Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis

An International Modified Delphi Survey

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Abstract

Rationale: Current diagnosis of chronic hypersensitivity pneumonitis (cHP) involves considering a combination of clinical, radiological, and pathological information in multidisciplinary team discussions. However, this approach is highly variable with poor agreement between centers.

Objectives: We aimed to identify diagnostic criteria for cHP that reach consensus among international experts.

Methods: A three-round modified Delphi survey was conducted between April and August 2017. A total of 45 experts in interstitial lung disease from 14 countries participated in the online survey. Diagnostic items included in round 1 were generated using expert interviews and literature review. During rounds 1 and 2, experts rated the importance of each diagnostic item on a 5-point Likert scale. The *a priori* threshold of consensus was 75% or greater of experts rating a diagnostic item as very important or important. In the third round, experts graded the items that met consensus as important and provided their level of diagnostic confidence for a series of clinical scenarios.

Measurements and Main Results: Consensus was achieved on 18 of the 40 diagnostic items. Among these, experts gave the highest level of importance to the identification of a causative antigen, time relation between exposure and disease, mosaic attenuation on

chest imaging, and poorly formed nonnecrotizing granulomas on pathology. In clinical scenarios, the diagnostic confidence of experts in cHP was heightened by the presence of these diagnostic items.

Conclusions: This consensus-based approach for the diagnosis of cHP represents a first step toward the development of international guidelines for the diagnosis of cHP.

Keywords: hypersensitivity pneumonitis; interstitial lung disease; diagnosis; Delphi

At a Glance Commentary

Scientific Knowledge on the Subject: There are no widely accepted criteria or established international guidelines for the diagnosis of chronic hypersensitivity pneumonitis (cHP).

What This Study Adds to the Field: In an international modified Delphi survey, we identified 18 items that met the *a priori* definition of consensus as important for the diagnosis of cHP. We also described which combinations of diagnostic items experts feel are necessary for a confident diagnosis. This diagnostic approach may serve as an initial step toward the development of much needed international guidelines for the diagnosis of cHP.

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A complete list of members the HP Delphi Collaborators may be found before the beginning of the REFERENCES.

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Chronic hypersensitivity pneumonitis (cHP) is a fibrotic interstitial lung disease (ILD) resulting from long-term exposure to an offending antigen (1). In the diagnostic evaluation of patients with ILD, it can be challenging for clinicians to distinguish cHP from idiopathic pulmonary fibrosis (IPF) (2). However, this distinction is crucial, because it has implications for patient care and management (3, 4).

In contrast to IPF, there are no defined criteria or accepted guidelines for the diagnosis of cHP. Current practice is to integrate clinical, radiological, and pathological information at a multidisciplinary team (MDT) meeting to establish a diagnosis (5). Unfortunately, the lack of international consensus diagnostic guidelines for cHP means that this process is highly variable between ILD centers, and, consequently, diagnostic agreement between expert MDTs for cHP is poor (6).

In recent years, several expert groups have proposed diagnostic criteria and classification systems for cHP, highlighting the urgent need for an international consensus on diagnostic criteria for cHP (7–11). These proposals demonstrate substantial differences in expert opinion on how to best establish the diagnosis of cHP. A clearer definition of cHP, based on expert consensus, would benefit both clinicians and researchers. Therefore, the aim of this study was to perform a modified Delphi survey among a group of international ILD experts to identify and reach consensus on useful criteria for the diagnosis of cHP. The Delphi approach is a well-established method frequently used to reach consensus on diagnosis among healthcare professionals (12, 13). Advantages to this approach are that it alleviates the need for face-to-face meetings, eliminates geographic constraints, allows recruitment of a larger expert panel, and provides anonymity of the Delphi voting process, thus ensuring that all experts have the same weight in the consensus and that the decisions are not overly influenced by relatively few participants.

Methods

The Institutional Review Board of the Centre Hospitalier de l'Université de Montréal approved the study (Institutional Review Board No. 16.387).

