Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia Where We Stand and Where We Need to Go

Margaret L. Salisbury¹, Jeffrey L. Myers², Elizabeth A. Belloli¹, Ella A. Kazerooni³, Fernando J. Martinez⁴, and Kevin R. Flaherty¹

¹Division of Pulmonary and Critical Care Medicine, Department of Medicine, ²Department of Pathology, and ³Department of Radiology, University of Michigan, Ann Arbor, Michigan; and ⁴Division of Pulmonary and Critical Care Medicine, Department of Medicine, Cornell Medical College, New York, New York

ORCID ID: 0000-0001-8217-6955 (M.L.S.).

Hypersensitivity pneumonia (HP) is an interstitial lung disease (ILD) caused by sensitization to an inhaled antigen. Although the reported inciting antigens are numerous, most are classified as either avian, microbial (environmental fungi or bacteria), or chemical (usually organic compounds including isocyanates) in nature, but may remain unidentified after thorough evaluation. The true impact is unknown and likely varies geographically due to local climate and industry; agriculture appears to be associated with increased risk of exposure and disproportionate mortality burden (1). The incidence of HP is 0.9 cases per 100,000 person-years in the United Kingdom, with an age-adjusted death rate 0.19 per million overall in the United States (1, 2), compared with the idiopathic pulmonary fibrosis (IPF) incidence of approximately 4.6–16.3 per 100,000 person-years (3). HP is suspected to be underrecognized (4–7). Morell and colleagues highlighted the diagnostic overlap between IPF and fibrotic HP, describing a sizeable proportion of patients initially diagnosed with IPF later receiving a diagnosis of HP (5). Distinguishing fibrotic HP from IPF is important, as specific therapy is available for IPF whereas optimal treatment for fibrotic HP is poorly

defined (8, 9). The broad range of presenting symptoms, high-resolution computed tomography (HRCT) and histopathologic findings, and lack of validated diagnostic criteria make diagnosis difficult and have hindered the progress of research investigating treatment modalities. This Pulmonary Perspective reviews HP manifestations and phenotypes along with diagnostic and treatment strategies, focusing on fibrotic HP.

Clinical Presentation and Classification of HP

The clinical manifestations of HP are variable. Patients may experience episodic dyspnea, wheezing, cough, and systemic response with fevers and malaise, lasting hours to weeks, and a temporal relationship to antigen exposure. This syndrome is referred to as “acute” HP (10, 11), particularly when associated with complete resolution, and is not the focus here. Others develop pulmonary symptoms more insidiously over months to years, with or without intermittent systemic symptoms, presumably due to lower-grade continuous or recurrent exposure. An increase in symptoms may

be temporally related to recurrent or increased antigen exposure. A body of literature describes subgroups of HP in relation to the duration or nature of symptoms; however, these classifications are not linked to disease outcomes such as survival or treatment response (10–13). A better classification is based on the presence or absence of fibrosis. The presence and extent of histopathologic fibrosis are consistently associated with worse survival in HP (14–19). In patients without a lung biopsy, fibrotic HRCT features (described below) are a reliable surrogate associated with increased mortality (20, 21). We suggest the approach to diagnosis and treatment of HP be guided by this distinction.

Diagnostic Considerations

Overview

The last 20 years have seen refinements in the classification of idiopathic interstitial pneumonias, with hypersensitivity pneumonia included in the differential diagnosis for nearly all idiopathic interstitial pneumonias (22). As with any suspected ILD, the first step is to obtain a thorough clinical history with attention to potential causes including rheumatologic

(Received in original form August 19, 2016; accepted in final form December 20, 2016)

Supported by National Institutes of Health grants T32 HL007749-21 and K24 HL113136; funding sources supported M.L.S.'s salary and manuscript submission fees.

Author Contributions: Conception and design: M.L.S., F.J.M., and K.R.F.; drafting of the manuscript: M.L.S.; review and revision of the manuscript for important intellectual content: M.L.S., J.L.M., E.A.B., E.A.K., F.J.M., and K.R.F.

