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Diagnosis of Hypersensitivity Pneumonitis in Adults An Official ATS/JRS/ALAT Clinical Practice Guideline

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This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin[†] (June 2, 1956–October 17, 2019)

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX MAY 2020

Background: This guideline addresses the diagnosis of hypersensitivity pneumonitis (HP). It represents a collaborative effort among the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana del Tórax.

Methods: Systematic reviews were performed for six questions. The evidence was discussed, and then recommendations were formulated by a multidisciplinary committee of experts in the field of interstitial lung disease and HP using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

Results: The guideline committee defined HP, and clinical, radiographic, and pathological features were described. HP was classified into nonfibrotic and fibrotic phenotypes. There was limited evidence that was directly applicable to all questions. The need for a thorough history and a validated questionnaire to identify potential exposures was agreed on. Serum IgG testing against potential antigens associated with

HP was suggested to identify potential exposures. For patients with nonfibrotic HP, a recommendation was made in favor of obtaining bronchoalveolar lavage (BAL) fluid for lymphocyte cellular analysis, and suggestions for transbronchial lung biopsy and surgical lung biopsy were also made. For patients with fibrotic HP, suggestions were made in favor of obtaining BAL for lymphocyte cellular analysis, transbronchial lung cryobiopsy, and surgical lung biopsy. Diagnostic criteria were established, and a diagnostic algorithm was created by expert consensus. Knowledge gaps were identified as future research directions.

Conclusions: The guideline committee developed a systematic approach to the diagnosis of HP. The approach should be reevaluated as new evidence accumulates.

Keywords: hypersensitivity pneumonitis; fibrotic hypersensitivity pneumonitis; nonfibrotic hypersensitivity pneumonitis; interstitial lung disease; pulmonary fibrosis

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Question 1: Should patients with newly detected ILD on chest radiographs or a CT scan of the

chest, with or without an overt history of exposures capable of causing ILD in the patient's environment at home, work, or elsewhere, be subjected to *formal questioning using a questionnaire* to raise the possibility that a) potential inciting agents of HP are the etiology of the ILD and b) the diagnosis of the ILD is HP?

Question 2: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without an overt history of exposures capable of causing ILD in the patient's environment at home, work, or elsewhere, undergo *serum testing for IgG antibodies* against specific antigens to raise the possibility that a) potential inciting agents of HP are the etiology of the ILD and b) the diagnosis of the ILD is HP?

Question 3: Should patients with newly detected ILD on chest radiographs or a CT scan of the

chest, with or without a history of exposure capable of causing HP, undergo *BAL fluid lymphocyte cellular analysis* to diagnose HP?

Question 4: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo *transbronchial forceps lung biopsy* to diagnose HP?

Question 5: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo *transbronchial lung cryobiopsy* to diagnose HP?

Question 6: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo *SLB* to diagnose HP?

Future Directions

Conclusions

Summary of Recommendations

1. Hypersensitivity pneumonitis (HP) must be considered in the differential diagnosis for patients with newly identified interstitial lung disease (ILD).
2. The guideline committee categorized HP into two clinical phenotypes—nonfibrotic and fibrotic HP—and made separate recommendations for each:
 - a. **For patients with clinical and radiographic manifestations suggestive of nonfibrotic HP** (i.e., patients without radiological and/or histopathological evidence of fibrosis), the guideline committee:
 - i. makes no recommendation or suggestion for or against the use of a questionnaire to identify potential HP inciting agents and sources; instead, the guideline committee recommends development and validation of a questionnaire. *Remark:* Pending the availability of a validated questionnaire, the guideline committee advocates that clinicians

take a thorough history to identify potential exposures and sources in the patient's environment that are known to be associated with HP.

- ii. suggests performing serum IgG testing that targets potential antigens associated with HP (suggestion, very low confidence in the estimated effects).
 - iii. recommends obtaining bronchoalveolar lavage (BAL) fluid for lymphocyte cellular analysis (recommendation, very low confidence in the estimated effects).
 - iv. suggests transbronchial forceps lung biopsy (suggestion, very low confidence in the estimated effects).
 - v. makes no recommendation or suggestion for or against transbronchial lung cryobiopsy.
 - vi. suggests surgical lung biopsy only when all other diagnostic testing has not yielded a diagnosis (suggestion, very low confidence in the estimated effects).
- b. **For patients with clinical and radiographic manifestations**

suggestive of fibrotic HP

(i.e., patients with radiological and/or histopathological evidence of fibrosis), the guideline committee:

- i. makes no recommendation or suggestion for or against the use of a questionnaire to identify potential HP inciting agents and sources; instead, the guideline committee recommends development and validation of a questionnaire. *Remark:* Pending the availability of a validated questionnaire, the guideline committee advocates that clinicians take a thorough history to identify potential exposures and sources in the patient's environment that are known to be associated with HP.
- ii. suggests performing serum IgG testing that targets potential antigens associated with HP (suggestion, very low confidence in the estimated effects).
- iii. suggests obtaining BAL fluid for lymphocyte cellular analysis

- (suggestion, very low confidence in the estimated effects).
- iv. makes no recommendation or suggestion for or against transbronchial forceps lung biopsy.
 - v. suggests transbronchial lung cryobiopsy (suggestion, very low confidence in the estimated effects).
 - vi. suggests surgical lung biopsy; this recommendation is intended to apply when all other diagnostic testing has not yielded a diagnosis (suggestion, very low confidence in the estimated effects).

Introduction

HP is typically an immune-mediated disease that manifests as ILD in susceptible individuals after exposure to an identified or unidentified factor (1). Various alternative definitions of HP have been proposed, but agreement among experts regarding disease definition, diagnostic criteria, and diagnostic approach is lacking, despite efforts by international groups (2–8). Without a consensus definition, it is challenging to diagnose and research HP (7–11). Recent articles have highlighted substantial gaps in our knowledge about the epidemiology, pathogenesis, optimal diagnostic approach, classification, treatment, and follow-up of HP (9–11).

HP shares features of other acute and chronic pulmonary diseases; as a result, fibrotic/chronic HP can be misdiagnosed as idiopathic pulmonary fibrosis (IPF) or another idiopathic interstitial pneumonia (IIP) (12). Many inciting agents have been associated with HP since its recognition in 1700 (13), but the antigen and exposure are not identified in up to 60% of patients with HP, despite a thorough history (14–18). This highlights the difficulty in identifying a culprit exposure and raises the possibility that HP can occur in the absence of an inhalational exposure. It also emphasizes the difficulty in making a definitive diagnosis of HP (particularly fibrotic/chronic HP), which is the reason that a diagnosis of HP requires a multidisciplinary approach that includes radiologists and pathologists. There are many questions about the identification,

duration, quantity, frequency, intensity of exposure to the inciting agent and its source that is required to induce HP, and factors that may predispose people to develop HP.

Clinical practice guidelines (CPGs) for the diagnosis and management of HP are lacking. As a result, clinical practice varies substantially from region to region and among countries, agreement on HP diagnosis is poor (19), and some clinicians continue to use a consensus statement from nearly 30 years ago for guidance (6). This CPG was developed by an *ad hoc* committee of experts appointed by the American Thoracic Society (ATS), the Japanese Respiratory Society (JRS), and the Asociación Latinoamericana del Tórax (ALAT), as well as European and Australian experts in HP. The target audience of this CPG is clinicians (i.e., pulmonologists, radiologists, and pathologists) who care for adults with ILD. The main objective is to help clinicians who are evaluating patients with newly identified ILD to accurately recognize nonfibrotic HP and fibrotic HP in a timely manner that will lead to avoidance of culprit environmental factors and potentially change the disease course. It is also hoped that the CPG will stimulate research into environmental factors and measures to avoid exposure to factors known to induce HP in genetically susceptible persons, decreasing the incidence of HP and more severe forms of the disease.

How to Use These Guidelines

There are many similarities in the initial presentation of patients with fibrotic ILD. This similarity lends itself to the question, “When should clinicians use these guidelines and when should they use the 2018 ATS/European Respiratory Society (ERS)/JRS/ALAT guidelines on the diagnosis of IPF (20)?” because both guidelines address patients with newly identified fibrotic ILD.

Most patients with fibrotic ILD present with an insidious onset of cough, exertional dyspnea, and bibasilar crackles with radiological evidence of fibrosis in lower lobes. Both CPGs are applicable to such patients. Additional history is the first step in evaluating such patients and is essential to deciding which guideline to follow. If the

patient has a potential culprit exposure, this CPG should be followed, which means that the initial steps include a high-resolution computed tomography (HRCT) scan and BAL fluid lymphocyte cellular analysis, followed by a multidisciplinary discussion (MDD). If the patient has no culprit exposures and is a male former smoker >60 years old, the 2018 ATS/ERS/JRS/ALAT guidelines on the diagnosis of IPF (20) should be followed, which means that the initial steps include an HRCT scan followed by an MDD. For all other patients with newly identified fibrotic ILD, the decision of which CPG to initially follow should be made on a case-by-case basis. Regardless of which CPG is followed, the initial steps are similar, and ongoing diagnostic evaluation may be redirected on the basis of the MDD.

It should be emphasized that clinicians should apply the recommendations within this CPG in the clinical context of each individual patient, considering the patient’s values and preferences, and should not consider any recommendations as mandates. No CPG or recommendation can consider all potential clinical circumstances.

Methods

A multidisciplinary (pulmonologists, radiologists, methodologists, pathologists, and patient) panel of experts from the ATS, JRS, and ALAT was composed to identify clinically important questions about diagnostic testing for HP among patients with newly identified ILD. The CPG was created in two parts. The first portion describes clinical, radiological, and pathological features of HP while proposing a definition, diagnostic criteria, and a diagnostic algorithm. It was approached in a consensus fashion and informed by a nonsystematic review of the literature. The second portion makes graded recommendations that answer questions about whether to perform a diagnostic intervention. It was informed by National Academy of Medicine–adherent guideline methodology, including a full systematic review for each question and the formulation, writing, and grading of recommendations using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. For a detailed

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description of the methods, see the online supplement.

Implications of the different degrees of recommendation are described in Table 1. Using the GRADE approach, each recommendation was rated as either a “recommendation” or a “suggestion.” The meaning of a recommendation is the same as a strong recommendation in typical GRADE nomenclature, and the meaning of a suggestion is the same as a weak or conditional recommendation in typical GRADE nomenclature. Typical GRADE nomenclature was altered for this guideline to address prior criticism that the term “conditional” created uncertainty in the context of translation into non-English languages.

Definition

HP is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It typically results from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals.

HP was historically termed “extrinsic allergic alveolitis” and categorized as acute, subacute, or chronic. However, these categories are not easily demarcated, and their delineation has been variable and arbitrary in many studies. Because the presence of radiographic or histopathological fibrosis is the primary determinant of prognosis (3, 21–29), the guideline committee decided unanimously to categorize HP as either fibrotic (i.e., mixed inflammatory plus fibrotic or purely fibrotic) or nonfibrotic (i.e., purely inflammatory), given the greater clinical utility of this stratification. Some patients may have mixed features; in such circumstances, the categorization is determined by the predominance of features.

Although HP is characteristically associated with an inhaled antigen, exposures may not be identified, despite a thorough evaluation in patients with otherwise typical features of HP (some experts have used the term “cryptogenic HP” or “HP of undetermined cause”) (9, 14, 15, 21, 30, 31). It is unknown whether these situations represent unidentified exposure or whether these patients instead have features of HP that are primarily due to an independent, intrinsic/primary process.

Although virtually all diseases occur in “susceptible individuals,” this phrase was included in the definition of HP to emphasize the critical importance of sensitization in the pathogenesis of HP.

Clinical Manifestations

Subtypes of HP

HP is a disease with heterogeneous clinical presentations and outcomes, with subtypes historically categorized by disease duration at the time of presentation (i.e., acute, subacute, or chronic) (4). These categories were vaguely defined in the existing literature and were not consistently associated with outcomes; some patients have a benign course with complete recovery once the relevant exposure has been eliminated, whereas others do not recover and progress to respiratory failure, irrespective of their classification as having acute, subacute, or chronic HP (1, 14). On the basis of evolving knowledge and clinical experience, the guideline committee concluded that patients should be classified as having fibrotic HP or nonfibrotic HP, as determined by the predominant presence or absence of radiological and/or histopathological fibrosis. This new approach reflects the consensus that classification as fibrotic or nonfibrotic HP is more objective, may reflect disease presentation, and is likely to be more consistently associated with the clinical course and other outcomes (9, 10).

Symptoms and Signs

Common symptoms and signs of both nonfibrotic and fibrotic HP include dyspnea, cough, and midinspiratory squeaks (or chirping rales or squawks) (32). Less frequently, there may be constitutional symptoms such as weight loss, flu-like symptoms (chills, low-grade fever, and malaise), chest tightness, and wheezing, as well as physical examination findings of rales and cyanosis (1). Onset may be acute (developing over days to weeks, occasionally with pleural effusion) or may also be insidious (developing and worsening over months to years); episodes may be recurrent. Although an acute presentation with or without constitutional symptoms seems more consistent with nonfibrotic HP and the insidious presentation seems more consistent with

fibrotic HP, duration of symptoms has not been rigorously characterized with respect to fibrosis status (1, 33).

Prevalence of HP is highest among older individuals (i.e., 65 yr and older, with the average patient receiving a diagnosis in their fifth or sixth decade) (34). It can also be diagnosed among younger adults and children (14, 35). Patients with fibrotic HP are more likely to be older, have an unidentified inciting agent, and have a lower vital capacity (VC), diffusion capacity, and percentage of lymphocytes in their BAL fluid than patients with nonfibrotic HP (36).

Natural History and Prognosis

The natural history of HP ranges from improvement to progressive decline and death due to respiratory failure (15). Patients with nonfibrotic HP who avoid ongoing exposure to the inciting agent may have a favorable prognosis with the possibility of stabilization or full recovery (15, 37, 38). Patients with fibrotic HP, particularly those with a usual interstitial pneumonia (UIP)-like pattern, have reduced survival (15, 22, 23, 25, 29, 30, 38–42). Other features associated with poor prognosis include cigarette smoking, lower baseline VC, lack of BAL lymphocytosis (29, 42, 43), persistent exposure to the inciting agent, and/or inability to identify an inciting agent (15). Notably, it has been reported that an inciting agent is not identified in 30–50% of cases evaluated at ILD referral centers (15, 36, 44).

