17A-D, 18A-C) shows a pattern of fibrosing interstitial lung disease that by itself does not meet the pathologic criteria for the pattern of *typical fibrotic HP*, *compatible with fibrotic HP*, or an *alternative diagnosis*. This category can include cases that on biopsy show a pure UIP (Figs 17A-B) or NSIP pattern (Figs 18A-B) without features suggestive of fibrotic HP such as bronchiolocentricity or granulomas.[19,48,190,204] In such cases, HRCT findings can strongly favor HP rather than idiopathic NSIP (Figs 17C, 17D) or IPF (Fig 18C), respectively.

The category of *alternative diagnosis* is appropriate for biopsies that show definitive features of other interstitial lung diseases (Table 8).

Differential Diagnosis

The major differential diagnostic considerations for HP and their key histologic features are addressed in the category of Alternative Diagnoses. Table 9 lists several additional differential diagnoses that deserve special mention.

Diagnostic Approach

The presented diagnostic algorithm (Fig 1) illustrates a multidisciplinary team-based approach to the diagnostic process of HP based on seven diagnostic tenets and incorporating the evidence-based recommendations delineated in the guideline and expert panel report detailed in the previous section of this manuscript.

First, the diagnostic approach to HP is step-wise, patient-centered, and ideally based on multidisciplinary evaluation.

Second, while nonfibrotic HP cases with an identified IA may be solved by pattern recognition, complex cases including those with fibrotic HP may require a hypothetico-deductive diagnostic approach. Pending the availability of accurate and reliable precision medicine tools, this diagnostic approach includes the following

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steps : 1) form a hypothesis and estimate its likelihood, 2) decide how certain the HP diagnosis must be in the context of disease severity and behavior, as well as, the anticipated seriousness if left undiagnosed and untreated, 3) reassess the a priori probability of HP and choose an appropriate diagnostic test, 4) determine the posttest confidence of HP, and 5) determine if further testing or treatment is needed according to the properties of the test at the site where the patient is evaluated, the prognosis, and the nature of the treatment (eg, antigen avoidance, antiinflammatory and/or antifibrotic therapy).

Third, this diagnostic approach integrates the steps above into the multidisciplinary assessment to help establish the level of diagnostic confidence before determining the need for further testing during the HP diagnostic process.

Fourth, the diagnostic approach to HP is guided by the degree of diagnostic certainty required. Patients without a confident diagnosis but in whom HP is suspected have a *provisional diagnosis* underscoring the importance of reviewing the diagnosis (eg, an indeterminate IA) at regular intervals. That the *provisional diagnosis might change* highlights the value of seeking additional expertise or *multidisciplinary team consultation* to help confirm or reject the working diagnosis. The diagnostic process is iterative and should be re-visited as additional data become available.

Fifth, this diagnostic approach uses the terms: high or low confidence.[230] The ultimate goal of classification of a provisional diagnosis as high or low confidence is to prevent inappropriate testing, such as overutilization of TBC or VATS for diagnosis verification, in patients with a provisional high confidence diagnosis. However, in some cases, diagnostic uncertainty remains, even after VATS or TBC, preventing a clear differentiation of HP from an unclassifiable ILD. In this scenario, in the absence of a predominant alternative cause, the term "provisional" is used.

Sixth, the diagnostic algorithm does not supersede clinical judgment regarding when to stop diagnostic investigations and start treatment or the impact of disease behavior on informing test-treatment thresholds. For example, despite the importance of identifying and abating an IA, a timely and accurate diagnosis might not be possible or necessary in all fibrotic HP subjects with a progressive phenotype for treatment to be justified in the context of MDD consensus.

Finally, the presented imaging and histopathological categories and the diagnostic approach *do not capture each and every HP case. These should be viewed as conditional and will evolve as new evidence becomes available.*

Keeping these caveats in mind, a diagnosis of HP requires the exclusion of alternative causes of lung disease, including drug-related exposures, inorganic dust exposures, systemic diseases, and idiopathic interstitial pneumonias. Although commonly sporadic, HP can cluster in families. In some patients, HP can coexist with emphysema or present with autoimmune features. Thus, the diagnostic process requires careful integration and interpretation of multidisciplinary data to determine the dominant cause of lung disease, exclude or define a systemic autoimmune disorder, or establish a working diagnosis of HP.