Correspondence and requests for reprints should be addressed to Margaret L. Salisbury, M.D., Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Michigan, 1500 E. Medical Center Drive, 3916 Taubman Center, Ann Arbor, MI 48109. E-mail: msalisbu@med.umich.edu

Am J Respir Crit Care Med Vol 196, Iss 6, pp 690–699, Sep 15, 2017

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Originally Published in Press as DOI: 10.1164/rccm.201608-1675PP on December 21, 2016

Internet address: www.atsjournals.org

disease, occupational and environmental antigenic exposures, and drug toxicity. Dedicated multidisciplinary case review (i.e., pulmonologist, thoracic radiologist, and pathologist) is recommended to maximize agreement on ILD diagnosis, and consideration of referral to an expert center when multidisciplinary review is unavailable or the patient is not confidently diagnosed with IPF (23, 24). Although multidisciplinary case review increases diagnostic agreement among participating physicians, one report highlights ongoing disagreement about what constitutes HP. Agreement across multidisciplinary teams on an HP diagnosis was fair ($\kappa = 0.24$), whereas agreement on IPF ($\kappa = 0.60$) or connective tissue disease-associated ILD ($\kappa = 0.64$) was moderate to good (25). This likely reflects local practice variation and absence of consensus guidelines for diagnosing HP. HP is typically diagnosed in the presence of a consistent clinical syndrome, with results of HRCT scan, bronchoscopy, surgical lung biopsy, and environmental evaluation for inciting antigen adding to diagnostic confidence.

Performance of Specific Diagnostic Tests in HP

High-resolution computed tomography.

HRCT scan findings are often the first prompt for physicians to consider HP. Fibrotic ILD features include septal thickening, traction bronchiectasis, and honeycomb cysts (26, 27). In patients with radiologic fibrosis, specific HRCT findings prompting consideration of fibrotic or chronic HP include distribution of abnormality in a patchy or geographic pattern, often with upper lung predominance, ground-glass opacities, and centrilobular nodules, mosaic attenuation, and air trapping (28–30). Figure 1 shows examples of HRCT features in patients with HP. Several studies evaluating the performance of HRCT in identifying HP among other ILDs have shown that a “confident” radiologic HP diagnosis is 88–92% accurate and 44–61% sensitive (29, 30). However, the inclusion of limited alternative diagnoses may inflate the reported accuracy for HP in these studies. Johansson and colleagues (28) evaluated clinical and radiologic predictors of biopsy-confirmed chronic HP among a variety of

Figure 1. (A) Inspiratory and (B) expiratory high-resolution computed tomography images of a patient with hypersensitivity pneumonitis (HP). In A, arrows mark mosaic attenuation, defined by patchwork regions of differing attenuation, and in B arrows mark air trapping, suggested by the lack of normal increase in lung attenuation during expiration. (C and D) Examples of fibrotic high-resolution computed tomography features of mixed reticular and ground-glass densities with volume loss (arrows), along with features suggesting HP including fuzzy centrilobular nodules (boxed), together suggestive of fibrotic HP.

alternative ILD diagnoses. A high model-based HP score (incorporating age, down feather or bird exposure, and presence of diffuse ground-glass opacity and mosaic perfusion at HRCT) was associated with 91% specificity and 48% sensitivity for chronic HP. Together these data suggest that in select patients, HP may be diagnosed on the basis of clinical and HRCT criteria without proceeding to more invasive testing. These studies are notable for the relatively low sensitivity for HP and low “prevalence” (24–62%) of a confident radiologic diagnosis (6, 28–30). Many patients will not receive a confident diagnosis after clinical and HRCT evaluation, prompting additional diagnostic tests. Importantly, several alternative conditions result in an HRCT appearance of mixed interstitial and airway disease, including rheumatologic diseases, chronic sarcoidosis, and ILD with concurrent small-airway disease (asthma or smoking-related chronic obstructive pulmonary disease). Pulmonary vascular disease alongside ILD appears similar, with mosaic perfusion abnormality and fibrosis (31–35). When

this pattern is seen, careful consideration of alternative etiologies is prudent.