Epidemiology

The prevalence of HP varies with regional disparities in climate, occupational exposures, and environmental exposures (see Table E1 in the online supplement) (34, 45–57). Available studies estimate an incidence between 0.3 and 0.9 per 100,000 individuals (34, 45–57), although the incidence may be even higher according to one study that reported bird breeder’s disease in 4.9 per 100,000 individuals over a 10-year period or 54.6 per 100,000 bird breeders (58). Insurance claims–based analyses conducted between 2004 and 2013 estimated 1-year prevalence to be 1.67–2.71 per 100,000 in the U.S. population (34). The proportion of HP among all ILD cases varies tremendously, ranging from 2% to 47% in studies and registries (35, 59–67). Childhood HP is uncommon but may represent 50% of all childhood ILDs

Table 1. Strengths of Recommendations

From the GRADE working group	Recommendation (“We recommend . . .”)	Suggestion (“We suggest . . .”)
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not.	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy-makers	The recommendation can be adapted as policy in most situations, including for use as performance indicators.	Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.
From the ATS/JRS/ALAT Diagnosis of Hypersensitivity Pneumonitis Guidelines panel discussion	It is the right course of action for >95% of patients. “Just do it.” You would be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing. The recommended course of action may be an appropriate performance measure.	It is the right course of action for >50% of patients. “Slow down, think about it, discuss it with the patient.” You would not be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing; it is “style” or “equipoise.” The recommended course of action is not appropriate for a performance measure.

Definition of abbreviations: ALAT = Asociación Latinoamericana del Tórax; ATS = American Thoracic Society; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; JRS = Japanese Respiratory Society.

The meaning of a suggestion is the same as a weak or conditional recommendation in typical GRADE nomenclature.

(68–70). Sporadic outbreaks of HP have been reported in a variety of exposed groups, including lifeguards at swimming pools (71), automobile workers exposed to polyurethane (72), and office workers exposed to a contaminated humidifier (73) or forced-air climate control (74).

Pathogenesis

Inciting Agents

HP develops in susceptible individuals after repeated exposure to one or more inciting agents. Several potential inciting agents and hundreds of sources of such agents have been reported (11) (Table 2). These inciting agents are diverse, vary by geographic region, and are usually protein antigens derived from microorganisms, fungi, or

animals (e.g., avian antigens). They may also be polysaccharides or low-molecular-weight nonprotein chemicals (e.g., isocyanates) (9, 11, 12, 15, 75). The location of exposure can be occupational, household related, or recreational. In many cases, an exposure is not identified (12, 15). Relationships between exposure-specific factors (e.g., concentration, duration, frequency of exposure, particle size, and particle solubility) and clinical course are frequently observed but are not well delineated (4, 11, 76–78). It has been hypothesized that the inciting agent can be part of a mixture of microbes, proteins, or other matter (e.g., dust). Common antigenic motifs (epitopes) have also been hypothesized; under this theory, sensitization to one antigen may result in hypersensitivity

to multiple inciting agents (79–85). It is unknown why some exposed individuals also develop other types of lung pathology (e.g., the higher-than-expected prevalence of emphysema among patients with HP, independent of smoking status) (86, 87).

Immunological Dysregulation

In sensitized individuals, the immune reaction after exposure to an antigen appears to consist of both humoral (i.e., antigen-specific IgG antibodies) and T-helper cell type 1 (Th1) cellular immune responses (83, 88). These responses lead to a predominantly lymphocytic inflammatory pattern and granulomatous inflammation (11, 75, 89). Neutrophilic inflammation may play a role early in the disease course

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Table 2. Sources of Antigens Known to Cause HP

Matter	Typical Sources	HP "Disease"
Organic particulate matter		
I. Microbes		
Fungi/molds		
<i>Aspergillus</i> spp.	Contaminated plant material	Farmer's lung
<i>Alternaria alternata</i> , <i>Aureobasidium</i> spp.	Contaminated water	Humidifier lung
<i>Botrytis cinerea</i>	Contaminated houses (flooded)	Malt worker's lung
<i>Cephalosporium</i> spp.	Upholstered furniture	Woodworker's lung
<i>Cladosporium</i> spp.	Contaminated stucco	Indoor-air alveolitis (domestic HP)
<i>Cryptococcus</i> spp.	Contaminated raw materials in food-processing industry	Compost lung
<i>Fusarium</i> spp.	Organic wastes	Mushroom grower's lung
<i>Graphium</i> spp.	Contaminated sawdust	Malt worker's lung
<i>Mucor</i> spp.	Moldy wood	Stucco worker's lung
<i>Penicillium</i> spp.	<i>Aspergillus</i> enzyme in baking agents	Suberosis
<i>Rhizopus</i> spp.	Contaminated domestic ventilation and cooling systems	Baker's lung
<i>Trichoderma</i> spp.	Potted flowers, greenhouses	Waste sorter's lung
Phytase (enzyme from <i>Aspergillus</i> or <i>Trichoderma</i>)	Mold on grapes	Sauna taker's lung
	Contaminated wind instruments	Wine grower's lung
	Contaminated soil	Wind-instrument alveolitis
	Peat	Sequoiosis
		Peat worker's lung
		Cheese washer's lung
		Salami producer's lung
		Phytase alveolitis
Yeasts		
<i>Candida</i> spp.	Contaminated misting fountains and humidifiers	Humidifier lung
<i>Geotrichum candidum</i>	Moldy hay, compost, mushrooms	Farmer's lung
<i>Saccharomyces cerevisiae</i>	Contaminated swimming pools	Footcare alveolitis
<i>Saccharomonospora viridis</i>	Contaminated wind instruments	<i>Candida</i> alveolitis
<i>Saccharopolyspora rectivirgula</i>	Human intestine, fingernails, and skin	Indoor-air alveolitis
<i>Torulopsis glabrata</i>	Milk mold	Yeast-powder alveolitis
<i>Trichosporon cutaneum</i>	Baker's yeast, brewer's yeast, wine yeasts	Thatched-roof lung
	Contaminated houses	Mushroom worker's lung
	Dried grasses, leaves	Summer-type HP
	Compost	Wind-instrument lung
	Mushrooms	
Edible mushrooms		
Mushrooms (shiitake, bunashimeji, <i>Pleurotus</i> , <i>Pholiota</i> , <i>Lyophyllum</i> , <i>Agaricus</i>)	Mushrooms growing in indoor environments	Mushroom grower's lung
Bacteria		
<i>Acinetobacter</i> spp.	Contaminated water, whirlpools	Machine operator's lung
<i>Bacillus</i> spp.	Contaminated machine fluid	Humidifier lung
<i>Klebsiella</i> spp.	Sewage treatment plants	Woodworker's lung
<i>Nontuberculous mycobacteria</i>	Sawdust	Detergent worker's alveolitis
<i>Phoma</i> spp.	Moist wood	Summer-type HP
<i>Pseudomonas</i> spp.	Detergents	Farmer's lung
<i>Stenotrophomonas</i> spp.	Biological cleaning agents	Hot-tub lung
<i>Staphylococcus</i> spp.	Washing powders	Whirlpool alveolitis
<i>Streptomyces</i> spp.	Contaminated houses	Wind-instrument alveolitis
<i>Thermoactinomyces</i> spp.	Moldy plants	Indoor-air alveolitis
Endotoxin from pool-water sprays and fountains	Contaminated wind instruments	Steam-iron alveolitis
<i>Bacillus subtilis</i> enzymes (subtilisin)	Moldy shower curtains	Mushroom grower's lung
	Compost	Thatched-roof disease
	Edible mushroom manure	Bagassosis
	Contaminated soil	Compost lung
	Moldy thatched roofs	
Protozoa		
Amoebae	Contaminated humidifiers and air-conditioning systems	Humidifier lung

(Continued)

Table 2. (Continued)

Matter	Typical Sources	HP "Disease"
Nematodes		
Nematodes	Contaminated humidifiers and air-conditioning systems	Humidifier lung
Mite		
<i>Acarus siro</i>	Contaminated cheese	—
II. Proteins/enzymes		
Animal proteins		
Animal fur dust	Animal pelts	Furrier's lung
Avian droppings, serum, and feathers	Parakeets, canaries, budgerigars, pigeons, parrots, chicken, turkeys, geese, ducks, wild birds, pheasants	Bird fancier's disease, bird breeder's disease, pigeon breeder's lung, chicken breeder's lung
Avian feathers	Feather beds, pillows, duvets	Feather-duvet lung
Bats	Contact with bats	—
Carmine (from <i>Coccus cacti</i>)	Food and cosmetics	Carmine alveolitis, dyer's lung
Cow milk	Cow milk	Heiner syndrome
Fish feed	<i>Daphnia</i> , meat, mosquito larvae	Fish-feed alveolitis
Fish meal	Animal feed	Fish-meal alveolitis
Shell protein (oyster, sea snail, mussels)	Oyster-shell powder	Shellfish alveolitis, oyster-shell HP, mollusk-shell HP
Pig pancreas	Animal extracts	—
Pituitary proteins	Pituitary powder	Pituitary snuff-taker's lung
Rat and desert mouse (gerbil) urine, serum, pelts	Rats, gerbils	Alveolitis due to rat and mouse proteins
Silkworm proteins	Dust from silkworm larvae and cocoon	Silkworm rearer's lung
Weevils (corn, wheat) (<i>Sitophilus</i> spp.)	Contaminated grain or flour	Corn (wheat)-weevil lung
Plant proteins		
Alginate	Seaweed	—
Argan cake	Cosmetics, unsaturated fatty acids, phytosterol	—
Catechin	Green-tea powder	—
Esparto dust	Esparto grass	Esparto lung, plasterer's lung
Grain flour (wheat, rye, oats, maize)	Flour dust	Flour-dust alveolitis
Malt	Food-processing industry	—
Legumes (soy)	Legumes (soya) flour dust	Soya-dust alveolitis
Paprika	Paprika dust	Paprika splitter's lung
Pyrethrum	Plant-based insecticide	—
Spinach	Spinach powder	—
Tiger nut	Horchata (drink)	Tiger-nut alveolitis
Wood (cabreuva, cedar, mahogany, pine, ramin, umbrella pine)	Wood particles	Wood fiber alveolitis
Inorganic particulate matter		
I. Chemicals		
Acid anhydrides (pyromellitic and trimellitic anhydrides)	Polyurethane foams, spray paints, elastomers, glues, adhesives, mattresses, car parts, shoes, imitation leather, rubber products, chipboards, elastic synthetic fibers, electrical insulations	Acid anhydride alveolitis
Acrylate compounds (methyl methacrylate)	Dental materials, lacquer, resin, glues	Methacrylate alveolitis
Copper sulfate	Copper-sulfate Bordeaux mixture	Vineyard sprayer's lung
Chloroethylene (trichlorethylene)	Degreasing agents, cleaning agents, extraction agents	Chemical alveolitis
Dimethyl phthalate and styrene	Industrial solvents, plasticizers	—
HFC-134a	Coolant fluid in laser hair-removal devices	Hair-remover lung
Isocyanates (toluene diisocyanate, methylene diphenyl diisocyanate, hexamethylene diisocyanate, MIC, NDI, polyisocyanate)	As in acid anhydrides	Isocyanate alveolitis
Tetrachlorophthalic and hexahydrophthalic acid	Hardener for epoxy resin	Acid anhydride alveolitis
Sodium diazobenzene sulfate	Laboratory reagent, chromatography	Chemical alveolitis
Triglycidyl isocyanurate	Polyester powder (powder paints)	Painter's lung

(Continued)

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Table 2. (Continued)

Matter	Typical Sources	HP “Disease”
II. Pharmaceutical agents Penicillins, cephalosporins Methotrexate α -IFN Lenalidomide Pravastatin Venlafaxine Temozolomide	Antibiotics Immunosuppressive agents Immunomodulatory agents Hypolipidemics Antidepressants Alkylating agents	Drug-induced HP
III. Metals Cobalt Zinc (tungsten and alloys) Zirconium Beryllium TMI	Hard metals, alloys Zinc fumes Zircon Batteries, computers, neons Organometallic compound for semiconductors used in industry	Giant cell pneumonitis Zinc-fumes alveolitis Zirconium alveolitis Beryllium HP —

Definition of abbreviations: HFC-134a = hydrofluorocarbon 134a; HP = hypersensitivity pneumonitis; MIC = methylisocyanate; NDI = naphtylene-1,5-diisocyanate; TMI = trimethylindium.

Adapted from Reference 11.

and during subsequent fibrosis (90, 91), whereas impaired function of T regulatory cells may play a role in the exaggerated immune response (92). Some evidence suggests that a relative switch from Th1 to Th2 activity (93–95) as well as augmented epithelial apoptosis and abnormal fibroblast activity (96, 97) contribute to pulmonary fibrosis that may mimic patterns of fibrotic IIPs, including, most importantly, UIP. A subgroup of patients with HP has been shown to have concurrent autoimmune features, although the underlying mechanisms are still not known (98).

Genetic/Host Susceptibility

The best-studied host factor that creates a predisposition for HP development is genetic variation. Variants in genes involved with innate and adaptive immunity may enable sensitization to inciting agents (Table E2). Polymorphisms in major histocompatibility complex class II, proteasomes, transporter proteins, and tissue inhibitors of matrix metalloproteinases have been associated with HP (99–106). Among patients with fibrotic HP, the MUC5B (mucin 5B) promoter polymorphism is more prevalent than in the general population and is associated with shortened survival (107). HP has also been described in probands of familial pulmonary fibrosis, including those with telomere-related gene mutations (108, 109). A study performed in two cohorts of patients with chronic HP revealed that around 10% of the patients had rare, protein-altering variants in telomere-related genes, which were associated with short telomere length and significantly

reduced transplant-free survival (110). Microchimerism has been identified in a larger fraction of patients with HP compared with patients with IPF and healthy women; among women with HP, microchimerism is associated with a lower diffusion capacity (111). Preceding respiratory viral infection is another proposed host-sensitizing factor (112–114), and exposure to pesticides seems to increase the risk of HP in farmers (115).