There exists heterogeneity in the signs and symptoms, extent and severity of functional and gas-exchange impairment, and high-resolution CT abnormalities in patients with HP. Dyspnea on exertion, fatigue, and cough may be temporarily associated with an IA exposure or indicative of HP progression and severity. The presence of intermittent high-pitched inspiratory squeaks during unforced tidal breathing may represent airway-centered disease in HP. Given that the age at the time of diagnosis is typically 50 to 60 years, multicomorbidity is common and can add to symptoms of HP.[4,6]

Probabilistic Diagnostic Categories

This diagnostic approach is analogous to that suggested by the ontological framework for the classification of fibrotic ILD.[230] 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 treatment threshold is the disease probability (eg, $\geq$90% for HP) at and above which further testing is unnecessary and treatment is prescribed. Conversely, the test threshold is the probability below which the diagnosis is unlikely and excluded without further testing.[37] Diagnostic testing is most helpful when the probability of HP is between these two extremes of certainty.

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TABLE 9] Key Histologic Differential Diagnostic Considerations for HP

Differential Diagnosis	Comments
Fibrotic HP vs Usual Interstitial Pneumonia (UIP)	• As the UIP pattern can occur in HP, the distinction between UIP/IPF and fibrotic HP can be difficult or impossible due to frequent overlapping histologic features.[130,135] Wright et al suggested that extensive peribronchiolar metaplasia (increased fraction of bronchioles > 50%, and increased foci of peribronchiolar metaplasia per cm^2) and the presence of granulomas/giant cells favors fibrotic HP (Figs 15E, 15F) although less extensive peribronchiolar metaplasia does not exclude fibrotic HP.[130,210] In contrast, increased numbers of fibroblastic foci and increased thickness of subpleural fibrosis favor UIP/IPF • Features not helpful in the distinction of fibrotic HP from UIP/IPF include 1) peribronchiolar fibrosis adjacent to normal pleura, 2) increased peribronchiolar fibrosis, or 3) bridging fibrosis.[130,139] The difficulty in making this distinction is reflected in the finding that a confident diagnosis could not be made with these histologic features even after multidisciplinary discussion in one third of cases[130]
HP vs Connective Tissue Disease (CTD)-Interstitial Lung Disease (ILD)	• The distinction between nonfibrotic HP or fibrotic HP and CTD-ILD can also be difficult. Churg et. al found that no single morphologic feature can be used to distinguish HP from CT-ILD but suggested the diagnosis of HP was more likely in cases with extensive peribronchiolar metaplasia (Figs 15E, 15F). In contrast, the presence of germinal centers, large numbers of lymphoid aggregates or a high plasma cell to lymphocyte ratio favored CTD[129] • Features that did not help in this distinction included number or location of fibroblast foci, presence of giant cell/granulomas, volume proportion of lymphocytes or eosinophils, nor the location and pattern of interstitial fibrosis (centrilobular and/or subpleural or diffuse–NSIP-like)[129]
HP vs Hot tub Lung	• In contrast to typical HP, the granulomas of hot tub lung are 1) more conspicuous than the inflammatory infiltrates, 2) mostly situated within airspaces and bronchiolar lumens, 3) more well-formed than those in typical HP, and 4) they have a only a moderate rim of chronic inflammatory cells (Figs 19A, 19B).[222] Acid-fast bacilli and focal necrosis can be seen in the minority of cases.[222] Although the histology differs, hot tub lung is regarded as HP due to similar clinical and CT features[62]
HP vs Airway Centered Interstitial Lung Diseases	• ILD centered on airways has been reported under a variety of terms including: airway-centered interstitial fibrosis,[138,213,223] centrilobular fibrosis,[224] idiopathic bronchiolocentric interstitial pneumonia[225] and peribronchiolar metaplasia (Figs 19C, 19D).[226] Some of these patients may have represented fibrotic HP, as it has been documented that this pattern can be a pathologic manifestation in cases of confirmed diagnosis of fibrosing HP.[16,212] These studies describe a spectrum of lesions some of which after multidisciplinary discussion may fall into the category of *Compatible with Fibrotic HP* and others that belong in the category of *Indeterminate for Fibrotic HP*

HP = hypersensitivity pneumonitis; IPF = idiopathic pulmonary fibrosis.