Indirect or direct histopathologic evaluation. If the diagnosis remains in question after evaluation of clinical history and HRCT, direct or indirect histopathologic evaluation should be considered; options include bronchoscopy with bronchoalveolar lavage (BAL) cellular analysis, standard transbronchial biopsy/transbronchial cryobiopsy, or surgical lung biopsy.

Bronchoscopy with BAL cellular analysis, measurement of T-lymphocyte subpopulations (i.e., CD4⁺ cell:CD8⁺ cell ratio), and standard transbronchial biopsy or transbronchial cryobiopsy may be considered in the evaluation of patients with undifferentiated ILD (36, 37). Case series data, which are potentially subject to confirmation bias, indicate BAL lymphocytosis (mean BAL % lymphocytes, 29–57%) is seen in patients with HP with radiologic or histopathologic fibrosis (18, 38). In another series in which 7 of 15 patients with chronic HP underwent BAL, 85% (n = 6) had BAL % lymphocytes

greater than 20% (39). A prospective study using consistent HRCT findings plus BAL lymphocytosis greater than 30% (or 20% for current smokers) as the “gold standard” criteria for HP developed a prediction rule for identifying “active” HP; however, the proportion of patients with radiologic/histopathologic fibrosis is not reported in this study, making use of this rule less applicable to fibrotic HP (40). A retrospective analysis of patients meeting IPF diagnostic criteria shows that BAL lymphocytosis greater than 30% is present in a small proportion of patients and may be helpful in identifying alternative diagnoses, specifically idiopathic nonspecific interstitial pneumonia (NSIP) and HP (41). BAL lymphocytosis is also reported in NSIP, organizing pneumonia, and sarcoidosis. The test characteristics and appropriate diagnostic thresholds for BAL lymphocytosis useful for identifying HP in undifferentiated ILD have not been evaluated, and the above-described data suggest that the sensitivity and specificity of BAL lymphocytosis in isolation may be limited. A preponderance of data suggests that a low CD4⁺ cell:CD8⁺ cell ratio is not consistently seen in chronic or fibrotic HP, and measurement is therefore not recommended (38, 42).

Transbronchial biopsy (TBB) appears to be of limited value in establishing a diagnosis of fibrotic HP. A retrospective study of patients with acute farmer’s lung documented nonspecific TBB findings in one-half of the patients, and characteristic findings in only 11% (39, 43). Another study assessed agreement between TBB and surgical lung biopsy in patients with ILD, and found that a confident diagnosis reached after review of clinical, HRCT, and TBB data was in perfect agreement with surgical biopsy. Unfortunately, less than 25% of individuals were confidently diagnosed after TBB (44). Transbronchial cryobiopsy is an emerging technique that may modify ILD diagnosis confidence similar to surgical biopsy when applied in a multidisciplinary case review setting; at present, data assessing accuracy and yield against surgical lung biopsy as a gold standard in ILD are lacking (45, 46).

Surgical lung biopsy may reveal a classic triad of chronic cellular bronchiolitis, cellular (i.e., lymphocytes and plasma cells) “NSIP-like” chronic interstitial pneumonia with a bronchiolocentric distribution, and

small, loose nonnecrotizing granulomas and/or giant cells located within peribronchiolar interstitium (Figure 2A); this is considered classic for the “subacute” phase of HP (17, 47, 48). In a large biopsy series of patients with “active” farmer’s lung, all patients had a lymphoplasmacytic interstitial infiltrate, 65% had interstitial fibrosis, and 70% had granulomas and/or solitary giant cells (48). Patients with HP with interstitial fibrosis may manifest usual interstitial pneumonia (UIP)-like, fibrotic NSIP-like, or bronchiolocentric patterns of fibrosis, which can be seen with or without components of the classic triad (Figures 2B and 2C) (14, 49, 50). Residual giant cells and cholesterol clefts without granulomas can be seen in late-stage fibrotic disease, which may otherwise appear histopathologically identical to UIP, fibrotic NSIP, or end-stage honeycomb lung (12, 51). Cellular NSIP-like or organizing pneumonia patterns are reported, but may be less commonly associated with fibrotic lesions (15, 48, 52). Airway-centered inflammatory or fibrotic (i.e., peribronchiolar metaplasia) lesions are seen in fibrotic HP and, although not specific, may be a clue to the diagnosis (49, 53–55).