Radiological Features

Chest HRCT Scanning Protocol

The scanning protocol for the evaluation of suspected HP is identical to the protocol described in the ATS/ERS/JRS/ALAT diagnosis-of-IPF guidelines (Table 3) (20). It is based on high-resolution volumetric scanning of the chest, with special attention to the selection of parameters ensuring creation of motion-free images and adequate image quality at a reduced radiation dose. In both fibrotic and nonfibrotic HP, two series of images acquired in the supine position are obtained: one at deep inspiration and a second after prolonged expiration. All features of lung infiltration can be depicted on the inspiratory images, except for air trapping, which is an expiratory HRCT finding. Analysis of lung changes at expiration may increase diagnostic confidence in nonfibrotic HP and is necessary for better characterization of heterogeneous lung attenuation in both forms of the disease. Owing to the

widespread distribution of lung changes in HP, a third acquisition in the prone position is usually not necessary. The optimal chest HRCT scan for characterizing HP should be a noncontrast examination, except in the context of acute respiratory decline, in which case CT angiography may be justified to detect acute pulmonary embolisms. CT angiography should be preceded by a noncontrast chest HRCT scan to detect new ground-glass changes that raise the probability of acute exacerbation in the absence of pulmonary embolisms.

Radiological Features of HP

The imaging features of HP are influenced by the histopathological stage of disease at the time of diagnosis. Our proposed approach reconciles the committee’s preferred two-pattern description (i.e., nonfibrotic and fibrotic HP) with the three subtypes of HP previously considered (i.e., acute, subacute, and chronic forms). For nonfibrotic HP, we use consensus descriptions of the inflammatory and often reversible changes established in the literature (116–119). For fibrotic HP, we provide a novel approach that integrates 1) HRCT scan findings previously described as chronic HP (116–121) and 2) recent data on the diagnostic impact of several radiological patterns (7, 122, 123). Fibrotic HP is widely recognized to have a variable radiological appearance, and the approach proposed here does not consider potential geographical specificities that may influence the most prevalent HRCT pattern.

Table 3. Recommended Chest HRCT Scanning Parameters in the Diagnostic Approach of HP

1. Noncontrast examination
2. Volumetric acquisition with selection of:
 - Submillimetric collimation
 - Shortest rotation time
 - Highest pitch
 - Tube potential and tube current appropriate to patient size:
 - ✓ Typically: 120 kVp and ≤ 240 mAs
 - ✓ Lower tube potentials (e.g., 100 kVp) with adjustment of tube current encouraged for thin patients
 - ✓ Use of techniques available to avoid unnecessary radiation exposure (e.g., tube current modulation)
3. Reconstruction of thin-section CT images (≤ 1.5 mm):
 - Contiguous or overlapping
 - Using a high-spatial-frequency algorithm
 - Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)
4. Number of acquisitions
 - Supine position: inspiratory (volumetric) and expiratory (sequential or volumetric) acquisitions
 - Prone (optional): only inspiratory scans (can be sequential or volumetric)
 - Inspiratory scans obtained at full inspiration
5. Recommended radiation dose for the inspiratory volumetric acquisition:
 - 1–3 mSv (i.e., “reduced” dose)
 - Strong recommendation to avoid “ultra-low-dose CT” (< 1 mSv)

Definition of abbreviations: CT = computed tomography; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; kVp = kilovolt peak. Adapted from Reference 20.

The following descriptions are intended to provide a summary of HRCT findings that are 1) highly suggestive of HP, which we categorize as “typical HP”; 2) less frequently reported but compatible with HP, which we refer to as “compatible with HP”; or 3) “indeterminate for HP” when the HRCT findings are neither suggestive nor compatible with features of HP. Radiological terms related to the heterogenous lung attenuation are defined in Table 4.

Nonfibrotic HP. The typical HP pattern (Table 5) relies on the identification of diffusely distributed HRCT findings that include features of lung infiltration (i.e., ground-glass opacity [GGO], mosaic attenuation) plus at least one HRCT abnormality suggestive of small airway disease. HRCT features of small airway disease include ill-defined, small (< 5 mm) centrilobular nodules on inspiratory images and air trapping on expiratory images. Mosaic attenuation refers to coexisting areas of varying attenuation within the lung parenchyma on inspiratory HRCT images (Figures 1, E1, and E2). In nonfibrotic HP, mosaic attenuation typically reflects coexistent lobules affected by pneumonitis

(increased attenuation) interspersed with lobules of normal or slightly decreased attenuation (due to bronchiolar obstruction). These parenchymal patterns are usually bilateral and symmetric with a diffuse distribution, both axially and craniocaudally. Although a combination of parenchymal abnormalities and features of small airway disease is highly suggestive of nonfibrotic HP, isolated air trapping is another pattern that may be seen with HP. Three additional HRCT features have also been described in nonfibrotic HP: uniform and subtle GGO, airspace consolidation, and lung cysts (124–126). Each of these features is nonspecific but can be compatible with nonfibrotic HP in the appropriate clinical context.

Fibrotic HP. Coexisting lung fibrosis and signs of bronchiolar obstruction are highly suggestive of fibrotic HP (Table 6) (7, 40, 121, 127, 128).

Lung fibrosis in HP most frequently manifests as irregular fine or coarse reticulation with architectural lung distortion, sometimes with septal thickening, that can be seen alone or in association with traction bronchiectasis in areas of GGO. Honeycombing can be

present and is often described as minimal, but extensive honeycombing in severe forms of fibrotic HP may also occur. Lung fibrosis is most severe in the mid or mid and lower lung zones or equally distributed in the three lung zones with relative basal sparing. On axial images, there is often no central or peripheral predominance of lung fibrosis (Figures 1 and E3).

Bronchiolar obstruction manifests with several HRCT features in fibrotic HP. Like that observed in nonfibrotic HP, ill-defined centrilobular nodules and mosaic attenuation can be seen (7, 122). Bronchiolar obstruction is also present in an HRCT pattern combining three different lung densities (GGO, lobules of decreased attenuation and vascularity, and normal-appearing lung) that is highly specific to fibrotic HP (123). We coined the term “three-density pattern” to describe the presence of these three different lung densities, which some radiologists have referred to as the “headcheese sign” (Figure 2 and Table 4). This pattern emphasizes the diagnostic value of lobules with decreased attenuation and vascularity on inspiratory HRCT images, especially when concomitant with air trapping at expiration, both suggesting the presence of severe bronchiolar obstruction. These two individual HRCT features were the highest-ranked radiological features for fibrotic HP in an International Modified Delphi Survey (7).

In the context of fibrotic HP, mosaic attenuation is often described as “extensive” (128) and “marked” (20), but these descriptors do not state specific numerical values. In a recent study, the threshold of five or more lobules of mosaic attenuation in each of three or more lobes bilaterally was found to have the highest specificity for fibrotic HP and helped differentiate this disorder from IPF (123). Because air trapping is a nonspecific finding reflecting small airway alterations of variable cause and/or severity, it is not surprising that it is also found in non-HP ILDs (8), especially connective tissue disease (CTD)-associated ILD (CTD-ILD) (129) and sarcoidosis (130).

Some variants in the distribution of fibrosis are compatible with fibrotic HP, although they are less frequent (Figures 1 and E4). These include fibrosis with an axially peripheral (subpleural) or central (peribronchovascular) distribution, as well as basal-predominant disease. Although upper zone-predominant fibrosis has been described as a feature that may separate

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Table 4. Radiological Terms for Heterogenous Lung Attenuation

Terminology	Significance	Description
Mosaic attenuation*	<ul style="list-style-type: none"> • Generic term referring to a patchwork of regions of differing attenuation on inspiratory CT images • Can reflect the presence of vascular disease, airway abnormalities, or ground-glass interstitial or airspace infiltration 	<ul style="list-style-type: none"> • Term only used for description of inspiratory CT images • Combination of areas of low and high attenuation that can correspond to two main situations: <ol style="list-style-type: none"> a. Areas of GGO (“high”) and normal lung (“low”) or b. Areas of normal lung (“high”) and areas of decreased attenuation (“low”) • Areas of GGO reflect an infiltrative lung disease
Air trapping*	<ul style="list-style-type: none"> • Abnormal retention of air distal to airway obstruction • Recognized as parenchymal areas that lack the normal increase in attenuation and the volume reduction of normally ventilated lung • Mosaic attenuation and air trapping are not synonymous and cannot be used interchangeably 	<ul style="list-style-type: none"> • Term exclusively used for description of expiratory CT images • Air trapping appears as focal zones of hypoattenuation in the background of hyperattenuating normal lung on expiratory CT images
Mosaic perfusion†	<ul style="list-style-type: none"> • Regional differences in lung attenuation secondary to regional differences in lung perfusion • May be seen in vascular (<i>exclusive perfusion abnormalities</i>) or airway (<i>perfusion abnormalities resulting from abnormal regional lung ventilation</i>) diseases • Differential diagnosis facilitated by expiratory scans: <ol style="list-style-type: none"> a. In case of vascular disease: same gradient of attenuation between areas of low and high attenuation b. In case of airways disease: the attenuation differences are accentuated due to the additional depiction of air trapping 	<ul style="list-style-type: none"> • Term used for description of inspiratory CT images • Presence of decreased vascular sections within areas of low attenuation in comparison with areas of normal lung
“Three-density pattern”‡	<ul style="list-style-type: none"> • Term coined to replace the “headcheese” sign, as most individuals worldwide do not relate to the headcheese sign • Indicative of a mixed obstructive and infiltrative process: <ol style="list-style-type: none"> a. The obstructive abnormality (seen in small airway disease) is manifested by areas of decreased attenuation and decreased vascularity b. The infiltrative disorder results in GGO surrounding preserved normal lobules • Highly specific for fibrotic HP; has not been shown to be specific for nonfibrotic HP 	<ul style="list-style-type: none"> • Combination of three attenuations on inspiratory CT images: <ol style="list-style-type: none"> a. Normal-appearing lung b. High attenuation (GGO) c. Lucent lung (i.e., regions of decreased attenuation and decreased vascular sections) • Sharply demarcated from each other

Definition of abbreviations: CT = computed tomography; GGO = ground-glass opacity; HP = hypersensitivity pneumonitis.

*See Reference 326.

†See Reference 327.

‡The term “three-density pattern” was coined by this committee. This descriptive pattern was unanimously determined by the committee to be the preferred term. This pattern has been shown to differentiate fibrotic HP from idiopathic pulmonary fibrosis (123) and, thus, raises the index of suspicion for the diagnosis of fibrotic HP whenever present; however, it is unknown whether the pattern is also present in nonfibrotic HP. Some radiologists relate this pattern to the appearance of headcheese and, therefore, it has been referred to as the “headcheese sign” in the literature (328, 329). The guideline committee strongly discourages the use of the term “headcheese” to describe this pattern.

fibrotic HP from IPF (127), only a small proportion of patients with fibrotic HP (<10%) have upper lung–preponderant disease (35, 119, 121).

Fibrotic HP may also present with HRCT patterns that are neither suggestive nor compatible with features of HP; these

HRCT patterns should be classified as indeterminate for fibrotic HP (Figures 1 and E5). They include the patterns of UIP alone (i.e., no other features of HP accompanying the UIP pattern), fibrotic nonspecific interstitial pneumonia (NSIP), and organizing pneumonia (40, 127). The UIP

pattern is recognized by honeycombing with or without peripheral bronchiolectasis, with a subpleural and basal predominance. Fibrotic NSIP is suggested by the presence of bilateral, predominantly lower-lung-zone GGO with fine reticulation and traction bronchiectasis, with peribronchovascular

Table 5. Chest HRCT Scan Features of the Nonfibrotic HP Pattern

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The “typical HP” pattern is suggestive of a diagnosis of HP. It requires a) at least one HRCT abnormality indicative of parenchymal infiltration and b) at least one HRCT abnormality indicative of small airway disease, both in a diffuse distribution	“Compatible-with-HP” patterns are nonspecific patterns that have been described in HP	N/A
Relevant radiological findings	HRCT abnormalities indicative of parenchymal infiltration: <ul style="list-style-type: none"> • GGOs • Mosaic attenuation* HRCT abnormalities indicative of small airway disease: <ul style="list-style-type: none"> • Ill-defined, centrilobular nodules • Air trapping Distribution of parenchymal abnormalities: <ul style="list-style-type: none"> • Craniocaudal: diffuse (with or without some basal sparing) • Axial: diffuse 	Parenchymal abnormalities: <ul style="list-style-type: none"> • Uniform and subtle GGOs • Airspace consolidation • Lung cysts Distribution of parenchymal abnormalities: <ul style="list-style-type: none"> • Craniocaudal: diffuse (variant: lower lobe predominance) • Axial: diffuse (variant: peribronchovascular) 	N/A

Definition of abbreviations: GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; N/A = not applicable.

*Mosaic attenuation corresponding to parenchymal infiltration is created by GGOs adjacent to normal-appearing lung.

predominance in the axial distribution. The pattern of organizing pneumonia relies on the presence of consolidation in a peribronchovascular and/or peripheral distribution, often seen with GGO and sometimes associated with a reverse halo pattern. The presence of a reticular pattern superimposed on parenchymal consolidation suggests an “organizing pneumonia-like” pattern of fibrotic HP. As in other ILDs, HP may also present with a truly indeterminate HRCT pattern.

Combined pulmonary fibrosis and emphysema (82) and pleuroparenchymal fibroelastosis with emphysema (87) can also occur in HP (Figure E6), although they are infrequent. Purely emphysematous forms of HP can be seen independently of smoking history (Figure E7) (85, 116, 131, 132), and fibrotic HP may also be diagnosed at the time of an acute exacerbation (Figure E8) (133).

Histopathological Features

Lung biopsy often plays a pivotal role in ascertaining a diagnosis of HP. The criteria proposed for diagnosis are valid to any biopsy type but are based on historical descriptions of the histopathological findings in surgical lung biopsy (SLB)

specimens (1, 3, 12, 23, 28, 39, 40, 42, 134–142). The findings that make a diagnosis of HP likely apply to both nonfibrotic (i.e., cellular) and fibrotic variants, the difference being the presence or absence of a fibrotic pattern that may show histological overlap with fibrotic IIP (Table 7).