Identification of Modified Delphi Survey Items

To identify the diagnostic items to be included in the first round of the modified Delphi survey, we conducted a qualitative study. A total of 15 recognized experts in the field of ILD identified by publication record were invited by e-mail to participate in an individual, semistructured phone interview. During these interviews, J.M. led the discussion using an interview guide (Table 1) consisting of open-ended questions regarding the diagnostic process of cHP. The interviews were digitally recorded and subsequently transcribed verbatim. The transcripts were analyzed using the content analysis approach (14, 15). In addition, we performed a comprehensive review of the literature to summarize the diagnostic criteria previously used or proposed in prior cHP studies. We searched PubMed for studies published between January 2000 and April 2017, in either English or French, using the search terms “hypersensitivity pneumonitis,” “extrinsic allergic alveolitis,” and “diagnosis.” The results of the expert interviews and literature review were combined to form the set of diagnostic items used in the first round of the modified Delphi process.

Selection of Expert Panel

A total of 53 international ILD experts (including the experts that participated in the qualitative interviews) were invited by e-mail to participate in the web-based modified Delphi survey. Experts were selected based on their clinical expertise and previous publications in the field of ILD and cHP.

Modified Delphi Survey Execution

We conducted a three-round online survey between April and August 2017 using a

rigorous application of the Delphi methodology (16). The surveys were completed online using the Qualtrics survey platform (Qualtrics, LLC). We chose to use an online questionnaire to best facilitate consultation of experts worldwide (17). The Delphi collaborators completed a short baseline demographic questionnaire about their medical practice. In the first round, experts were asked to rate the degree of importance of the presented diagnostic items when making a diagnosis of cHP on a five-point Likert scale (very important, important, less important, not important, and not sure). The diagnostic items were clustered in thematic categories: clinical, radiological, BAL, pathological, indirect measures of exposure, and discussion in MDT meeting. Experts were also asked to list any other diagnostic features not included in the original list that they considered relevant for the diagnosis of cHP. In the second round, the amended list of items (including the items generated in round 1) and the results of round 1 were presented to the experts, and they were asked to rate the items again on the five-point Likert scale. Finally, in the third round, experts were asked to rank relative importance of the diagnostic items that reached consensus by round 2. In addition, because the diagnosis of cHP cannot be made solely on the presence of one diagnostic item, but requires a multimodal integration of data, we created real-life clinical scenarios using different combinations of diagnostic items and asked experts to provide a level of diagnostic confidence for each scenario according to a recent standardized diagnostic ontology approach for ILD (18). This new ontological framework proposes to

Table 1. Interview Guide

No.	Question
1	How many years have you been caring for ILD patients?
2	What percentage of your clinical work is spent caring for ILD patients?
3	How do you make a diagnosis of cHP?
4	What clinical clues suggest a diagnosis of cHP?
5	What radiologic clues suggest a diagnosis of cHP?
6	What pathology clues suggest a diagnosis of cHP?
7	What diagnostic tests do you order/perform in cases of suspected cHP?
8	How do you distinguish cHP from idiopathic pulmonary fibrosis?
9	What do you think are the challenges when trying to establish a diagnosis of cHP?

Definition of abbreviations: cHP = chronic hypersensitivity pneumonitis; ILD = interstitial lung disease.

categorize patients in to three different categories according to the level of diagnostic confidence: confident diagnosis (diagnosis that meets guidelines criteria or $\geq 90\%$ confidence); “provisional” diagnosis (high confidence diagnosis = 70%–89% confidence and low confidence diagnosis = 51%–69%); and unclassifiable ILD. We limited this section to 48 case scenarios to balance information gained on the most important and common clinical scenarios with feasibility. The elaboration of these scenarios was guided by our clinical experience, the results of the qualitative interviews performed before the Delphi process, and the first two rounds of the modified Delphi survey. Experts could also suggest additional diagnostic tests they would typically obtain for each of the scenarios. This method allowed us to identify the minimum combination of diagnostic items that experts considered necessary to make a confident diagnosis of cHP.

Statistical Analysis

We conducted and reported the results of this study according to the proposed methodological criteria for Delphi studies (16). Delphi results were analyzed anonymously. Our *a priori* threshold of consensus as important was 75% or greater of experts rating a diagnostic item as very important or important (12, 16). Our *a priori* threshold as unimportant was 15% or greater of experts rating a diagnostic item as not important. The same threshold of 75% or greater of experts was used for the analysis of the third round of the modified Delphi survey (e.g., for a clinical scenario to be classified as a confident diagnosis of cHP, 75% or greater of experts needed to have rated it as a confident diagnosis). STATA version 14 (Stata Corp.) was used for all statistical analyses.