Environmental evaluation and specific antigen testing. Attention to environmental exposures is of high importance before assigning a diagnosis of idiopathic interstitial pneumonia. This was highlighted in a study revealing that 43% of patients diagnosed with IPF based on current guidelines (specifically, meeting HRCT criteria for the UIP pattern) were subsequently diagnosed with fibrotic HP after additional testing, largely based on a more rigorous evaluation for a causative antigen (3, 5). All patients presenting with undifferentiated interstitial lung disease should be questioned about exposure to common antigens at the initial visit; we suggest using a questionnaire tailored to the practice locale. If a potential antigen is identified, details about exposure duration and relationship to pulmonary or systemic symptoms should be obtained. To our knowledge, no validated set of questions specific to HP exposures is available. If a potential inciting antigen is identified, the choice of subsequent testing should be guided by this knowledge.

In patients presenting with ILD and an identifiable inciting antigen, specific

Figure 2. (A) Low-magnification photomicrograph of a surgical lung biopsy showing classic findings of hypersensitivity pneumonia, including a cellular interstitial pneumonia centered on airways with scattered multinucleated giant cells within the peribronchiolar interstitium (hematoxylin and eosin stain; original magnification, $\times 40$). (B) Low-magnification photomicrograph showing a combination of patchwork fibrosis and honeycomb change nearly indistinguishable from usual interstitial pneumonia in a patient with fibrotic hypersensitivity pneumonia (hematoxylin and eosin stain; original magnification, $\times 17$). (C) Low-magnification photomicrograph of biopsy from a different site in the same patient as in B, showing features typical of hypersensitivity pneumonia including multiple isolated giant cells in peribronchiolar interstitium with associated calcified Schaumann bodies (hematoxylin and eosin stain; original magnification, $\times 40$).

inhalation challenge, involving delivery of nebulized antigen with subsequent monitoring of physiological parameters, could be considered to confirm HP diagnosis. Prospective assessment in bird-exposed patients with ILD reveals good

sensitivity and specificity (100% and 82%, respectively) for discrimination of chronic HP from a range of alternative ILDs (56). Low-quality evidence suggests reasonable performance when testing against avian or fungal antigens, but others indicate reduced sensitivity when nonavian antigens are included, particularly with advanced fibrosis (39, 50, 57, 58). *In vitro* lymphocyte proliferation testing is described in avian HP, but is not standardized or widely available (15, 59). Most centers are unable to perform individualized antigen challenge testing.

Unfortunately, in many cases of chronic HP an inciting antigen is not identified, exceeding 50% in some series, making testing for reactivity to specific antigen difficult (21, 47, 60). Several commercially available panels measure serum IgG against various microbial and avian antigens, but the value of results is limited because many antigens are unrepresented, non-ill exposed individuals often test positive, and no information is provided on location of exposure to facilitate environmental remediation. A pilot study on targeted environmental sampling with testing of samples against patient serum for the presence of IgG in patients with HP (80% fibrotic) identified a potential antigen in almost all subjects suspected to have ongoing exposure (61). Further refinement of the sensitivity of these assays, with the addition of reactivity testing when antigens are identified, could prove a useful tool in the diagnosis of suspected HP or undifferentiated ILD. In summary, thoughtful search for an antigen should proceed, but given current testing limitations, antigen identification need not be required for HP diagnosis confirmation.

Putting It Together: Toward Diagnostic Criteria for Fibrotic HP

On the basis of the disease heterogeneity described above, patients are likely to receive a confident diagnosis of inflammatory or fibrotic HP by meeting a variable number and type of criteria. It should be recognized that a sizeable proportion will not manifest classic markers, such as clear-cut reproduction of symptoms with antigen exposure, or have a biopsy specimen showing all of the classic HP features (21, 47, 48, 60). We suggest following an algorithm as outlined in Figure 3. Evidence-supported