Histopathological Features of Nonfibrotic, or Cellular, HP

A confident histopathological diagnosis of nonfibrotic HP requires the presence of typical histopathological features. These include 1) a cellular interstitial pneumonia accentuated around small airways (“bronchiolocentric”) accompanied by 2) a cellular chronic bronchiolitis, 3) a distinctive pattern of granulomatous inflammation, and 4) no histopathological features to suggest a more likely alternative (Figure 3 and Table 7) (3, 39, 44, 137, 141–144). This combination of findings is often present in a single biopsy specimen. In other patients, each of several biopsy sites may demonstrate only a subset of findings, requiring review of all specimens to appreciate the complete set of features required for a confident histological diagnosis of HP.

The interstitial pneumonia is bronchiolocentric in distribution and comprises predominantly small lymphocytes. The inflammatory infiltrate is

typically polymorphic in that it includes smaller numbers of plasma cells and occasionally eosinophils in some patients. Lymphoid aggregates, especially those with secondary germinal centers, are either absent or very focal and relatively inconspicuous. Follicular lymphoid hyperplasia and a plasma cell–predominant infiltrate suggest other possibilities, including underlying CTD or various forms of immunodeficiency. Prominent peribronchiolar lymphoid hyperplasia accompanied by granulomatous inflammation should raise concern for the possibility of granulomatous-lymphocytic ILD, which is characteristic of common variable immunodeficiency and is a lesion type usually separable from HP by the extent of the lymphoid hyperplasia, which tends to more closely resemble lymphoid interstitial pneumonia and/or low-grade lymphoma (145).

The chronic bronchiolitis characteristic of nonfibrotic HP is a continuum with bronchiolocentric interstitial pneumonia and comprise expansion of the peribronchiolar interstitium by the same lymphocyte-predominant inflammatory infiltrate, without or with only focal lymphoid aggregates that generally lack secondary germinal centers. Affected small airways may show associated organizing

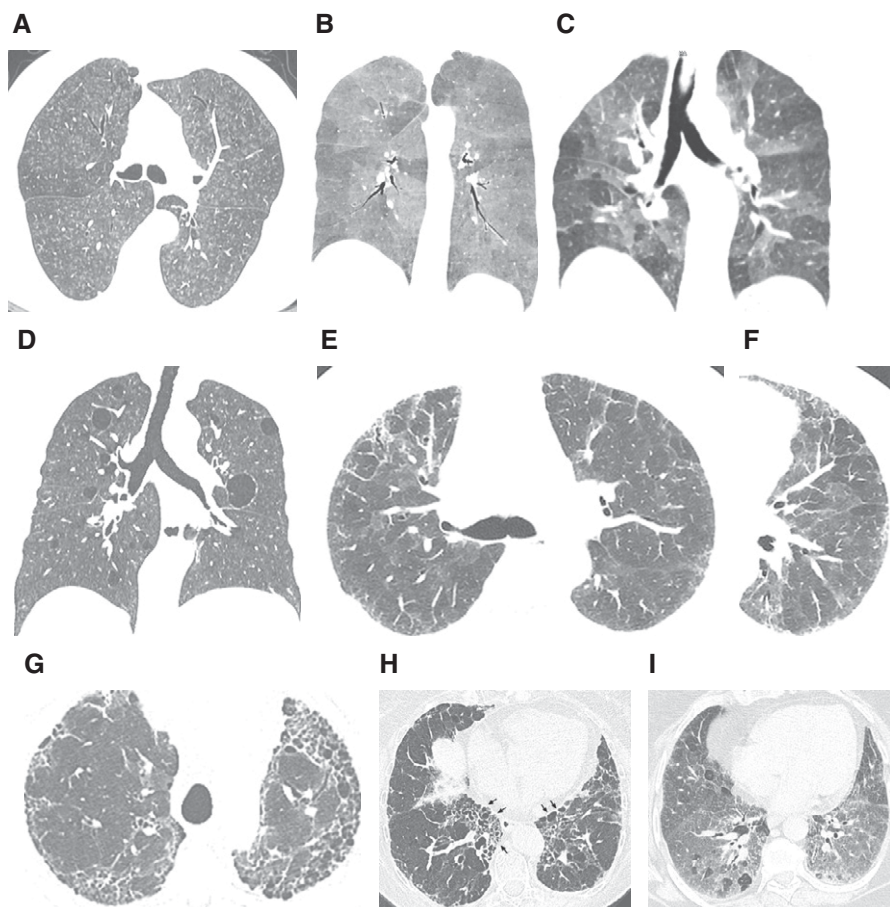


Figure 1. “Typical hypersensitivity pneumonitis (HP)” and “compatible-with-HP” high-resolution computed tomography patterns. The nonfibrotic typical HP pattern is characterized by (A) centrilobular nodules, (B) mosaic attenuation on an inspiratory scan, and (C) air trapping on an expiratory scan. (D) The nonfibrotic compatible-with-HP pattern is exemplified by uniform and subtle ground-glass opacity and cysts. The fibrotic typical HP pattern consists of (E) coarse reticulation and minimal honeycombing in a random axial distribution with no zonal predominance in association with (F) small airway disease. The fibrotic compatible-with-HP pattern varies in the patterns and/or distribution of lung fibrosis (e.g., basal and subpleural predominance, [G] upper-lung-zone predominance, [H] central [or peribronchovascular] predominance [arrows], or [I] fibrotic ground-glass attenuation seen alone or in association with small airway disease). The fibrotic indeterminate-for-HP pattern includes the usual interstitial pneumonia pattern, nonspecific interstitial pneumonia pattern, organizing pneumonia-like pattern, or truly indeterminate findings.

pneumonia that is exquisitely bronchiolocentric. Foamy alveolar macrophages may be conspicuous in peribronchiolar air spaces and are a form of microscopic obstructive pneumonia that reflects small airway dysfunction.

Granulomatous inflammation completes the triad that allows a confident diagnosis of HP on the basis of histology alone, but the diagnostic value is heavily dependent on the qualitative features of the granulomas (Figure 4) (44, 142, 144). The granulomas of HP are typically small and poorly formed, comprising loose, poorly circumscribed clusters of epithelioid and multinucleated

cells (macrophages) that tend to be most prevalent in the peribronchiolar interstitium. Isolated multinucleated giant cells are common and often show nonspecific cytoplasmic inclusions such as Schaumann bodies, asteroid bodies, or cholesterol-like clefts. The poorly formed granulomas and multinucleated giant cells spill into peribronchiolar air spaces, where they may be intimately associated with organizing pneumonia but should also involve the peribronchiolar interstitium (144). Well-formed granulomas resembling those seen in sarcoidosis and granulomatous infections are uncommon and should raise the likelihood

of other conditions if they predominate (134, 135). Aspiration is another important consideration that is characterized by well-formed intraluminal granulomas, often with small foci of central necrosis and associated neutrophils. The granulomas are often affiliated with aspirated foreign material, including a combination of organic and/or nonorganic particulates such as excipients used in oral medications (146). This is true of “hot-tub lung,” a diffuse lung disease (DLD) associated with *Mycobacterium avium* complex with clinical and radiological findings that overlap with classical types of HP, in which well-formed granulomas with or without central necrosis tend to be limited to the lumens of distal bronchioles (Figure E9) (147).

Probable HP refers to cases in which only some of the features described above are present. It requires the presence of both a lymphocyte-rich, bronchiolocentric interstitial pneumonia and an associated bronchiolitis, but without the granulomatous inflammation characteristic of classical HP. Indeterminate HP refers to cases in which either a cellular bronchiolocentric interstitial pneumonia or an otherwise unexplained cellular chronic bronchiolitis is present, but without the characteristic granulomatous inflammation. The chronic bronchiolitis may include peribronchiolar metaplasia (PBM), characterized by expansion of the peribronchiolar interstitium by mild, nondistorting fibrosis that extends into contiguous alveolar septa in which lining pneumocytes have been replaced by a columnar bronchiolar epithelium, without any of the other features to suggest fibrotic HP, as discussed below. Foci of organizing pneumonia may also be present in these categories.

Histopathological Features of Fibrotic HP

Fibrotic HP differs from nonfibrotic HP in that the underlying chronic interstitial pneumonia and/or bronchiolitis is complicated by fibrosis. Typical histopathological features of fibrotic HP include subpleural and centriacinar fibrosis, with or without bridging fibrosis that spans both subpleural and centriacinar regions, or with neighboring centriacinar fibrotic lesions (Figure 5) (23, 137, 140). The pattern of fibrotic interstitial pneumonia may include features that overlap with a UIP pattern, including patchy collagen

Table 6. Chest HRCT Scan Features of the Fibrotic HP Pattern

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The “typical HP” pattern is suggestive of a diagnosis of HP. It requires a) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and b) at least one abnormality that is indicative of small airway disease	“Compatible-with-HP” patterns exist when the HRCT pattern and/or distribution of lung fibrosis varies from that of the typical HP pattern; the variant fibrosis should be accompanied by signs of small airway disease	The “indeterminate-for-HP” pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: <ul style="list-style-type: none"> • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: <ul style="list-style-type: none"> • Ill-defined, centrilobular nodules and/or GGOs • Mosaic attenuation, three-density pattern,* and/or air trapping (<i>often in a lobular distribution</i>) 	Variant patterns of lung fibrosis: <ul style="list-style-type: none"> • UIP pattern: basal and subpleural distribution of honeycombing with/without traction bronchiectasis (<i>per 2018 diagnosis of IPF guidelines</i> [20]) • Extensive GGOs with superimposed subtle features of lung fibrosis Variant (predominant) distributions of lung fibrosis: <ul style="list-style-type: none"> • Axial: peribronchovascular, subpleural areas • Craniocaudal: upper lung zones HRCT abnormalities indicative of small airway disease: <ul style="list-style-type: none"> • Ill-defined centrilobular nodules, or • Three-density pattern* and/or air trapping 	Lone patterns (i.e., not accompanied by other findings suggestive of HP) of: <ul style="list-style-type: none"> • UIP pattern (<i>as per 2018 IPF diagnosis guidelines</i> [20]) • Probable UIP pattern (<i>as per 2018 IPF diagnosis guidelines</i> [20]) • Indeterminate pattern for UIP (<i>as per 2018 IPF diagnosis guidelines</i> [20]) • Fibrotic NSIP pattern • Organizing pneumonia–like pattern • Truly indeterminate HRCT pattern

Definition of abbreviations: GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Rarely, fibrotic HP may be seen 1) as a component of combined pulmonary fibrosis and emphysema or pleuroparenchymal fibroelastosis with emphysema, 2) as a pure emphysematous form of HP, or 3) in acute exacerbation.

*The three-density pattern was formerly called the “headcheese sign.” It is described in detail in Table 4.

fibrosis, fibroblast foci, and associated subpleural-dominant honeycombing (3, 12, 39, 40, 42, 142, 143, 148, 149). Some have applied the term “UIP-like” to draw attention to the histological overlap with a UIP pattern, which frequently poses problems in the differential diagnosis (3, 23, 28, 39). Given the potentially confusing nature of the term “UIP-like” we have chosen not to apply it in this manuscript, although we acknowledge the histological overlaps and highlight those histological features helpful in distinguishing fibrotic HP from other diffuse fibrotic lung diseases. In others, the interstitial pneumonia may have a more uniform and diffuse distribution without honeycomb change and may more closely resemble a fibrotic NSIP pattern (“NSIP-like”). Bronchiolar fibrosis typically takes the form of PBM with fibrosis, a finding that shows significant histological overlap with

descriptions of interstitial airway-centered fibrosis (150, 151). Neither PBM nor airway-centered fibrosis is unique to HP, and they therefore do not by themselves establish the diagnosis (140, 152), but they are characteristic and tend to be more profuse in patients with fibrotic HP compared with patients with fibrotic IIPs (140).

Distinguishing fibrotic HP from fibrotic IIPs requires identification of centriacinar fibrotic lesions and the features described in nonfibrotic HP. The latter features are usually observed in less fibrotic lung tissue. This often requires sampling of more than one site. One site may show findings indistinguishable from a fibrotic interstitial pneumonia, whereas another may show features typical of nonfibrotic HP, including those that might be more appropriately characterized as “probable” or “indeterminate” (143). This

sort of diagnostic discordance between sites is analogous to the histopathological variability documented in patients with IPF, in whom NSIP-like changes are common and may be the sole finding in some samples (153). In other patients, much of a single-site biopsy specimen may mimic a fibrotic IIP, whereas the evidence in support of HP is patchy and often limited to less fibrotic lung tissue. Centriacinar fibrotic lesions, in addition to the subpleural-dominant fibrotic lesions with or without honeycombing, prominent PBM, and/or isolated peribronchiolar giant cells, often with conspicuous Schaumann bodies, may be the clues to search more diligently for the features that would make a diagnosis of HP more likely. It is important to document the fibrotic component when diagnosing HP, as this is an adverse prognostic factor.

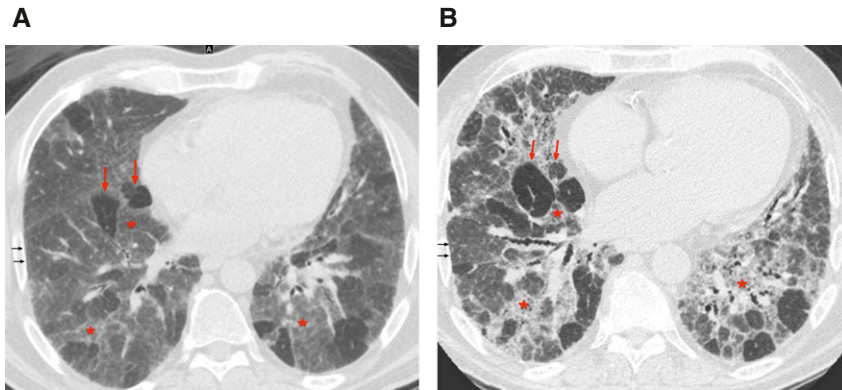


Figure 2. Three-density pattern. High-resolution computed tomography (A) inspiratory and (B) expiratory images from a patient with hypersensitivity pneumonitis demonstrating the three different densities: high attenuation (ground-glass opacity) (red stars), lucent lung (regions of decreased attenuation and decreased vascular sections) (red arrows), and normal lung (black arrows), which are sharply demarcated from each other.