Results

Expert Interview and Literature Review

A total of 11 (73%) of the 15 invited experts agreed to participate in the semistructured individual interviews. Their characteristics are presented in Table 2. Interviews led to identification of 19 potential diagnostic items (Figure 1). In addition, experts highlighted the numerous challenges they commonly face in clinical practice when trying to establish a diagnosis of cHP.

Table 2. Expert Characteristics

Characteristics	Expert Interview (n = 11)	Modified Delphi (n = 45)
Response rate, n/total (%)	11/15 (73.3)	45/53 (84.9)
Female, n (%)	4 (36.4)	14 (31.1)
Country, n (%)		
Australia	—	3 (6.7)
Belgium	—	1 (2.2)
Brazil	—	1 (2.2)
Canada	1 (9.1)	5 (11.1)
France	—	1 (2.2)
Germany	1 (9.1)	4 (8.9)
Greece	—	1 (2.2)
Italy	1 (9.1)	5 (11.1)
Japan	—	1 (2.2)
Mexico	1 (9.1)	1 (2.2)
The Netherlands	1 (9.1)	1 (2.2)
Spain	—	1 (2.2)
United Kingdom	—	3 (6.7)
United States	6 (54.5)	17 (37.8)
Years in clinical practice, median (IQR)	16 (13–21)	20 (10–25)
% of clinical time dedicated to ILD, median (IQR)	75 (50–90)	61 (40–82)

Definition of abbreviations: ILD = interstitial lung disease; IQR = interquartile range.

All agreed that the lack of established diagnostic criteria, the limited comprehension of the disease pathophysiology, and several specific clinical situations (e.g., patient unable to undergo lung biopsy or in whom no potential antigen or exposure can be identified) make diagnosing cHP a challenging task. A literature review of recent publications in cHP identified 40 diagnostic items: the 19 items generated in the interviews plus 21 additional diagnostic items. These 40 diagnostic items were presented to the Delphi collaborators in round 1 (Figure 1).

Modified Delphi Survey

Of the 53 invited expert pulmonologists, 45 (85%), from 14 different countries, agreed to participate. The Delphi collaborators have extensive clinical experience and dedicate a high percentage of their time to the care of patients with ILD (Table 2). All 45 experts completed the first round, whereas 42 (93%) and 40 (89%) completed the second and third rounds, respectively. During round 1, the Delphi collaborators suggested nine additional diagnostic items that were included in round 2 (Figure 2). The detailed results of rounds 1 and 2 are presented in Tables E1 and E2 in the online supplement. After the 2 initial rounds, 18 diagnostic items were considered important by consensus,

14 were considered unimportant by consensus, and 17 failed to reach consensus (Table 3). The results of sensitivity analyses using less strict thresholds of consensus as important (i.e., $\geq 60\%$ or $\geq 70\%$ of experts rating a diagnosis item as very important or important) are presented in Table E3. Using a more relaxed threshold of 70% or greater, the following features would have been designated important by consensus: absence of extrapulmonary manifestations; a combination of reticulation, ground-glass opacities, and centrilobular nodules on high-resolution computed tomography (HRCT); upper lobe predominance on HRCT; or organizing pneumonia on pathology. Moreover, restriction on pulmonary function tests, BAL lymphocytosis greater than 30%, and bronchiolitis and lymphocytic interstitial inflammation on lung biopsy would have met a consensus established at 60% or greater of experts rating a diagnostic item as very important or important.

Among the 18 diagnosis items that were considered important by consensus, experts highly valued the identification of an exposure known to cause HP and the presence of a temporal relationship between exposure and disease onset (Table 4). Air trapping and mosaic attenuation on HRCT, and poorly formed nonnecrotizing granulomas on lung biopsy

Figure 1. Source of the 40 diagnosis items. Items that originated from multiples sources are positioned in overlapping areas. CTD = connective tissue disease; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

were the highest-ranked radiological and pathological features, respectively.