minimum noninvasive criteria to establish a confident HP diagnosis include the presence of typical HRCT features (described above) plus BAL lymphocytes comprising more than 20–30% of total leukocytes (40), or typical HRCT features plus a plausible and temporally related exposure (28). Although available evidence supports using a combination of HRCT features plus BAL lymphocytosis or plausible exposure to raise confidence in a diagnosis of HP, robust, prospective data testing against histopathologic evaluation are lacking. Patients not meeting these criteria require additional testing, often meaning a surgical lung biopsy when feasible, based on patient characteristics. The presence of the classic HP triad at lung biopsy should prompt strong consideration of an HP diagnosis, even when seen in combination with other histopathologic patterns and when plausible antigen and typical HRCT features are absent (15, 47–49), provided that histopathologic mimics are excluded (33–35, 62). Individual features of the HP triad seen alongside other biopsy patterns can also suggest HP in the correct context (i.e., when consistent HRCT features or antigen exposure are present). The proposed algorithm is largely structured around the presence or absence of HP-associated HRCT features. Unanswered questions regarding application of this approach warrant further evaluation including the following: (1) How many HP-associated HRCT features sufficiently raise pretest probability such that BAL rather than surgical biopsy is an appropriate confirmatory test? (2) What are the test characteristics of the intermediate steps in the algorithm? and (3) How successful is this approach in reducing the need for surgical biopsy?

The most difficult cases of fibrotic lung disease to diagnose involve two scenarios: (1) there is a plausible exposure (i.e., long-standing exposure to domestic birds) but HP-associated HRCT and histopathologic findings are absent, and (2) a patient meets most of the criteria for an idiopathic interstitial pneumonia, but HRCT or biopsy shows nonspecific features sometimes associated with HP, such as mild air-trapping/mosaic attenuation on HRCT or biopsy showing rare giant cells, minor lymphocytic bronchiolitis, or airway-centered fibrosis (3). Collectively, limited low-quality evidence in patients

with “unclassifiable” ILD suggests that with advanced fibrosis or low diffusing capacity of the lung for carbon monoxide (DL_{CO}), the outcome is poor and more in line with IPF than HP (16, 63). Biopsy results that conflict with clinical and radiologic data are a common reason for inability to reach a diagnosis in patients with unclassifiable disease (63). More research is needed to clarify the best course of action in these patients, as they are often left without a clear diagnosis and therefore without access to specific treatments. With better development of environmental sampling, specific antigen testing, or serum or other biomarkers specific to fibrotic HP, we may find that some of these patients are best classified as having HP (5, 61). Rigorous longitudinal study of disease course in patients with discordant HRCT and histopathologic findings may also assist with patient classification.

Management of Fibrotic HP

Consideration of treatment for fibrotic HP should begin with a brief overview of the pathobiology of fibrotic lung disease. IPF is understood as a disease of aberrant wound healing after repetitive injury with up-regulation of proliferation, remodeling, and myofibroblast genes, whereas inhaled antigens lead to T-cell activation and increased expression of immune response genes in HP (64–66). The mechanism of fibrosis in HP is complex and remains poorly understood, with host factors such as genetics and environmental factors likely contributing (67). Human and animal studies suggest that reduced number or function of $\gamma\delta$ T cells (important in immune response attenuation) is associated with fibrosis in HP (38, 68, 69). IL-17A may be important, with reduced inflammation and less collagen formation when IL-17 is absent or neutralized (70–72). Neutrophils are implicated as the source of IL-17 (70), and are correlated with the extent of fibrosis in human fibrotic HP lungs (73). The inflammatory/fibrotic response to IL-17 may be independent of transforming growth factor (TGF)- β , with increased neutrophils and no change in soluble collagen levels after partial TGF- β inhibition (70). This is in contrast to understanding the role of TGF- β in fibrosis development in IPF and other fibrosis