Diagnostic Criteria

The diagnosis of HP requires integration of multiple domains that are ideally considered in the context of an MDD. Given the multitude of presenting features, fibrotic HP should be considered in the differential diagnosis for all patients with a fibrotic ILD. This is particularly challenging, given the absence of an identifiable exposure in up to 50% of patients with fibrotic HP (87, 122, 131–133). Nonfibrotic HP is usually associated with a clear exposure and less frequently poses a diagnostic dilemma, but it similarly lacks a single diagnostic pathway. For these reasons, a comprehensive multidisciplinary approach is important in diagnosing HP, particularly fibrotic HP; however, there remains substantial diagnostic disagreement across experienced MDD teams that likely reflects the absence of standardized diagnostic criteria (17).

Previous studies have identified features that increase the likelihood of HP, with diagnostic algorithms or criteria proposed by multiple groups (1, 5–10). The studies on which these proposals are based all have methodological limitations, most notably incorporation bias (e.g., serum IgG and BAL studies), incomplete consideration of all potentially informative features, absence of appropriate control groups, and inadequate validation (e.g., questionnaires). Despite these limitations, some key features are consistently identified as increasing the likelihood of an HP diagnosis, including

exposure to a known offending agent (1, 7, 8), typical imaging findings (7, 8, 122, 154), and typical biopsy findings (7). BAL lymphocytosis is an important feature (1, 7); serum-specific immunoglobulins might also be helpful (1, 155, 156). Female sex, midinspiratory squeaks (or chirping rales or squawks) (157, 158), absence of a smoking history, and obstructive or mixed restrictive/obstructive physiology have also been identified as potential predictors of an HP diagnosis, but with more limited diagnostic utility. Other features are less frequently identified (e.g., episodes of symptoms and symptoms 4–8 h after exposure) (12), likely reflecting variable proportions of fibrotic and nonfibrotic HP in previous studies.

Although the diagnosis of HP is predominantly based on exposure identification, chest HRCT scan pattern, and bronchoscopic/histopathological findings, a major challenge is that no individual feature is sufficient in isolation, nor are any mandatory. This results in the potential for multiple combinations of abnormalities that can result in a diagnosis of HP. Although a single diagnostic algorithm may be applied to both fibrotic and nonfibrotic HP, these populations have frequent differences in their underlying features. For example, patients with nonfibrotic HP more often have an acute and identifiable exposure, rapid onset of both pulmonary and systemic symptoms, presence of centrilobular nodularity on chest CT scans, and lymphocytosis on BAL cellular analysis (3, 25, 105–107).

Conversely, patients with fibrotic HP are less likely to have an identified exposure and more frequently have an insidious and chronic onset of isolated pulmonary symptoms, fibrotic changes with or without more specific features of HP on chest imaging, and a nonspecific differential cell profile on BAL analysis (4, 105–107). Additional features may be useful in the context of an MDD to increase or decrease the diagnostic confidence of HP on a case-by-case basis, but these are not sufficiently sensitive or specific to justify inclusion in formal diagnostic criteria.

There is often substantial uncertainty in the diagnosis of HP. This occurs most frequently in the distinction between fibrotic HP and IPF (12), reflecting the overlapping features and lack of a single, definitive gold-standard test for both diagnoses. The diagnostic criteria for HP provided in this guideline emphasize the importance of three primary domains: 1) exposure identification (e.g., clinical history with or without a questionnaire, serum IgG testing against potential antigens associated with HP, and/or specific inhalational challenge), 2) imaging pattern, and 3) BAL lymphocytosis/histopathological findings, with each described in detail in the corresponding sections of this document. Although the specific features that satisfy each domain are different for fibrotic and nonfibrotic HP, a single approach is used for all patients who have a clinical presentation consistent with HP.

The diagnostic criteria are presented in a way that explicitly conveys the diagnostic confidence associated with common combinations of specific features. We used an approach similar to the approach proposed by an international working group, which categorized ILD diagnoses on the basis of confidence (159). We categorized diagnoses as definite ($\geq 90\%$ confidence), high-confidence (80–89%), moderate-confidence (70–79%), and low-confidence (51–69%) diagnoses. This approach is supported by recent studies suggesting the potential therapeutic and prognostic utility of assigning diagnostic confidence in this manner (160, 161).

Criteria and an algorithm for establishing a diagnosis of HP are provided in Figures 6 and 7, which may be applied to patients with a clinical presentation consistent with

Table 7. Histopathological Criteria for the Diagnosis of HP (Other than “Hot-Tub Lung”*)

HP	Probable HP	Indeterminate for HP
<p>Nonfibrotic HP (cellular HP) Typical histopathological features of nonfibrotic HP; at least one biopsy site showing all three of the following features:</p> <ol style="list-style-type: none"> Cellular interstitial pneumonia <ul style="list-style-type: none"> Bronchiolocentric (airway-centered) Cellular NSIP-like pattern Lymphocyte-predominant Cellular bronchiolitis <ul style="list-style-type: none"> Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers ±Organizing pneumonia pattern with Masson bodies ±Foamy macrophages in terminal air spaces Poorly formed nonnecrotizing granulomas[†] <ul style="list-style-type: none"> Loose clusters of epithelioid cells and/or multinucleated giant cells ± intracytoplasmic inclusions Situated in peribronchiolar interstitium, terminal air spaces, and/or organizing pneumonia (Masson bodies) <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p> <ul style="list-style-type: none"> Plasma cells > lymphs Extensive lymphoid hyperplasia Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas Aspirated particulates 	<p>Both of the following features (1 and 2 from first column) in at least one biopsy site:</p> <ol style="list-style-type: none"> Cellular interstitial pneumonia <ul style="list-style-type: none"> Bronchiolocentric (airway-centered) Cellular NSIP-like pattern Lymphocyte-predominant Cellular bronchiolitis <ul style="list-style-type: none"> Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers ±Organizing pneumonia pattern with Masson bodies ±Foamy macrophages in terminal air spaces <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p> <ul style="list-style-type: none"> Plasma cells > lymphs Extensive lymphoid hyperplasia Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas Aspirated particulates 	<p>At least one biopsy site showing one of the following:</p> <ul style="list-style-type: none"> 1 or 2 from the first column Selected IIP patterns <ul style="list-style-type: none"> Cellular NSIP pattern Organizing pneumonia pattern Peribronchiolar metaplasia <i>without</i> other features to suggest fibrotic HP <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p> <ul style="list-style-type: none"> Plasma cells > lymphs Extensive lymphoid hyperplasia Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas Aspirated particulates
<p>Fibrotic HP[‡] Typical histopathological features of fibrotic HP; 1 or 2 <i>and</i> 3 in at least one biopsy site:</p> <ol style="list-style-type: none"> Chronic fibrosing interstitial pneumonia <ul style="list-style-type: none"> Architectural distortion, fibroblast foci ± subpleural honeycombing Fibrotic NSIP-like[§] pattern Airway-centered fibrosis <ul style="list-style-type: none"> ±Peribronchiolar metaplasia ±Bridging fibrosis <p>±Cellular interstitial pneumonia</p> <p>±Organizing pneumonia pattern</p> <p>±Cellular bronchiolitis</p> <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p>	<p>Both of the following features (1 or 2 from first column) in at least one biopsy site:</p> <ol style="list-style-type: none"> Chronic fibrosing interstitial pneumonia <ul style="list-style-type: none"> Architectural distortion, fibroblast foci ± subpleural honeycombing Fibrotic NSIP-like pattern Airway-centered fibrosis <ul style="list-style-type: none"> ±Peribronchiolar metaplasia ±Bridging fibrosis <p>±Cellular interstitial pneumonia</p> <p>±Organizing pneumonia pattern</p> <p>±Cellular bronchiolitis</p> <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p>	<p>Either one of the following features in at least one biopsy site:</p> <ol style="list-style-type: none"> Chronic fibrosing interstitial pneumonia <ul style="list-style-type: none"> Architectural distortion, fibroblast foci ± honeycombing Fibrotic NSIP-like pattern <p>±Cellular interstitial pneumonia</p> <p>±Cellular bronchiolitis</p> <p>±Organizing pneumonia pattern</p> <p><i>and</i></p> <p>Absence of features in any biopsy site to suggest an alternative diagnosis</p> <ul style="list-style-type: none"> Plasma cells > lymphs Extensive lymphoid hyperplasia Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas

(Continued)

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Table 7. (Continued)

HP	Probable HP	Indeterminate for HP
3. Poorly formed nonnecrotizing granulomas [†] ± Cellular interstitial pneumonia ± Cellular bronchiolitis ± Organizing pneumonia pattern <i>and</i> Absence of features in any biopsy site to suggest an alternative diagnosis <ul style="list-style-type: none"> • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates 	<ul style="list-style-type: none"> • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates 	<ul style="list-style-type: none"> • Aspirated particulates

Definition of abbreviations: HP = hypersensitivity pneumonitis; IIP = idiopathic interstitial pneumonias; lymphs = lymphocytes; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

*Histological findings in hot-tub lung are distinctly different from nonfibrotic and fibrotic forms of classic HP.

[†]Granulomas in HP are smaller, less tightly clustered, and lack the perigranulomatous hyaline fibrosis commonly seen in sarcoidosis.

[‡]Fibrotic HP may show classic features of nonfibrotic HP (cellular HP) in less fibrotic or nonfibrotic areas; if present, this combination of findings is a histological clue to the diagnosis of HP.

[§]Updates to the classification of IIPs by Travis and colleagues (330) and diagnostic guidelines for idiopathic pulmonary fibrosis (20, 128) tightly link a UIP pattern with idiopathic pulmonary fibrosis and an NSIP pattern with idiopathic NSIP.

^{||}Bridging fibrosis spans subpleural and centriacinar or neighboring centriacinar fibrotic foci.

either fibrotic or nonfibrotic HP. Both were developed through iterative discussion and consensus by the full guideline committee on the basis of the evidence syntheses and recommendations presented below, supplemented by the guideline committee's collective clinical experience.

The primary goal in the diagnosis of ILD is to make a confident diagnosis using the least invasive approach. HP can be diagnosed with high confidence in patients in whom an exposure has been identified and who have a typical HP pattern at HRCT and have BAL lymphocytosis; such patients do not require additional testing. Patients with any other combination of exposure history, HRCT pattern, and BAL results should undergo an MDD that includes an experienced expert in ILD (pulmonologist), a chest radiologist, and, if transbronchial lung biopsies were performed at the time of BAL, a pathologist familiar with histopathological features of interstitial pneumonias and HP. Additional histopathological sampling should be considered after the MDD in some patients with a high-confidence diagnosis, moderate-confidence diagnosis, or low-confidence diagnosis or in patients for whom an alternative diagnosis has not been established (161). A low-confidence diagnosis may be

adequate in patients for whom the differential diagnosis has been sufficiently narrowed such that further investigations are unlikely to alter management, when invasive testing has unacceptable risks, or when such tests are declined by the patient. The diagnosis should be reconsidered at subsequent visits, particularly for patients without a definite diagnosis.

Diagnostic Interventions

Question 1: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without an overt history of exposures capable of causing ILD in the patient's environment at home, work, or elsewhere, be subjected to formal questioning using a questionnaire to raise the possibility that a) potential inciting agents of HP are the etiology of the ILD and b) the diagnosis of the ILD is HP?

Summary of evidence. A systematic search of the literature identified 1,141 potentially relevant articles. The full text of 32 articles was reviewed, and 2 observational studies were selected to inform the guideline committee (12, 162). One study enrolled

19 patients with definite or probable HP and used clinical history, a 22-item questionnaire, and serum IgG testing against HP-associated antigens to identify potential inciting agents of HP. The environments of patients with positive findings were sampled, and potential inciting agents were confirmed or excluded (162). Another study enrolled 46 patients with IPF and used a nine-item questionnaire, serum IgG testing against HP-associated antigens, and bronchial-challenge testing to identify potential inciting agents of HP. BAL was performed, and histopathological specimens were revisited to confirm IPF or reclassify the condition as chronic HP (12). Neither questionnaire had been evaluated in previous studies.