What determines the performance of diagnostic thresholds—the test (~51% for low-confidence or ~70% for high-confidence) and treatment thresholds (~69% for low-confidence or ~89% for high-confidence)—is a function of the properties of the diagnostic test (low-quality evidence for HP), the disease prognosis, and the nature of the treatment.[37,38] For example, when considering VATS for suspected nonfibrotic provisional cases (less serious than progressive pulmonary fibrosis), the test threshold may be higher because of the invasiveness and risks of the test. Clinicians may choose to monitor a patient closely and treat empirically after MDD.

To distinguish the use of radiological and histological confidence levels also applied to other conditions including IPF, the terms typical-HP, compatible-HP, or indeterminate-HP are used in the present diagnostic approach (Fig 1).

Per this diagnostic approach, a confident diagnosis of HP is made in the clinical context when there is an identifiable exposure and CT findings are typical of HP.

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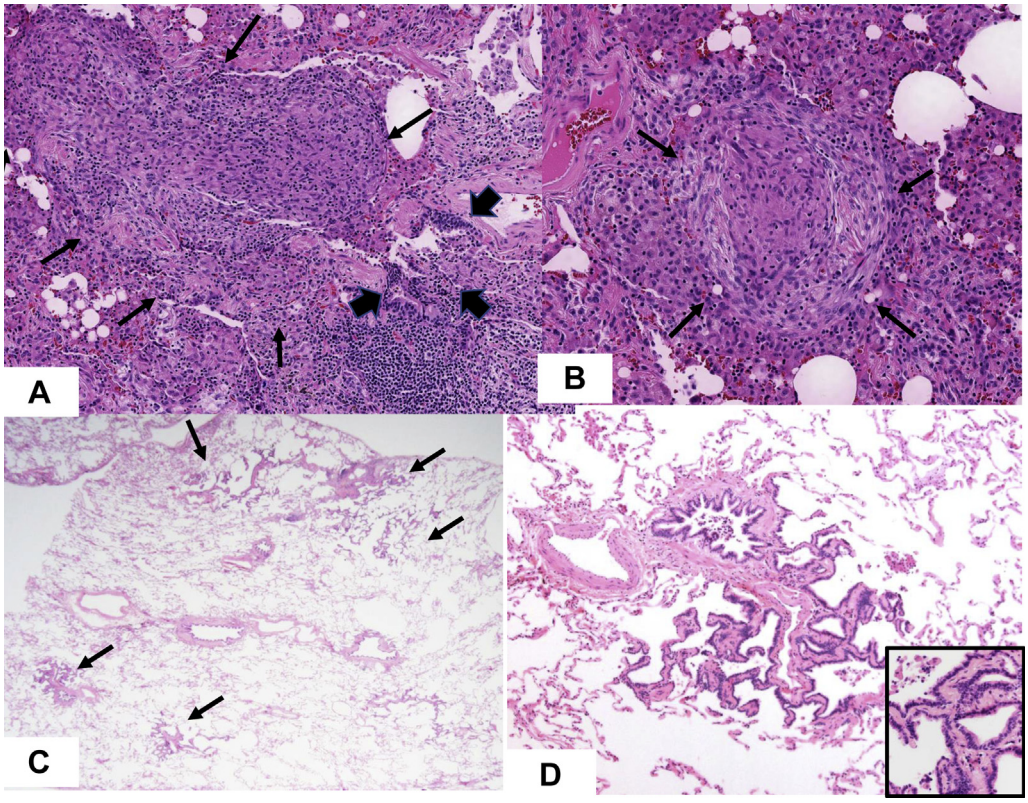