The high value of these diagnostic items was also reflected in the clinical scenarios (Tables E4a and E4b). Scenarios that exhibited plausible antigen identification and HRCT features suggestive of cHP (either combination of mosaic attenuation, ground-glass opacities, and normal lung, the so-called headcheese sign [19, 20], or the combination of HRCT signs of fibrosis and mosaic attenuation) were rated as at least a high-confidence provisional diagnosis of cHP (i.e., confidence level of 70–89%) by a majority of experts (77.5% and 80%). The addition of high lymphocyte count (>40%) on BAL in these scenarios increased the diagnosis probability to a confident diagnosis of cHP (i.e., confidence level >90%). Moreover, in all scenarios that included both the identification of a plausible antigen and a lung biopsy with features suggestive of cHP (chronic bronchiolocentric inflammation, poorly formed nonnecrotizing granulomas, giant cells, airway-centered interstitial fibrosis,

and absence of alternative diagnosis), a large majority ($\geq 80\%$) of experts was confident in the cHP diagnosis (i.e., $\geq 90\%$ confidence), independent of HRCT pattern. For scenarios with an identified exposure and HRCT patterns of possible or definite UIP (21), more diagnostic items were required to increase the diagnostic confidence. In these cases, pathologic features suggestive of cHP were required to reach a confident diagnosis of cHP. Scenarios combining antigen identification, HRCT pattern of definite or possible UIP, and BAL with greater than 40% lymphocytes were rated by most experts as at least low-confidence provisional diagnosis of cHP (i.e., confidence of 51–69%). Similarly, in the absence of a plausible causative antigen on history, only scenarios that combined many different diagnostic items in different domains (radiological, BAL, pathological) reached higher levels of diagnosis confidence. Figure 2 summarizes the results of the third round of the Delphi.

Although experts agreed on the level of diagnostic confidence for most of the clinical scenarios, we obtained a range of answers regarding the need for and choice of additional tests. An exception was that a lung biopsy with features suggestive of cHP alleviated the need for additional testing by most experts. In other clinical scenarios, where experts thought that lung tissue was required, consensus was not met regarding the choice of lung biopsy technique.

Discussion

In this study, we identified 18 diagnostic items that reached consensus as important for the diagnosis of cHP among a panel of international ILD experts from 14 different countries. We also described, using a series of clinical scenarios, which combinations of diagnostic items experts considered necessary to make a confident diagnosis of cHP. Two different scenario types were felt to represent a

Figure 2. Approach to the diagnosis of chronic hypersensitivity pneumonitis. *Consider additional test: bronchoscopy with bronchoalveolar lavage, transbronchial lung biopsy, transbronchial lung cryobiopsy, or surgical lung biopsy. #Consider additional test: transbronchial lung biopsy, transbronchial lung cryobiopsy, or surgical lung biopsy. cHP = chronic hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

confident diagnosis of cHP: 1) combination of identified antigen on history, HRCT features suggestive of cHP, and BAL lymphocytosis greater than 40%; and 2) any scenario that included an identified exposure and lung biopsy with features suggestive of cHP. None of the scenarios that lacked exposure identification were believed to achieve a confident diagnosis even after the inclusion of features suggestive of cHP on lung biopsy. To our knowledge, this is the first study to involve such a broad range of international expertise to identify diagnostic criteria for cHP.

Similar to previously proposed diagnostic approaches, identification of an exposure known to cause HP plays a pivotal role in the diagnostic process of cHP,

significantly influencing the level of diagnostic confidence (9, 10, 22, 23). Accordingly, an identified exposure combined with HRCT features of cHP and BAL lymphocytosis greater than 40% was the only scenario experts believed sufficient to establish a diagnosis of cHP without the need for a lung biopsy. The combination of an identified exposure plus HRCT features typical of cHP was categorized by more than 75% of the Delphi panel as having a diagnostic confidence higher than 70%. In this scenario, most experts recommended proceeding to a bronchoscopy with BAL to increase diagnostic confidence. The utility of BAL in the work-up of patients with ILD is controversial, and its use varies among different centers (24, 25). Although a proportion of patients with cHP will have

a high lymphocyte percentage on BAL, the performance characteristics of this diagnostic test remain poorly characterized, particularly in patients with fibrotic HP (2, 22, 26–31). In our study, BAL lymphocytosis thresholds of greater than 40% and greater than 50% reached consensus among experts, which is consistent with the most recent guidelines on the role of BAL in diagnosis of ILD and IPF (21, 27). Inclusion of multiple “thresholds” for a quantitative diagnostic measure like BAL lymphocytosis complicates the Delphi process, because there are no validated Delphi methods for establishing a consensus threshold in this setting. In our results, the panel agreed on the importance of higher thresholds of lymphocytosis (i.e., >40% or 50%)