In the former study, the questionnaire identified a potential inciting agent in 19 out of 19 (100%) patients; only 7 patients underwent subsequent environmental testing, with the potential inciting agent confirmed in 5 out of the 7 (71%) (162). In the latter study, the questionnaire identified a potential inciting agent in 27 out of 46 (59%) patients; the final diagnosis was reclassified from IPF to chronic HP in 18 out of 27 (67%) (12). A questionnaire was more likely to identify a potential inciting agent when compared

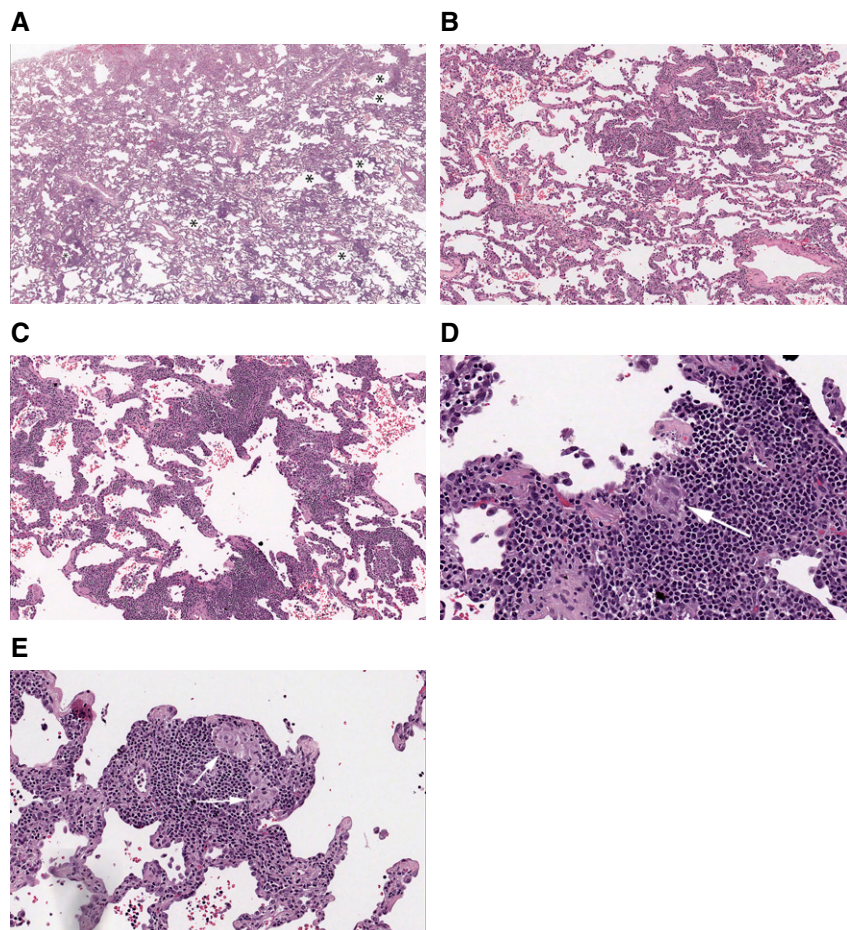


Figure 3. Surgical lung biopsy specimen from a patient with nonfibrotic hypersensitivity pneumonitis (HP). (A) Low-magnification photomicrograph showing preservation of lung architecture and a cellular chronic interstitial pneumonia that is accentuated around bronchioles (asterisks). Magnification, 20 \times . (B) Higher-magnification photomicrograph showing expansion of distal acinar and peribronchiolar interstitium by a cellular infiltrate of mononuclear inflammatory cells. Magnification, 88 \times . (C) Photomicrograph showing a cellular bronchiolitis in which the peribronchiolar interstitium is expanded by cellular infiltrate, predominantly comprising lymphocytes without lymphoid aggregates or follicles. Magnification, 108 \times . (D) Higher-magnification view of airway illustrated in C, demonstrating a poorly formed nonnecrotizing granuloma (arrow) characteristic of HP comprising loose clusters of epithelioid cells (macrophages). Magnification, 400 \times . (E) High-magnification photomicrograph illustrating another poorly formed nonnecrotizing granuloma (arrows) in the same biopsy specimen from a patient with nonfibrotic HP. Magnification, 264 \times . Hematoxylin and eosin staining was used.

with clinical history (relative risk [RR], 3.80; 95% confidence interval [CI], 1.79–8.06) or serum IgG testing (RR, 1.58; 95% CI, 1.12–2.23), but there was no difference when a questionnaire was compared with the combination of serum IgG testing against potential antigens associated with HP plus bronchial-challenge testing (RR, 0.90; 95% CI, 0.65–1.24).

Committee discussion. The guideline committee appreciated the potential of a questionnaire to facilitate the systematic

identification of inciting agents of HP in a patient's environment, compared with clinical history-taking alone, which may be less systematic. However, there is no questionnaire that has been validated for this purpose, and it seems likely that different questionnaires are appropriate for different locations and populations (163). Thus, the guideline committee concluded that it is premature to recommend using a specific questionnaire but that use of a questionnaire may be an important adjunct to the care of patients

with newly detected ILD in the future. In the interim, the committee encourages clinicians to take a thorough history to identify potential exposures and to develop and use their own questionnaires to ensure routine inquiry about potential exposures whenever they evaluate a patient with newly detected ILD. Such questionnaires should include ambient and occupational causes of HP relevant to the patient's geographical location and cultural habits.

Recommendation. For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP or fibrotic HP, the guideline committee makes no recommendation or suggestion for or against the use of a specific questionnaire to identify potential inciting agents of HP; instead, the guideline committee recommends the development and validation of a questionnaire. Voting results: unanimous, no recommendation or suggestion. *Remark:* Pending the availability of a validated questionnaire, the guideline committee advocates that clinicians take a thorough history to identify potential exposures and sources in the patient's environment that are known to be associated with HP.

Question 2: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without an overt history of exposures capable of causing ILD in the patient's environment at home, work, or elsewhere, undergo serum testing for IgG antibodies against specific antigens to raise the possibility that a) potential inciting agents of HP are the etiology of the ILD and b) the diagnosis of the ILD is HP?

Summary of evidence. A systematic search of the literature identified 926 potentially relevant articles. The full text of 49 articles was reviewed, and 15 observational studies were selected to inform the guideline committee (1, 12, 155, 164–175). Most studies enrolled patients with known HP, usually farmer's lung disease or bird fancier's disease, and determined the sensitivity and specificity of serum IgG testing against potential antigens associated

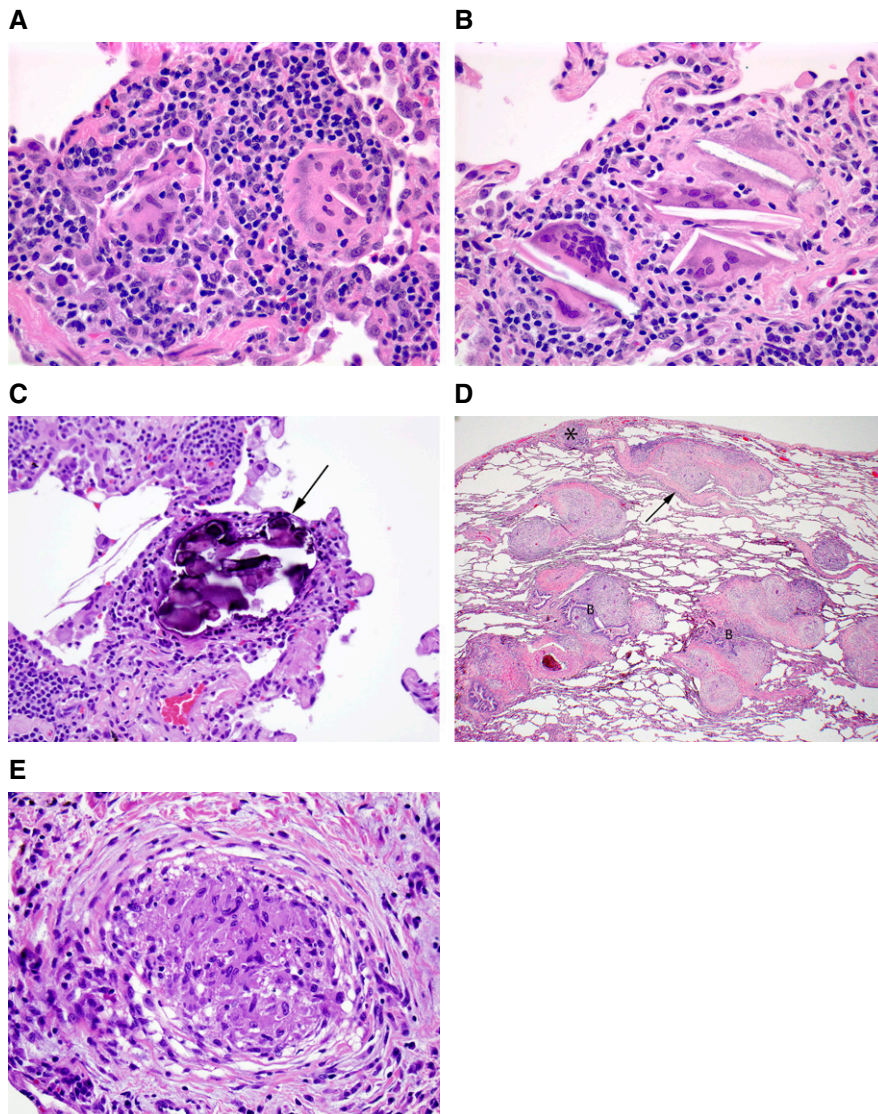


Figure 4. (A–C) Poorly formed granulomas characteristic of hypersensitivity pneumonitis (HP) contrasted with (D and E) well-formed granulomas more typical of sarcoidosis. (A) High-magnification photomicrograph illustrating isolated multinucleated giant cells in a surgical lung biopsy specimen from a patient with nonfibrotic HP. Magnification, 400 \times . (B) Another photomicrograph illustrating giant cells in a patient with HP. These giant cells are distinguished by cytoplasmic cholesterol-like clefts, a nonspecific but common finding. Magnification, 400 \times . (C) In this high-magnification photomicrograph of a surgical lung biopsy specimen, the giant cells are largely obscured by cytoplasmic Schaumann bodies (arrow), another nonspecific but characteristic feature of the granulomatous response in HP. Magnification, 400 \times . (D) Low-magnification photomicrograph of surgical lung biopsy specimen from a patient with sarcoidosis showing characteristic “lymphangitic” distribution, in which the granulomas are limited to the interstitium and involve visceral pleura (asterisk), interlobular septa (arrow), and bronchovascular bundles. Magnification, 20 \times . (E) High-magnification photomicrograph showing a well-formed nonnecrotizing granuloma in a surgical lung biopsy specimen from a patient with sarcoidosis. The well-circumscribed, tight cluster of epithelioid cells (macrophages) is affiliated with a characteristic pattern of circumferential lamellar fibrosis. Magnification, 400 \times . Hematoxylin and eosin staining was used. B = bronchovascular bundle.

with HP using ELISA or precipitins, the latter including double diffusion, immunoelectrophoresis, or electrosyneresis. The antigens to which serum IgG were

measured varied from study to study. Many studies included exposed and unexposed control groups, the latter most often comprising blood donors.

Serum IgG testing against potential antigens associated with HP distinguished HP from other ILDs with a sensitivity and specificity of 83% and 68%, respectively, derived from bivariate analysis of the summary receiver operator curve created by pooling four studies. Serum IgG testing against potential antigens associated with HP performed best when ELISA was the method used.

Serum IgG testing against potential antigens associated with HP distinguished patients with HP from exposed control subjects with a sensitivity and specificity of 90% and 91%, respectively, derived by pooling eight studies. Serum IgG testing against potential antigens associated with HP performed similarly for ELISA and precipitin testing but performed best for patients with metal worker’s lung, followed by farmer’s lung, bird fancier’s lung, and bagassosis.

Serum IgG testing against potential antigens associated with HP distinguished patients with HP from unexposed control subjects with a sensitivity and specificity of 93% and 100%, respectively, derived by pooling seven studies. Serum IgG testing against potential antigens associated with HP performed similarly for ELISA and precipitin testing, and among all types of HP.

A sensitivity analysis was performed to assess potential incorporation bias (overestimation of sensitivity and specificity due to the inclusion of studies that used a positive serum IgG test result as a diagnostic criterion for HP). Five such studies were removed from the analyses, and the results remained similar. Therefore, the studies were kept in the final analysis.

Committee discussion. The evidence synthesis estimated that serum IgG testing against HP-associated antigens distinguishes HP from other ILDs with a sensitivity and specificity of 83% and 68%, respectively. The committee was unanimous in the opinion that both test characteristics are suboptimal. Most committee members considered testing convenient and adequate for generating supportive data; however, they acknowledged that testing is insufficient for confirming or excluding a diagnosis of HP because the test characteristics are inferior to most screening tests currently in use.

It was emphasized that a positive serum IgG result does not mean that the exposure

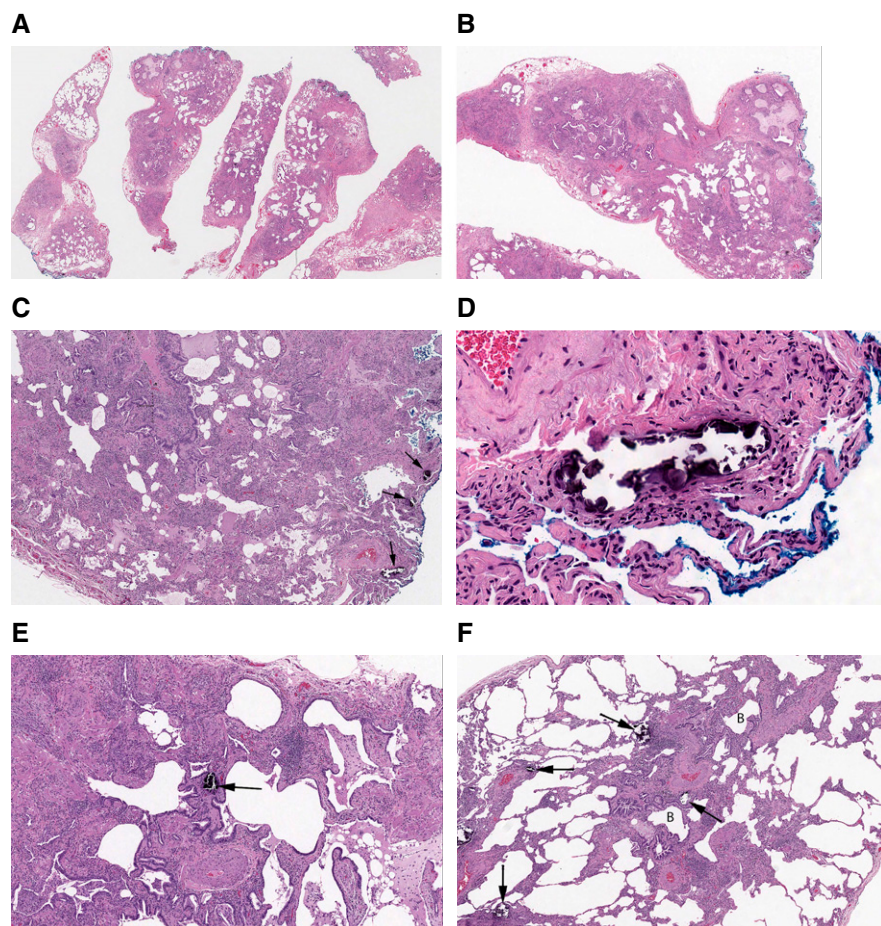


Figure 5. Photomicrographs of surgical lung biopsy specimens from two different sites in a patient with fibrotic hypersensitivity pneumonitis. (A) Scanning magnification view showing multiple sections of a right-lower-lobe biopsy specimen. There is patchy fibrosis with architectural distortion, a combination of findings that resembles usual interstitial pneumonia. Magnification, 6 \times . (B) Low-magnification photomicrograph showing one of the sections illustrated in A, characterized by a pattern of patchy fibrosis with subpleural honeycomb change that resembles usual interstitial pneumonia. Magnification, 17 \times . (C) Higher-magnification view showing expansion of the peribronchiolar interstitium by a cellular infiltrate of mononuclear inflammatory cells (upper left) and isolated Schaumann bodies (arrows) at the edge of the biopsy specimen. Magnification, 46 \times . (D) High-magnification photomicrograph showing one of the isolated Schaumann bodies illustrated in C. Magnification, 400 \times . (E) Photomicrograph from another section illustrated in A showing an isolated Schaumann body (arrow) in the fibrotic peribronchiolar interstitium. Magnification, 63 \times . (F) Low-magnification photomicrograph of a right-middle-lobe biopsy specimen from the same patient showing features more closely resembling nonfibrotic hypersensitivity pneumonitis. There is a more cellular chronic interstitial pneumonia accentuated around bronchioles with scattered calcified Schaumann bodies (arrows) marking isolated multinucleated giant cells. Magnification, 43 \times . Hematoxylin and eosin staining was used. B = bronchiole.

is the cause of the lung condition; it only indicates that the patient has likely been exposed to a potential cause of HP at some point in his or her life, and it may be worthy of further consideration to explore the source of the potential causative agent in the patient's domestic, social, and/or work environment before assignment of a diagnosis of HP, particularly when other diagnostic findings of HP are less certain

(e.g., no BAL lymphocytosis, probable or indeterminate CT or biopsy patterns).