Figure 19 – ***Hot tub lung.*** *A, Within the lumen of this bronchiole (arrowheads) and adjacent airspaces (arrows) there are granulomas consisting of rounded collections of epithelioid histiocytes. B, This well-formed granuloma has a sharply circumscribed border with few chronic inflammatory cells. In contrast to typical hypersensitivity pneumonitis in which inflammation overshadows granulomas at scanning power magnification, in hot tub lung the granulomas are what tend to stand out.* ***Airway-centered fibrosis: peribronchiolar metaplasia-interstitial lung disease.*** *C, This biopsy showed multiple small nodules centered on bronchioles at low power (arrows). D, These nodules on medium power show the lesion of peribronchiolar metaplasia. This consists of slight fibrotic thickening of the bronchiolar wall, but the surrounding alveolar walls are mildly thickened, and the pneumocytes lining alveolar walls are replaced by bronchiolar-type epithelium. The surrounding alveolar parenchyma is relatively normal with preserved architecture. High power of the bronchiolar epithelium consists of ciliated and nonciliated columnar and cuboidal epithelial cells (insert). Such a case would be included in the category of indeterminant for hypersensitivity pneumonitis.*

BAL fluid lymphocytosis is unlikely to substantially change posttest diagnostic certainty in this scenario.

In the absence of alternative causes, if the exposure is identified and CT imaging is compatible with HP, BAL fluid lymphocytosis may provide additional support for a provisional high confidence diagnosis after careful multidisciplinary evaluation. Similarly, if the exposure is indeterminate or unidentified and CT imaging is typical of HP, BAL fluid lymphocytosis may provide additional support for a provisional high-confidence diagnosis.

When CT imaging is compatible with HP, the overall posttest probability of HP is higher in patients with an indeterminate IA (higher pretest likelihood) than in patients with an unidentified IA. However, in these two clinical settings further testing such as VATS or TBC may be considered, particularly in the absence of BAL fluid lymphocytosis (provisional low-confidence or HP unlikely), if a confident diagnosis is sought.

In cases where histological sampling is considered, if the pre-VATS or TBC confidence is low, a confident diagnosis can be made when a biopsy is typical for HP (or on occasions with HP [Fig 1]) and reviewed through a multidisciplinary evaluation. However, if the biopsy is indeterminate for HP or compatible with HP, a provisional diagnosis can be made after careful consensus MDD. 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.

Referral to an ILD center is suggested for patients with a provisional HP diagnosis. When possible, the decision to proceed with TBC or VATS, among patients with a provisional high- or low-confidence HP diagnosis

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should be made in the context of MDD consensus, patient preferences, and if results may enhance therapeutic goals and treatment strategies. It should not be pursued in patients at high risk for perioperative complications.

Future Directions

Considering the evidence on diagnosis of HP, the panel recognizes the need for improved reporting of sensitivity, specificity, likelihood ratio, predictive values, and ROCs and the minimization of systematic and random errors in the literature. Furthermore, there is a need to validate studies evaluating diagnostic and exposure assessment testing, particularly in subjects with a provisional diagnosis of HP. Future diagnostic studies in HP should adhere to diagnostic reporting guidelines. Specific areas of reporting that require attention are the provision of estimates of disease prevalence and IA exposure, description of study patient populations or spectrum of HP subjects, and details of the MDD consensus diagnostic process.

In addition to rigorously phenotyped HP patient cohorts, future HP studies will benefit from implementing standardized and valid regionally relevant environmental and occupational questionnaires. These questionnaires can also help monitor trends, patterns, and types of IAs in HP and ILD registries. Such exposure information from national or regional registries can then provide pretest estimates of HP for diagnostic studies according to geographic location.

Further research on the comparative utility of standard commercial or center-specific quantitative antigen-specific antibody panels and immunoassays to quantify the level of antibodies to mold antigen in extracts of surface cultures as an adjunct to a systematic assessment of indoor environmental IA investigations in HP patients with an indeterminate or suspected exposure is needed.