Table 3. General Results from Delphi Rounds 1 and 2

Items That Reached “Important” Threshold*	Items That Reached “Unimportant” Threshold†	Items That Did Not Meet Consensus
Clinical Clinical improvement with antigen avoidance History of environmental exposure known to cause HP Negative CTD serology and no signs/symptoms of CTD Presence of compatible clinical features (dyspnea, cough) Reduced DL _{CO} Time relation with exposure	Age Ethnicity Sex Family history Symptoms for >24 wk Symptoms for >1 yr Systemic symptoms Wheezing on exam	Absence of extrapulmonary manifestation Crackles on exam Hypoxemia at rest or on exertion Improvement with prior steroid therapy Inspiratory squeaks on exam Restriction on PFTs Smoking history
Radiological Air trapping—mosaic attenuation Airway-centric disease Centrilobular nodules Ground-glass opacities	Consolidation	Combination of reticulations, ground-glass and centrilobular nodules Peribronchovascular interstitial thickening Reticular opacities Upper lobe predominance
Bronchoalveolar lavage BAL lymphocytosis > 50% BAL lymphocytosis > 40%	BAL lymphocytosis > 20% CD4/CD8 < 1	BAL lymphocytosis > 30%
Pathological Absence of an alternative diagnosis that could account for the pathologic findings Airway-centered interstitial fibrosis Chronic bronchiolocentric inflammation Giant cells Poorly formed nonnecrotizing granulomas	Fibrosis with a pattern that resembles UIP	Bronchiolitis Fibrosis with a pattern that resembles NSIP Lymphocytic interstitial inflammation (pathology) Organizing pneumonia
Indirect measure of exposure	Positive lymphocyte proliferation test Positive specific inhalation challenge	Positive precipitating antibodies
Multidisciplinary discussion Case discussion in multidisciplinary team meeting		

Definition of abbreviations: CTD = connective tissue disease; HP = hypersensitivity pneumonitis; NSIP = nonspecific interstitial pneumonia; PFTs = pulmonary function tests; UIP = usual interstitial pneumonia.

*A priori threshold of consensus for important was ≥75% of experts rating a diagnosis item as very important or important.

†A priori threshold for unimportant was ≥15% of experts rating a diagnosis item as not important.

whereas the experts who were interviewed in the initial step of the study also valued lower levels (i.e., >20% or 30%). These results highlight the need for further research to identify the optimal threshold for BAL lymphocytosis in the diagnosis of cHP.

Laboratory measures of exposure, such as precipitin tests, specific inhalation challenge, and lymphocyte proliferation tests, failed to meet consensus as important in the Delphi process. The lack of consensus on these tests probably reflects the limited information on their test characteristics, lack of standardization, or limited availability (32–34). Positive precipitating antibodies did not significantly impact

diagnostic confidence when added to clinical scenarios. Further research is needed to better characterize and validate the role of ancillary laboratory testing in the evaluation of patients with cHP.

The different radiological diagnostic items that reached consensus as supportive of cHP among our expert panel—mosaic attenuation, centrilobular nodules, airway-centric disease, and ground-glass opacities—are frequently reported features in studies of HRCT characteristics of cHP (23, 35–38). The third round of the Delphi process identified a combination of criteria—BAL lymphocytosis greater than 40%, identified exposure, and HRCT pattern suggestive of cHP—as sufficiently

diagnostic without need for lung biopsy. This scenario is analogous to the clinical and radiological IPF diagnosis, where a definite UIP pattern on HRCT in the appropriate clinical context is considered diagnostic without pathologic confirmation (21).

In patients presenting with HRCT patterns less suggestive of cHP (e.g., possible UIP or definite UIP [21]) or lacking an identified exposure, experts highlighted the need to obtain lung tissue to clarify the diagnosis. The pathological diagnostic items that met consensus in the Delphi process were consistent with previous reports of pathologic findings commonly found in cHP (8, 39–41). However, the

Table 4. Consensus Diagnostic Items Ranked by Importance—Results from Delphi Round 3