The committee acknowledged the lack of standardization of serum IgG testing against potential antigens associated with HP, with no standardized, internationally accepted "HP panel" and different commercial kits being used by different laboratories. In addition, there was discussion of how the performance of

serum IgG testing may vary with some serum IgG testing being more helpful with some antigens than others and in some parts of the world. Development and validation of a standard or personalized hypersensitivity panel was considered a priority for future clinical investigation.

Recommendations.

1. **For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP, the guideline committee suggests performing serum IgG testing that targets potential antigens associated with HP** (suggestion, very low confidence in the estimated effects). Voting results: recommendation for, 8; suggestion for, 12; no recommendation or suggestion, 3; suggestion against, 5; recommendation against, 0.
2. **For patients with newly identified ILD whose differential diagnosis includes fibrotic HP, the guideline committee suggests performing serum IgG testing that targets potential antigens associated with HP** (suggestion, very low confidence in the estimated effects). Voting results for fibrotic HP: recommendation for, 8; suggestion for, 14; no recommendation or suggestion, 3; suggestion against, 3; recommendation against, 0.

Question 3: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo BAL fluid lymphocyte cellular analysis to diagnose HP?

Summary of evidence. A systematic search of the literature identified 1,500 potentially relevant articles. The full text of 340 articles was reviewed, and 84 observational studies were selected to inform the guideline committee (12, 105, 176–255). Most studies enrolled patients with known HP or other types of ILD, performed BAL with lymphocyte cellular analysis, and compared the percentage of lymphocytes among patients with different conditions. Farmer's lung and bird fancier's lung disease were the most common types of HP, whereas IPF and sarcoidosis were the most common non-HP ILDs enrolled.

A meta-analysis of 36 studies (1,643 patients) demonstrated that patients

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4C/FPO

HRCT

Typical for HP
Compatible with HP
Indeterminate for HP

History of exposure and/or serum IgG testing	Typical for HP		Compatible with HP		Indeterminate for HP	
	Exposure +	Exposure -	Exposure +	Exposure -	Exposure +	Exposure -
No BAL or BAL without lymphocytosis and either no histopathology or indeterminate histopathology	Moderate confidence	Low confidence	Low confidence	Not excluded	Not excluded	Not Excluded
BAL lymphocytosis without histopathology sampling	High confidence	Moderate confidence	Moderate confidence	Low confidence	Low confidence	Not excluded
BAL lymphocytosis with indeterminate histopathology	Definite	High confidence	Moderate confidence	Moderate confidence	Low confidence	Not excluded
Probable HP histopathology	Definite	High confidence	High confidence	Moderate confidence	Moderate confidence	Low confidence
Typical HP histopathology	Definite	Definite	Definite	Definite	Definite	High confidence*

Figure 6. Hypersensitivity pneumonitis diagnosis based on incorporation of imaging, exposure assessment, BAL lymphocytosis, and histopathological findings. All confidence levels are subject to multidisciplinary discussion. *Confidence may increase to “definite” if the pathologist’s conclusion persists after reevaluation in the context of additional clinical information or an expert second opinion on histopathology. HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography.

with HP had a higher proportion of BAL fluid lymphocytes than patients with IPF (mean difference [MD], 30%; 95% CI, 27–34%). This effect was seen regardless of whether the study enrolled patients with nonfibrotic HP (9 studies; MD, 34%; 95% CI, 29–40%), fibrotic HP (12 studies; MD, 21%; 95% CI, 14–27%), or mixed populations with both nonfibrotic and fibrotic HP (15 studies; MD, 36%; 95% CI, 32–40%).

Similarly, a meta-analysis of 53 studies (3,112 patients) demonstrated that patients with HP had a higher proportion of BAL fluid lymphocytes than patients with sarcoidosis (MD, 19%; 95% CI, 17–21%). This effect was seen regardless of whether the study enrolled patients with nonfibrotic HP (17 studies; MD, 25%; 95% CI, 22–27%), fibrotic HP (16 studies; MD, 16%; 95% CI, 11–20%), or mixed populations with both nonfibrotic and fibrotic HP (21 studies; MD, 18%; 95% CI, 15–20%).

In studies with few patients, HP was compared with other ILDs, including CTD-ILD, idiopathic NSIP, and cryptogenic organizing pneumonia, but the number of

patients was too small to make meaningful comparisons.

For distinguishing fibrotic HP from IPF, BAL fluid lymphocyte thresholds of 20%, 30%, and 40% yielded sensitivities of 69%, 55%, and 41%, respectively, and specificities of 61%, 80%, and 93% respectively, with an area under the curve of 0.54 (95% CI, 0.51–0.58). For distinguishing fibrotic HP from sarcoidosis, BAL fluid lymphocyte thresholds of 20%, 30%, and 40% yielded sensitivities of 69%, 55%, and 41%, respectively, and specificities of 26%, 43%, and 61% respectively, with an area under the curve of 0.44 (95% CI, 0.41–0.47). Finally, for distinguishing nonfibrotic HP from sarcoidosis, BAL fluid lymphocyte thresholds of 20%, 30%, and 40% yielded sensitivities of 95%, 88%, and 76%, respectively, and specificities of 26%, 43%, and 61% respectively, with an area under the curve of 0.71 (95% CI, 0.67–0.74). A sensitivity analysis was performed to assess potential inclusion bias (overestimation of sensitivity and specificity due to the inclusion of studies that used BAL fluid lymphocytosis as a

diagnostic criterion for HP); the results remained the same, and the studies were therefore kept in the final analysis.

Committee discussion. The large MD identified when the proportion of BAL fluid lymphocytes among patients with HP was compared with the proportion of BAL fluid lymphocytes among patients with IPF or sarcoidosis led most of the guideline committee to conclude that BAL fluid cellular lymphocyte analysis can play a key role in distinguishing fibrotic HP from IPF and sarcoidosis and in distinguishing nonfibrotic HP from sarcoidosis. The committee was unwilling to extrapolate the results to other ILDs, given the paucity of data, and identified such comparisons as a key research priority.

The committee did not identify a threshold proportion of BAL fluid lymphocytes that distinguishes HP from non-HP ILD, given the poor area under the curve for each comparison. The seeming discordance of the MD and the area under the curve was attributed to the large standard deviation of many studies. In the absence of empirical evidence, the committee’s collective clinical experience

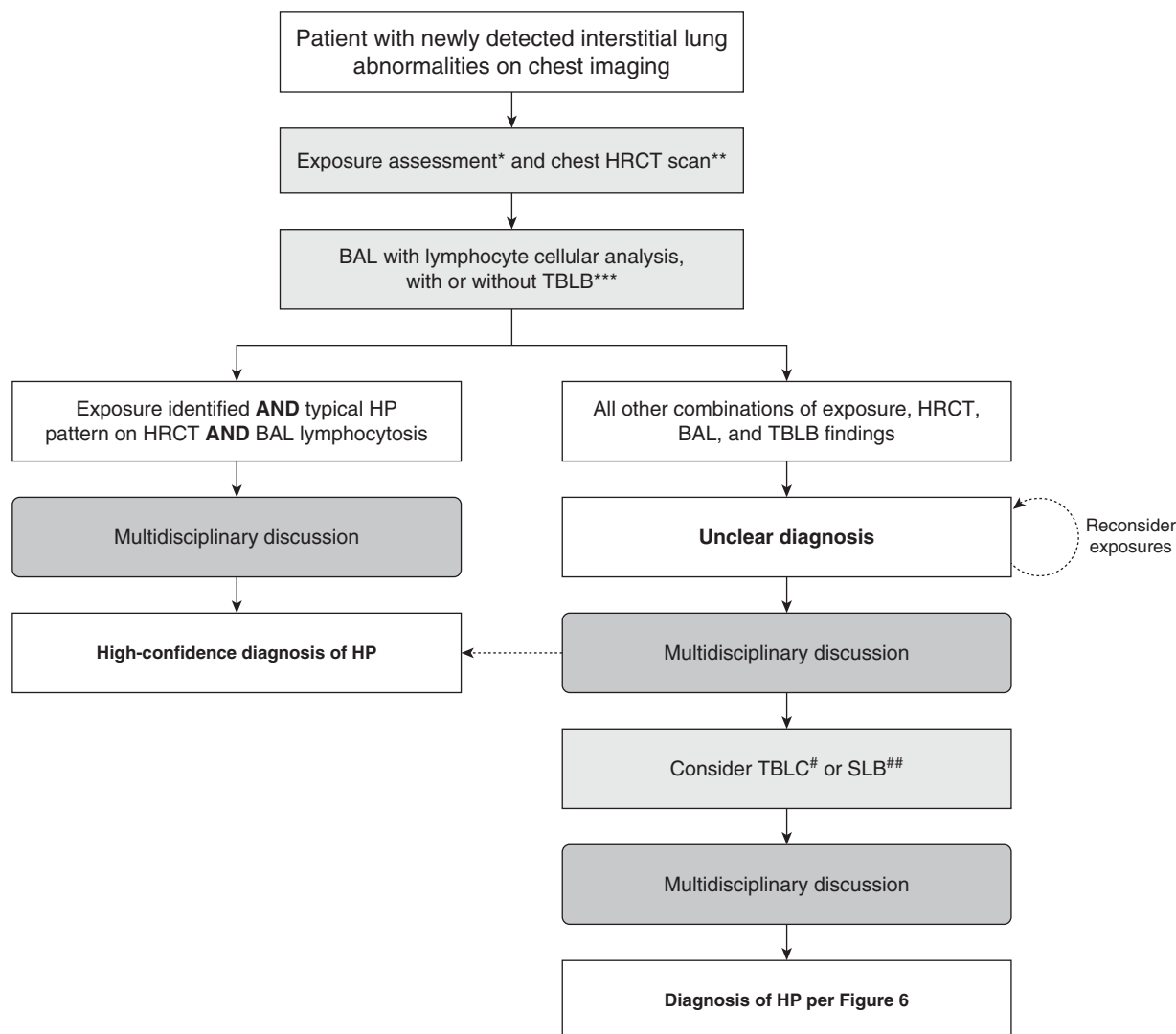


Figure 7. Algorithm for the diagnostic evaluation of possible hypersensitivity pneumonitis (HP). Specific features are described for all steps of the algorithm in the corresponding sections of the manuscript. A provisional diagnosis may be adequate in patients for whom the differential diagnosis has been sufficiently narrowed such that further investigations are unlikely to alter management, when invasive testing has unacceptable risks, or when such tests are declined by the patient. *Exposure assessment includes a thorough clinical history and/or serum IgG testing against potential antigens associated with HP and/or, in centers with the appropriate expertise and experience, specific inhalational challenge testing as described in References 9, 323, 324, and 325. **High-resolution computed tomography should be performed using the technique described in Table 3 and then reviewed with a thoracic radiologist. ***Transbronchial lung biopsy is suggested for patients with potential nonfibrotic HP (see question 4, recommendation 1). #TBLC is suggested for patients with potential nonfibrotic HP, depending on local expertise (see question 5, recommendation 2). ##SLB is infrequently considered in patients with nonfibrotic HP. HRCT = high-resolution computed tomography; SLB = surgical lung biopsy; TBLB = transbronchial lung biopsy; TBLC = transbronchial lung cryobiopsy.

indicated that healthy nonsmokers have a proportion of BAL fluid lymphocytes of 10–15% and, therefore, the committee considered a 30% threshold to be reasonable (256).

Although the guideline committee concluded that BAL fluid cellular lymphocyte analysis is indicated to increase the diagnostic likelihood of

HP, the committee made a stronger recommendation for BAL in patients with suspected nonfibrotic HP than for patients with suspected fibrotic HP because there is an additional reason for BAL in patients with suspected nonfibrotic HP—to identify or exclude pulmonary infection, especially *M. tuberculosis* in patients from endemic areas with a high prevalence of *M.*

tuberculosis, which can progress to death if untreated.

Recommendations.

1. **For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP, the guideline committee recommends BAL with lymphocyte cellular analysis** (recommendation, very low confidence in the estimated effects).

Voting results: recommendation for, 19; suggestion for, 11; no recommendation or suggestion, 0; suggestion against, 1; recommendation against, 0.

2. **For patients with newly identified ILD whose differential diagnosis includes fibrotic HP, the guideline committee suggests BAL with lymphocyte cellular analysis** (suggestion, very low confidence in the estimated effects). Voting results: recommendation for, 10; suggestion for, 18; no recommendation or suggestion, 0; suggestion against, 3; recommendation against, 0.