Figure 3. A diagnostic algorithm for patients with possible hypersensitivity pneumonia (HP) centers around initial evaluation for clinical features suggesting alternative interstitial lung disease (ILD) etiologies, followed by further diagnostic testing based on high-resolution computed tomographic (HRCT) findings and exposures in patients with ILD suspected of having HP. “HP Triad” refers to chronic cellular bronchiolitis, cellular chronic interstitial pneumonia with a bronchiolocentric distribution, and small, loose nonnecrotizing granulomas and/or giant cells located within the peribronchiolar interstitium. “Suggestive biopsy” refers to presence of one or more of the individual biopsy findings suggesting HP listed in the box. BAL = bronchoalveolar lavage; IPF = idiopathic pulmonary fibrosis. *Although we believe evidence supports using a combination of HRCT features plus BAL lymphocytosis or plausible exposure to raise confidence in a diagnosis of HP, robust, prospective data testing against histopathologic evaluation are lacking.

models, where inhibition of the TGF- β pathway is associated with reduced fibrosis (74). Evidence suggests that fibrocytes, important in IPF but typically few or absent in normal lungs, infiltrate HP lungs, including those with and without well-established fibrosis (75). These cells appear to induce fibroblasts to express collagen I and lymphocytes to express CCL2, leading to recruitment of macrophages, neutrophils, and more fibrocytes (76). This suggests a portion of the HP fibrosis pathway in common with IPF, with evidence on commonalities otherwise scanty (66).

HP treatment involves antigen avoidance, consideration of treatment with steroids and/or cytotoxic drugs directed at suppression of ongoing

inflammatory/immune response, and management of comorbidities. In patients with suspected or confirmed HP, a search for inciting antigen should ensue, with remediation of exposure when identified. Patients with fibrotic HP in whom an antigen is identified seem to have less risk of mortality after adjustment for relevant clinical factors (60), with longer exposure duration associated with reduced capacity for recovery of pulmonary function after removal (77). A larger quantity of avian antigen in the home environment is associated with FVC decline and worse survival in chronic HP (78). Unfortunately, the appropriate means of antigen remediation is not well defined. The presence of avian antigen in the home environment can be documented

many months after bird removal, sometimes in spite of professional cleaning (79). When the causative antigen is unknown, there is no widely available, standardized method for environmental evaluation (61), leading some to recommend complete change of environment including changing homes.

Evidence to guide drug treatment in fibrotic HP is lacking, and thus suggestions regarding specific drug treatments are based entirely on observational data and expert opinion. A single randomized, placebo-controlled trial tested an 8-week tapering course of prednisone versus placebo in acute farmer’s lung. Pulmonary function improved on average in both groups, with no between-group difference after

12 months (80). Although not prospectively tested in a randomized controlled trial, use of corticosteroids and cytotoxic agents, such as mycophenolate mofetil or azathioprine, in fibrotic HP is common (13, 16, 18, 21, 81). In a retrospective analysis of patients with fibrotic HP treated with mycophenolate mofetil or azathioprine, patients experienced no change in FVC and significant improvement in DL_{CO} after 1 year of treatment (82). A small series reports the use of rituximab in HP refractory to other immunosuppression, with mixed outcomes (83).

In devising a treatment regimen, we suggest consideration of whether there is evidence of active inflammation, including ground-glass attenuation or centrilobular nodules on HRCT, BAL lymphocytosis, or histopathologic cellular interstitial pneumonia or granulomatous inflammation, as outlined in Table 1. A trial of immunosuppression may be reasonable in patients with active inflammation, using change in pulmonary function and/or HRCT appearance as measures of effectiveness. Given the lack of efficacy and potential harm in the use of combination corticosteroid/cytotoxic treatment in patients with IPF (84), we advise caution in initiation or continuation of immunosuppression in patients with fibrotic HP with minimal inflammation or lack of initial response to an adequately dosed trial of corticosteroids. How treatment response is defined is an area of continued uncertainty. Improving pulmonary function is consistent with a treatment response. Little evidence is available to indicate whether disease stability during immunosuppression is a treatment response or failure. Table 1 suggests consideration of drug withdrawal when disease is stable but unimproved, placing a high value on avoidance of medication side effects. Progressive fibrotic disease despite immunosuppression likely indicates treatment failure, and we suggest withdrawal of drugs in this setting. Whether the presence of inflammatory features confers a propensity for improvement with immunosuppressive treatment is also uncertain. In patients undergoing dual immunosuppression (i.e., prednisone and mycophenolate or azathioprine) or those taking more than 20 mg of prednisone for a prolonged period, pneumocystis