Diagnosis Item	Mean Rank (SD)*
History of environmental exposure known to cause HP	3.01 (3.11)
Mosaic attenuation—air trapping on HRCT	4.80 (2.38)
Time relation with exposure (temporal relation between exposure and disease)	6.28 (4.10)
Poorly formed nonnecrotizing granulomas on pathology	6.30 (3.18)
Clinical improvement with antigen avoidance	6.95 (4.60)
Centrilobular nodules on HRCT	7.53 (4.01)
Chronic bronchiolocentric inflammation on pathology	8.55 (3.78)
Case discussion in multidisciplinary team meeting	8.68 (5.68)
Presence of compatible clinical features (dyspnea, cough)	9.95 (5.53)
Airway-centric disease on HRCT	9.97 (3.94)
Ground-glass opacities on HRCT	10.00 (3.43)
BAL with lymphocytosis >50%	10.03 (3.93)
BAL with lymphocytosis >40%	10.13 (3.96)
Negative CTD serology and no signs/symptoms of CTD	10.35 (4.67)
Airway-centered interstitial fibrosis on pathology	10.78 (4.22)
Giant cells on pathology	11.83 (3.77)
Absence of an alternative diagnosis that could account for the pathologic findings	13.83 (3.79)
Reduced DL _{CO}	14.35 (3.51)

Definition of abbreviations: CTD = connective tissue disease; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography.

*Potential range = 1 (most important) to 18 (least important).

method of choice for lung biopsy remains unclear. Transbronchial lung cryobiopsy (TBLC), a recently introduced method of histologic sampling, has been shown to increase the diagnostic confidence of multidisciplinary discussion, and may have a lower rate of complications and mortality compared with surgical lung biopsy (SLB) (42, 43). This method is increasingly being used in clinical practice, but its diagnostic accuracy has yet to be directly compared with SLB (44, 45). The addition of this new technique introduces a layer of complexity to the diagnostic algorithm for cHP. In some centers, BAL and TBLC are systematically performed in the same procedure during the workup of patients with undefined ILD, whereas, in other centers, SLB remains the gold standard to obtain lung tissue. This variation in practice is reflected in the results of the last Delphi round, where expert responses lacked unanimity regarding the choice of biopsy technique. This section of the algorithm will require refinement as more data on the diagnostic accuracy of TBLC become available.

Finally, case discussion in MDT was unanimously and highly valued by Delphi panelists, likely reflecting the need for integration of complex data from clinical, radiological, and pathological domains

to diagnose cHP (46). Our hope is that MDT guided by international consensus guidelines will improve agreement and accuracy of cHP diagnosis across expert centers in a manner similar to that achieved for IPF (6).

Recently, Schoenberg and colleagues (13) evaluated the concordance between consensus thresholds in the modified Delphi process, reflecting expert-based opinions and systematic review-based recommendations in guideline development methodologies. At a level of consensus of 70%, the concordance rate between Delphi results and systematic review-based recommendation is excellent (98%). In our study, choosing a definition of consensus of 70% would have resulted in four additional diagnostic items being categorized as important: absence of extrapulmonary manifestations; combination of reticulation, ground-glass opacities, and centrilobular nodules on imaging; upper lobe predominance on imaging; and organizing pneumonia on lung biopsy. Our protocol was elaborated before this publication by Schoenberg and colleagues, and we chose a stricter consensus definition in hopes of identifying items with strong consensus among the several controversial items proposed for the diagnosis of cHP.

This study has important limitations to consider. First, the decision to include only pulmonologists on the expert panel was made because pulmonologists are the clinician members of the MDT who must ultimately integrate all relevant information and the MDT discussion to arrive at a final diagnosis. However, this decision could have biased our results and/or limited more nuanced granularity of radiologic and pathologic criteria. In addition, we were unable to examine the threshold intensity (i.e., duration, extent, and profusion) of features needed to fulfill individual clinical, radiological, or pathological criteria. Further research is needed to precisely define these criteria. Second, although the level of participation for each round of Delphi was satisfactory, it was not complete. Third, it was not feasible to include all possible combinations of diagnostic items in the round 3 clinical scenarios. Such an exhaustive list of clinical scenarios would have been prohibitively extensive, and likely would have led to survey fatigue and reduced completion rates. The expert panel vote is therefore limited to the scenarios that were presented in the third round, and could have been influenced by the limited options. It is possible that additional clinical scenarios, not included in this analysis, would also have been considered by experts to represent a confident diagnosis of cHP. Fourth, the experts ($n = 11$) who were interviewed in the initial step of the study also participated in the Delphi surveys. This overlap could potentially have overly influenced our results for the opinions of these experts. Fifth, the Delphi results could have been influenced and biased by the wording of the questions in the surveys and the choice of our Likert scale. Our choice of a simpler Likert scale could have influenced the experts to rate the diagnostic items as either important or unimportant, as there were fewer neutral categories available than if we had used a more complex scale. Moreover, our choice of wording for the questions presented in rounds 1 and 2 could have led to identification of diagnostic items that are important for the diagnosis of all ILDs, and not only specific to the diagnosis of cHP. Sixth, because the clinical scenarios were only presented in the third round of this study, a true Delphi expert consensus on these scenarios could not be achieved. Another modified Delphi survey study, consisting of multiples iterations, would