Question 4: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo transbronchial forceps lung biopsy to diagnose HP?

Summary of evidence. A systematic search of the literature identified 2,465 potentially relevant articles. The full text of 24 articles was reviewed, and 13 observational studies were selected to inform the guideline committee (14, 35, 257–267). Four studies enrolled patients with known HP, six enrolled patients with ILD, and three enrolled patients with DLD. We initially considered ILD and DLD to be synonymous, but, on noting different diagnostic results in the two groups, we opted to analyze each separately. All studies performed transbronchial forceps lung biopsy (TBBx), and most reported the histopathological diagnostic yield of the procedure; some also reported the frequency of adverse effects.

Adequate specimens were obtained in 87% (95% CI, 79–96%) of sampling procedures. The diagnostic yield (defined as the number of procedures that yielded a histopathological diagnosis among the total number of procedures performed) among patients with ILD was 37% (95% CI, 32–42%). Inclusion of TBBx in the multimodality diagnostic approach of patients with ILD increased the likelihood of arriving at a diagnosis compared with an approach without TBBx (RR, 1.67; 95% CI, 1.21–2.30). The diagnostic yield among patients with DLD was 68% (95% CI, 50–86%). Patients with DLD were more likely than patients with ILD to receive a non-ILD diagnosis like malignancy, infection, etc. The diagnostic yield could not be calculated for

patients with known HP, but 41% (95% CI, 25–56%) of such patients who underwent TBBx were confirmed to have HP.

Among the studies that enrolled patients with ILD or DLD, two studies reported the pneumothorax rate (7%; 95% CI, 1–13%), two studies reported periprocedural mortality (no cases; one study monitored for 24 h and the other monitored for 6 mo), two studies reported respiratory exacerbation or failure (no cases), four studies reported moderate-to-severe bleeding (4%; 95% CI, 0–8%), and six studies reported severe bleeding (no cases). One study reported the number of pneumothoraces that required a chest tube (6%; 95% CI, 0–13%), with none lasting longer than 72 hours. The studies that enrolled patients with known HP did not report adverse outcomes.

Committee discussion. There was general agreement that the diagnostic yield of TBBx was suboptimal, with only half of procedures resulting in a diagnosis and with the exact frequency depending on the population. However, the guideline committee was divided regarding the interpretation of the evidence. Some members argued that roughly half of patients who undergo TBBx will be spared an SLB, and other members contended that roughly half of patients will require two sampling procedures instead of one, with the former favoring TBBx and the latter arguing against TBBx. An additional concern is the potential for diagnostic misclassification based on potentially suboptimal TBBx specimens.

Notably, the guideline committee observed that the diagnostic yield was substantially higher among patients with DLD than among patients with ILD (68% vs. 37%). This was extrapolated to the notion that diagnostic yield may be higher among patients with suspected nonfibrotic HP than among patients with suspected fibrotic HP. This potential difference was supported by nonsystematic clinical observations that granulomas are more likely to be detected and to be diagnostic among patients with nonfibrotic HP than among patients with fibrotic HP. Thus, TBBx was judged to be worthwhile in patients with suspected nonfibrotic HP, but not in patients with suspected fibrotic HP.

The committee acknowledged that TBBx is safe, available in most institutions, minimally burdensome, and inexpensive and that most pulmonary clinicians have experience performing the procedure. The

patient representative indicated that he would choose a TBBx in the hope of avoiding SLB, even with the knowledge that a second procedure would be necessary if the TBBx were nondiagnostic.

Recommendations.

1. **For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP, the guideline committee suggests TBBx** (suggestion, very low confidence in the estimated effects). Voting results: recommendation for, 1; suggestion for, 20; no recommendation or suggestion, 4; suggestion against, 3; recommendation against, 0.
2. **For patients with newly identified ILD whose differential diagnosis includes fibrotic HP, the guideline committee makes no recommendation or suggestion for or against TBBx.** Voting results: recommendation for, 1; suggestion for, 13; no recommendation or suggestion, 6; suggestion against, 7; recommendation against, 1.

Question 5: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo transbronchial lung cryobiopsy to diagnose HP?

Summary of evidence. A systematic search of the literature identified 695 potentially relevant articles. The full text of 34 articles was reviewed, and 24 observational studies were selected to inform the guideline committee (257, 261, 262, 264, 268–287). One study enrolled patients with known or suspected HP, 19 enrolled patients with ILD, and 4 enrolled patients with DLD. All studies performed transbronchial lung cryobiopsy (TBLC) and reported the diagnostic yield of the procedure; some also reported the frequency of adverse effects.

The diagnostic yields were 91% (95% CI, 83–99%), 82% (95% CI, 78–86%), and 82% (95% CI, 73–90%) among patients with known or suspected HP, ILD, and DLD, respectively. Among patients with known or suspected HP in whom a diagnosis was made by TBLC, 100% (95% CI, 91.4–100%) were confirmed to have HP and none had an alternative ILD or a non-ILD diagnosis. Among patients with ILD in whom a diagnosis was made by TBLC, 7.2% (95% CI, 5.6–9.2%) were determined to

have HP, 77.5% (95% CI, 74.5–80.3%) were found to have an alternative type of ILD, and 15.3% (95% CI, 13–18%) were determined to have a non-ILD diagnosis, such as an infection. Among patients with DLD in whom a diagnosis was made by TBLC, 13.4% (95% CI, 10.9–16.2%) were determined to have HP, 71.5% (95% CI, 67.9–74.9%) were found to have an alternative type of ILD, and 15.1% (95% CI, 12.5–18.1%) were determined to have a non-ILD diagnosis.

Several studies reported adverse events of TBLC. In the only study that enrolled patients with known or suspected HP, bleeding of any severity occurred in 4% (95% CI, 0–10%) and pneumothoraces occurred in 27% (95% CI, 14–40%). Among studies that enrolled patients with ILD or DLD, 16 studies reported procedural mortality (rare cases; 95% CI, 0–1%); 11 studies did not specify the follow-up duration, three studies employed 30 days of follow-up, one study used 90 days of follow-up, and one study had both 30 days and 90 days of follow-up. Nine studies reported post-procedural exacerbation or respiratory failure (rare cases; 95% CI, 0–1%), 17 studies reported bleeding of any severity (11%; 95% CI, 7–15%), 18 studies reported severe bleeding (0%; 95% CI, 0–1%), and 23 studies reported pneumothoraces (10%; 95% CI, 8–13%).

Notably, several studies directly evaluated TBLC and TBBx within the same populations (257, 261, 262). The studies reported higher diagnostic yield with TBLC, although the incidence of bleeding was also higher with TBLC.

Committee discussion. There was general agreement among members of the guideline committee that the diagnostic yield of TBLC is favorable, with 82–91% of patients potentially avoiding SLB. Histopathological patterns of UIP identified by TBLC have been shown to have substantial agreement with findings from SLB, including both histopathological agreement (κ , 0.70; 95% CI, 0.55–0.86) and diagnostic agreement at MDD (κ , 0.62; 95% CI, 0.47–0.78) (288). The safety profile of TBLC is also favorable compared with SLB. However, the committee acknowledged that most medical centers, particularly community medical centers, currently cannot provide TBLC due to lack of equipment and expertise, nor do they have a large enough volume to justify establishing a TBLC program.

The guideline committee related the evidence from studies that enrolled patients with ILD to its recommendations for patients with suspected fibrotic HP and related the evidence from studies that enrolled patients with known or suspected HP to its recommendations for patients with suspected nonfibrotic HP. They concluded that, in TBLC-capable medical centers, TBLC should be offered to those with suspected fibrotic HP because it may lead to avoidance of a more burdensome, expensive, uncomfortable, and potentially harmful SLB. However, there was lack of agreement about whether TBLC should be similarly offered to patients with suspected nonfibrotic HP because most centers that offer TBLC can also perform TBBx; TBBx probably has fewer complications and was recommended for this patient group as described above.

Recommendations.

- For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP, the guideline committee makes no recommendation or suggestion for or against TBLC.** Voting results: recommendation for, 4; suggestion for, 10; no recommendation or suggestion, 7; suggestion against, 6; recommendation against, 0.
- For patients with newly identified ILD whose differential diagnosis includes fibrotic HP, the guideline committee suggests TBLC** (suggestion, very low confidence in estimated effects). Voting results: recommendation for, 8; suggestion for, 11; no recommendation or suggestion, 5; suggestion against, 3; recommendation against, 0.

Question 6: Should patients with newly detected ILD on chest radiographs or a CT scan of the chest, with or without a history of exposure capable of causing HP, undergo SLB to diagnose HP?

Summary of evidence. A systematic search of the literature identified 501 potentially relevant articles. The full text of 56 articles was reviewed, and 34 nonrandomized studies were selected to inform the guideline committee (14, 289–322). One study enrolled patients with known or suspected HP, 27 enrolled patients with ILD, and 6 enrolled patients with DLD. All studies performed SLB and reported the diagnostic

yield of the procedure; some also reported the frequency of adverse effects.

The diagnostic yields were 96% (95% CI, 90–100%), 98% (95% CI, 98–99%), and 96% (95% CI, 93–99%) among patients with known or suspected HP, ILD, and DLD, respectively. Among patients with known or suspected HP in whom a diagnosis was made by SLB, 91% (95% CI, 79.3–96.5%) were confirmed to have HP and 9% (95% CI, 3.5–20.7%) had an alternative ILD. Among patients with ILD (not specifically suspected or known to have HP) in whom a diagnosis was made by SLB, 9% (95% CI, 5.9–13.1%) were determined to have HP, 61% (95% CI, 54.3–66.4%) were found to have an alternative type of ILD, and 31% (95% CI, 25.1–36.6%) were determined to have a non-ILD diagnosis, such as an infection. Among patients with DLD in whom a diagnosis was made by SLB, 9% (95% CI, 8.1–10.3%) were determined to have HP, 61% (95% CI, 59.2–62.9%) were found to have an alternative type of ILD, and 30% (95% CI, 28.1–31.6%) were determined to have a non-ILD diagnosis.

Many studies reported adverse events of SLB. Procedural mortality was 2% (95% CI, 1–3%; after 30 days of follow-up). Post-procedural exacerbations or respiratory failure occurred in 2% (95% CI, 1–3%). Bleeding was detected in 1% (95% CI, 0–1%). Pneumothorax persistence after chest tube removal was observed in 4% (95% CI, 2–5%), with a prolonged air leak occurring in 3% (95% CI, 2–4%). Respiratory infection and delayed wound healing were complications in 3% (95% CI, 2–3%) and 3% (95% CI, 1–5%), respectively.

Committee discussion. The differential diagnosis for ILD is wide, and management varies substantially among the causes of ILD. Thus, making a definitive or highly confident diagnosis is usually beneficial to patients. The guideline committee concluded that the diagnostic yield was sufficiently large and the adverse events sufficiently few to warrant SLB, despite its burdens and costs, once other diagnostic tests had failed to result in a definitive diagnosis (including other forms of biopsy). The committee emphasized that the decision to perform a SLB should be made after a comprehensive assessment of all available data, ideally in the context of an MDD, as well as after a thorough discussion with the patient about the potential benefits and risks of this procedure.

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Recommendations.

1. **For patients with newly identified ILD whose differential diagnosis includes nonfibrotic HP, the guideline committee suggests SLB; this recommendation is intended for after alternative diagnostic options have been exhausted** (suggestion, very low confidence in estimated effects). Voting results: recommendation for, 1; suggestion for, 20; no recommendation or suggestion, 1; suggestion against, 7; recommendation against, 1.
2. **For patients with newly identified ILD whose differential diagnosis includes fibrotic HP, the guideline committee suggests SLB; this recommendation is intended for after alternative diagnostic options have been exhausted** (suggestion, very low confidence in estimated effects). Voting results: recommendation for, 6; suggestion for, 23; no recommendation or suggestion, 1; suggestion against, 0; recommendation against, 0.

Future Directions

The guideline committee recognized an urgent need to improve knowledge on several topics, including 1) understanding the nature and pathophysiology of HP, 2) diagnostic approaches, 3) disease behavior and natural history, and 4) therapeutic

approaches. Key questions on pathophysiology include genetic susceptibility and both host and environmental factors. For diagnostic approaches, important needs include the validation and standardization of questionnaires, BAL lymphocytosis threshold, specific antibodies, and biomarkers. In addition, new techniques like genomic classifiers and artificial intelligence to improve diagnosis and prognosis need to be assessed. Questions about disease behavior range from prevention to the phenotyping of HP. Regarding phenotyping, the differences between predominantly inflammatory and fibrotic subtypes are important questions. Finally, now that this guideline has established a standardized diagnostic approach to HP, future work needs to address the management of the different subtypes of HP in clinical trials and other research. For a full list of questions deemed important by the guideline committee, see the online supplement.

Registries can play an important role in acquiring knowledge. To maximize their potential, HP-specific registries are needed. Such registries would be particularly helpful in determining the worldwide and national incidence and prevalence of all HP, subtypes of HP (i.e., fibrotic and nonfibrotic HP), and phenotypes of HP (e.g., HP with autoimmune features, HP with progressive fibrotic behavior, etc.), including those without an

identifiable inciting agent by serum IgG testing against potential antigens associated with HP and a thorough evaluation. Registries can also help us understand the frequencies of various detectable and nondetectable exposures and can serve as a biobank for blood and tissue specimens, chest HRCT images, and antigen quantification from the home and workplace.

Conclusions

When a patient presents with newly detected ILD identified by HRCT, the clinician should be prompted to elicit a careful and thorough history and possibly utilize formal questionnaires to reveal the possibility of a temporal relationship between environmental factors/exposures and the onset of symptoms. Serum IgG antibody testing against potential antigens associated with HP may also be performed to detect exposure to potential inciting agents of HP. Many patients should proceed to BAL with lymphocyte cellular analysis with or without transbronchial lung biopsy, and if this information, accompanied by the HRCT patterns, is insufficient to make a definitive diagnosis, they should undergo an MDD with consideration of TBBx, TBLC, or SLB. This approach is recommended by experts in HP on the basis of the best available evidence. The approach should be reevaluated as new evidence becomes available and should be modified as needed. ■

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