BAL diagnostic thresholds and confidence intervals should be further studied in patients with HP. The role of BAL should be characterized as a function of exposure history and CT probabilities and how they influence the MDD diagnostic process and VATS or TBC decisions. Similarly, the additive discriminative diagnostic yield of TBB when added to BAL and test independence according to pretest and CT HP probabilities is unknown and requires further study, as does the diagnostic yield and test independence of BAL when added to TBC. Also, the diagnostic performance characteristics of TBC in modifying the pretest likelihood of HP in the context of MDD need to be established.

The interobserver agreement of the recommended diagnostic confidence classification in the context of a stepwise and transparent MDD approach should be investigated.

Finally, there is a critical need to evaluate the diagnostic yield and validity of molecular markers for the discrimination of fibrotic HP from other fibrotic ILDs and the potential enhanced diagnostic accuracy compared to clinical variables alone.

Conclusions

Based on a systematic review of the literature and evidence-based recommendation drafting process, this analysis provides guidance on approaches to the diagnosis of HP. For research questions with an acceptable level of evidence, recommendations were developed and graded based on consideration of the balance of benefits and harms inherent to a diagnostic approach and the strength and quality of the evidence. For questions with insufficient evidence identified by the systematic review, an ungraded consensus-based statement was generated via a modified Delphi approach by the panelists who have extensive clinical expertise in the diagnosis and management of HP.

This analysis highlights several key findings:

- Because of the complexity of the clinical diagnosis of HP early referral and accurate diagnosis are crucial. A probabilistic approach to clinical diagnosis allows not only a clinically useful interpretation of the test results but also identifies a subgroup of patients with a high or low probability of HP in whom further workup may or may not be needed in the context of MDD.
- As with any ILD, the diagnostic process of a patient suspected of having HP is iterative and benefits from a consensus-based MDD that incorporates all available data. Serial evaluations are key to help reduce diagnostic uncertainty and to develop a more precise understanding of disease behavior and severity to inform the diagnostic and management process.
- We recognize that an MDD consensus diagnosis or serial MDDs at a referral center is not possible in all cases. The objective of these guidelines is not to discourage physicians who do not have access to all the components of the multidisciplinary process from making a confident diagnosis of HP, but to urge a systematic diagnostic approach.

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- A systematic approach to environmental and occupational exposure characterization—pretest estimates—combined with the high-resolution CT level of confidence is necessary for determining a high or low probability of HP and for classifying the disease.
- In subjects with a suspected occupational or indeterminate environmental exposure, consultation with an occupational medicine specialist and environmental hygienist, after MDD evaluation, for indoor environmental assessment can help determine the likelihood of an IA exposure as the cause of HP or identify an otherwise unrecognized IA.
- In subjects with an indeterminate exposure, serum antigen-specific antibody testing as an adjunct to a patient-centered environmental and occupational survey may suggest a putative exposure. However, based on very-low quality evidence the guideline panel formed a conditional recommendation against making a clinical diagnosis of HP based on solely on exposure assessment using SIC, LPT and serum antigen-specific antibody testing, using these assessment tools for confirmatory diagnostic testing, or routinely using these tests when the IA is identified.
- Response to treatment and antigen avoidance may narrow the differential diagnosis and support a provisional diagnosis, mainly in patients with nonfibrotic HP.
- BAL fluid lymphocytosis may increase diagnostic confidence if the clinical context, exposure history, and HRCT findings are suggestive, but is not definitive.
- Similar to HRCT confidence levels, the guideline panel suggests the use of categories reflecting the level of confidence that a histopathological specimen is likely to represent HP when examining VATS or TBC diagnostic samples from suspected cases.

The recommendations put forth in these guidelines for the diagnosis and evaluation of HP are based on information available at the time of the final literature review. These recommendations should be viewed as provisional as they are based on very-low quality evidence and will likely change as new evidence becomes available.

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Additional information: The e-Appendixes, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

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