be required to obtain consensus on the case scenarios. Finally, the Delphi methodology is useful to obtain consensus among experts, but its results require clinical validation.

In conclusion, using the modified Delphi method, we developed a consensus-based diagnostic approach for cHP. We believe that this study is a vital first step toward the development of international guideline recommendations for the diagnosis of cHP. ■

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

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References

- Selman M, Pardo A, King TE Jr. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. *Am J Respir Crit Care Med* 2012;186:314–324.
- Morell F, Villar A, Montero MA, Muñoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. *Lancet Respir Med* 2013;1:685–694.
- Spagnolo P, Oldham JM, Jones MG, Lee JS. Personalized medicine in interstitial lung diseases. *Curr Opin Pulm Med* 2017;23:231–236.
- Johannson K, Ryerson CJ. Making an accurate diagnosis of chronic hypersensitivity pneumonitis. *Can Respir J* 2014;21:370–372.
- Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al.; British Thoracic Society Interstitial Lung Disease Guideline Group, British Thoracic Society Standards of Care Committee; Thoracic Society of Australia; New Zealand Thoracic Society; Irish Thoracic Society. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;63:v1–v58. [Published erratum appears in *Thorax* 63:1029.]
- Walsh SL, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, et al. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. *Lancet Respir Med* 2016;4:557–565.
- Kouranos V, Jacob J, Nicholson A, Renzoni E. Fibrotic hypersensitivity pneumonitis: key issues in diagnosis and management. *J Clin Med* 2017;6:62.
- Miller R, Allen TC, Barrios RJ, Beasley MB, Burke L, Cagle PT, et al. Hypersensitivity pneumonitis: a perspective from members of the Pulmonary Pathology Society. *Arch Pathol Lab Med* 2018;142:120–126.
- Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and treatment of fibrotic hypersensitivity pneumonia: where we stand and where we need to go. *Am J Respir Crit Care Med* 2017;196:690–699.
- Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. *Am J Respir Crit Care Med* 2017;196:680–689.
- Molyneux PL, Maher TM. Time for an international consensus on hypersensitivity pneumonitis: a call to arms. *Am J Respir Crit Care Med* 2017;196:665–666.
- Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. *J Clin Epidemiol* 2003;56:1150–1156.
- Schoenberg NC, Barker AF, Bernardo J, Deterding RR, Ellner JJ, Hess DR, et al. A comparative analysis of pulmonary and critical care medicine guideline development methodologies. *Am J Respir Crit Care Med* 2017;196:621–627.
- Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004;24:105–112.
- Cavanagh S. Content analysis: concepts, methods and applications. *Nurse Res* 1997;4:5–16.
- Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014;67:401–409.
- Holloway K. Doing the E-Delphi: using online survey tools. *Comput Inform Nurs* 2012;30:347–350.
- Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, et al. A standardized diagnostic ontology for fibrotic interstitial lung disease: an international working group perspective. *Am J Respir Crit Care Med* 2017;196:1249–1254.
- Hirschmann JV, Pipvath SN, Godwin JD. Hypersensitivity pneumonitis: a historical, clinical, and radiologic review. *Radiographics* 2009;29:1921–1938.
- Chong BJ, Kanne JP, Chung JH. Headcheese sign. *J Thorac Imaging* 2014;29:W13.
- Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, et al.; HP Study Group. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2003;168:952–958.
- Johannson KA, Elicker BM, Vittinghoff E, Assayag D, de Boer K, Golden JA, et al. A diagnostic model for chronic hypersensitivity pneumonitis. *Thorax* 2016;71:951–954.
- Mooney JJ, Koth LL. Surgical lung biopsy over bronchoalveolar lavage in chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2014;189:371–372.
- Hodnett P, Naidich D. Reply: surgical lung biopsy over bronchoalveolar lavage in chronic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2014;189:372.
- Ohshimo S, Bonella F, Cui A, Beume M, Kohno N, Guzman J, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:1043–1047.
- Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al.; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med* 2012;185:1004–1014.
- Cormier Y, Bélanger J, LeBlanc P, Laviolette M. Bronchoalveolar lavage in farmers' lung disease: diagnostic and physiological significance. *Br J Ind Med* 1986;43:401–405.
- Ratjen F, Costabel U, Griese M, Paul K. Bronchoalveolar lavage fluid findings in children with hypersensitivity pneumonitis. *Eur Respir J* 2003;21:144–148.
- Yoshizawa Y, Ohtani Y, Hayakawa H, Sato A, Suga M, Ando M. Chronic hypersensitivity pneumonitis in Japan: a nationwide epidemiologic survey. *J Allergy Clin Immunol* 1999;103:315–320.
- Pardo A, Smith KM, Abrams J, Coffman R, Bustos M, McClanahan TK, et al. CCL18/DC-CK-1/PARC up-regulation in hypersensitivity pneumonitis. *J Leukoc Biol* 2001;70:610–616.
- Muñoz X, Sánchez-Ortiz M, Torres F, Villar A, Morell F, Cruz MJ. Diagnostic yield of specific inhalation challenge in hypersensitivity pneumonitis. *Eur Respir J* 2014;44:1658–1665.
- Rodrigo MJ, Benavent MI, Cruz MJ, Rosell M, Murio C, Pascual C, et al. Detection of specific antibodies to pigeon serum and bloom antigens by enzyme linked immunosorbent assay in pigeon breeder's disease. *Occup Environ Med* 2000;57:159–164.