Table 1. Treatment Strategies in Hypersensitivity Pneumonia

Inflammatory Features* Present
<ul style="list-style-type: none"> • Environmental evaluation and antigen remediation • Consider a trial of immunosuppression. Watchful waiting is also an option in stable and/or mild disease, or if an antigen is identified and removed • Suggested immunosuppressive regimen[†]: <ol style="list-style-type: none"> 1. Corticosteroids (0.5–1 mg/kg daily prednisone equivalent) ± cytotoxic agent^{‡§} <ol style="list-style-type: none"> a. Taper prednisone to 20 mg daily in the first 3 mo b. Close interval monitoring of FEV₁, FVC, and DL_{CO} (consider every 1–2 mo initially) 2. Taper corticosteroid to <20 mg daily when pulmonary function plateaus (presuming initial improvement) <ol style="list-style-type: none"> a. Interval pulmonary function every 3–4 mo. Consider HRCT at 3–6 mo b. If disease worsens during steroid taper, consider cytotoxic agent (if not already initiated). Evaluate for infection or reintroduction of antigen, as indicated • Tailor maintenance treatment to the clinical scenario[†]: <ol style="list-style-type: none"> 1. Initial improvement followed by pulmonary function plateau: <ol style="list-style-type: none"> a. Consider gradual withdrawal of drugs versus maintenance with cytotoxic agent b. Drug withdrawal is favored if an antigen is identified and removed c. Closely monitor for deterioration; consider reinstitution of immunosuppression if observed 2. Stable disease but no improvement with immunosuppression: <ol style="list-style-type: none"> a. Consider gradual withdrawal of drugs b. Closely monitor for deterioration; consider reinstitution of low-dose cytotoxic agent if observed 3. Progressive disease despite treatment escalation/change: Consider gradual withdrawal of immunosuppression
Inflammatory Features* Absent
<ul style="list-style-type: none"> • Environmental evaluation and antigen remediation • Consider watchful waiting in stable and/or mild disease, or if an antigen can be identified and removed. Trial of immunosuppression can be considered after review of risks and expected benefits • If a trial of immunosuppression is elected, proceed with immunosuppression regimen as described above, with the following caveat: <p>In patients with advanced fibrosis and no sign of inflammation, we suggest limiting a treatment trial to 3 mo of corticosteroids, and taper off if no improvement is observed. Addition of a cytotoxic agent may be of little benefit and result in untoward side effects</p> • Tailor maintenance treatment to the clinical scenario: <ol style="list-style-type: none"> 1. Initial improvement followed by pulmonary function plateau: <ol style="list-style-type: none"> a. Consider gradual withdrawal of drugs versus maintenance with low-dose cytotoxic agent b. Drug withdrawal is favored if an antigen is identified and removed c. Closely monitor for deterioration; consider reinstitution of immunosuppression if observed 2. Stable or progressive disease: Consider gradual withdrawal of immunosuppression • Assessment of efficacy and safety of antifibrotic drugs in fibrotic HP is needed
Ancillary Treatments
<ul style="list-style-type: none"> • Frequent reassessment for antigen sources if not initially identified, or consideration of alternative diagnosis • Pulmonary rehabilitation • Lung transplantation evaluation if progressive disease, when appropriate • Assess and treat comorbidities • Assess and treat infectious and other complications

Definition of abbreviations: DL_{CO} = diffusing capacity of the lung for carbon monoxide; HP = hypersensitivity pneumonia; HRCT = high-resolution computed tomography.

*Inflammatory features include ground glass on HRCT, bronchoalveolar lavage lymphocytosis, or histopathologic cellular interstitial pneumonia or granulomatous inflammation.

[†]All recommendations for specific drug treatments are based on observational data and expert opinion.

[‡]Consider corticosteroid plus initial cytotoxic agent if antigen is not easily identified or remediated.

[§]Consider pneumocystis prophylaxis with dual immunosuppression.

^{||}This strategy places high value on avoidance of medication side effects when treatment is ineffective. In fibrotic hypersensitivity pneumonia, it is unclear whether stable disease on immunosuppressive treatment (i.e., no initial improvement but no deterioration) should be considered a treatment response (i.e., stable when the patient would have declined without treatment) or treatment failure (based on failure to improve). If a patient with observed stability while immunosuppressed deteriorates after treatment cessation, reinstitution of immunosuppression should certainly be considered.

prophylaxis should be considered. Future research should address the safety and effectiveness of immunosuppression in patients with fibrotic HP, stratified by the presence or absence of inflammation. Better knowledge of the expected disease course in subsets of patients with fibrotic HP would be useful in designing such trials. An intriguing question concerns whether antifibrotic therapies proven effective in slowing disease progression in IPF (8, 9) may also benefit fibrotic HP, given some evidence of mechanistic overlap (75, 85). Forthcoming trials targeting non-IPF fibrotic ILD may help answer this question.

Acute disease exacerbations not explained by identified infection, cardiac disease, or venous thromboembolism are described in patients with fibrotic HP, and behave similarly to acute exacerbations of IPF with high mortality (86, 87). An animal model of pulmonary fibrosis indicates that infection with *Streptococcus pneumoniae* may trigger fibrosis progression, mimicking an acute disease exacerbation, with antibiotic treatment or vaccination attenuating this effect (88, 89). Thus, in patients with fibrotic HP and acute disease worsening, the possibility of infection should be thoroughly evaluated and treated with appropriate antibiotics.

In patients with progressive fibrotic HP, attention to issues such as quality of life, candidacy for lung transplantation, and observation for complications such as acute disease exacerbations is important. Patients with fibrotic HP have significantly worse Health-Related Quality of Life scores compared with patients with IPF after accounting for

disease severity, with more dyspnea and fatigue in patients with HP (90). These symptoms should be assessed and managed. Lung transplantation may be an option in select patients with HP, with favorable outcomes in a single-center study in spite of several cases of recurrent HP in allografts (4). Secondary pulmonary hypertension can develop as a complication of advanced fibrotic lung disease including HP. Elevated pulmonary arterial pressure on Doppler echocardiography was seen in 19% of patients with fibrotic HP in one series, and was associated with older age and increased risk of short-term mortality (91). Few data are available to recommend specific therapy in patients with HP with group 3 pulmonary hypertension. Current IPF treatment guidelines suggest prescription of supplemental oxygen when there is significant resting hypoxia, but prospective evidence of symptomatic or survival benefit in fibrotic ILD is lacking (3). Gastroesophageal reflux disease and asymptomatic reflux are common in pulmonary fibrosis, and weak evidence suggests that treatment (with acid suppression or surgery) may be associated with stable disease course. The role for treatment of asymptomatic gastroesophageal reflux disease in fibrotic HP has not been studied; treating symptomatic patients with acid-suppressing drugs is probably reasonable (3). One report describes a group of patients with HP and concurrent autoimmune features who appear to have worse outcomes (92). It is unclear whether these patients actually have ILD due to rheumatologic disease, if it is a

comorbid condition related to female-predominant sex distribution in both diseases, or if there is some immunologic overlap/stimulation related to antigen exposure in the lung, as is reported in other environmentally triggered ILDs. Providers caring for patients with HP should remain vigilant for these and other comorbidities.

Conclusions

Despite important advances in the classification and management of ILDs, fibrotic hypersensitivity pneumonia remains difficult to diagnose, and specific therapies remain unstudied. Better ways to identify patients with HP with ongoing antigen reactivity/exposure are needed, ideally linked to identification and remediation of the culprit environment. Biomarkers with good sensitivity and specificity for HP (vs. idiopathic or rheumatologic disease) would also be useful for aiding diagnosis. Important unanswered questions regarding treatment remain, including whether immunosuppression is helpful (or harmful) in specific subgroups of patients with fibrotic HP (namely, based on the presence or absence of ongoing inflammation alongside fibrosis), and whether antifibrotic drug therapies may benefit patients with HP with established fibrosis. We think the first step toward answering many of these remaining questions is the establishment of expert agreement on specific guidelines with sets of minimum necessary “criteria” by which a patient could attain a diagnosis of fibrotic HP. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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