34. Millerick-May ML, Mulks MH, Gerlach J, Flaherty KR, Schmidt SL, Martinez FJ, *et al.* Hypersensitivity pneumonitis and antigen identification—an alternate approach. *Respir Med* 2016;112:97–105.
35. Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. *Eur Radiol* 2012;22:1672–1679.
36. Chung JH, Zhan X, Cao M, Koelsch TL, Manjarres DCG, Brown KK, *et al.* Presence of air trapping and mosaic attenuation on chest computed tomography predicts survival in chronic hypersensitivity pneumonitis. *Ann Am Thorac Soc* 2017;14:1533–1538.
37. Tateishi T, Ohtani Y, Takemura T, Akashi T, Miyazaki Y, Inase N, *et al.* Serial high-resolution computed tomography findings of acute and chronic hypersensitivity pneumonitis induced by avian antigen. *J Comput Assist Tomogr* 2011;35:272–279.
38. Silva CI, Churg A, Müller NL. Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. *AJR Am J Roentgenol* 2007;188:334–344.
39. Jones KD, Urisman A. Histopathologic approach to the surgical lung biopsy in interstitial lung disease. *Clin Chest Med* 2012;33:27–40.
40. Takemura T, Akashi T, Kamiya H, Ikushima S, Ando T, Oritsu M, *et al.* Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia. *Histopathology* 2012;61:1026–1035.
41. Wang P, Jones KD, Urisman A, Elicker BM, Urbania T, Johansson KA, *et al.* Pathologic findings and prognosis in a large prospective cohort of chronic hypersensitivity pneumonitis. *Chest* 2017;152:502–509.
42. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, *et al.* Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:745–752.
43. Ravaglia C, Bonifazi M, Wells AU, Tomassetti S, Gurioli C, Piciocchi S, *et al.* Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video-assisted thoracoscopic lung biopsy and a systematic review of the literature. *Respiration* 2016;91:215–227.
44. Johansson KA, Marcoux VS, Ronksley PE, Ryerson CJ. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease: a systematic review and metaanalysis. *Ann Am Thorac Soc* 2016;13:1828–1838.
45. Sriprasart T, Aragaki A, Baughman R, Wikenheiser-Brokamp K, Khanna G, Tanase D, *et al.* A single US center experience of transbronchial lung cryobiopsy for diagnosing interstitial lung disease with a 2-scope technique. *J Bronchology Interv Pulmonol* 2017;24:131–135.
46. Elicker BM, Jones KD, Henry TS, Collard HR. Multidisciplinary approach to hypersensitivity pneumonitis. *J Thorac Imaging* 2016;31:92–103.