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A Systematically Derived Exposure Assessment Instrument for Chronic Hypersensitivity Pneumonitis

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BACKGROUND: Chronic hypersensitivity pneumonitis (CHP) is an immune-mediated interstitial lung disease (ILD) caused by inhalational exposure to environmental antigens, resulting in parenchymal fibrosis. By definition, a diagnosis of CHP assumes a history of antigen exposure, but only half of all patients eventually diagnosed with CHP will have a causative antigen identified. Individual clinician variation in eliciting a history of antigen exposure may affect the frequency and confidence of CHP diagnosis.

METHODS: A list of potential causative exposures were derived from a systematic review of the literature. A Delphi method was applied to an international panel of ILD experts to obtain consensus regarding technique for the elicitation of exposure to antigens relevant to a diagnosis of CHP. The consensus threshold was set at 80% agreement, and median ≤ 2, interquartile range $= 0$ on a 5-point Likert scale (1, strongly agree; 2, tend to agree; 3, neither agree nor disagree; 4, disagree; 5, strongly disagree).

RESULTS: In two rounds, 36/40 experts participated. Experts agreed on 18 exposure items to ask every patient with suspected CHP. Themes included CHP inducing exposures, features that contribute to an exposure's relevance, and quantification of a relevant exposure. Based on the results from the literature review and Delphi process, a CHP exposure assessment instrument was derived. Using cognitive interviews, the instrument was revised by patients with ILD for readability and usability.

CONCLUSIONS: This Delphi survey provides items that ILD experts agree are important to ask in all patients presenting with suspected CHP and provides basis for a systematically derived CHP exposure assessment instrument. Clinical utility of this exposure assessment instrument may be affected by different local prevalence patterns of exposures. Ongoing research is required to clinically validate these items and consider their impact in more geographically diverse settings.

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ABBREVIATIONS: CHP = chronic hypersensitivity pneumonitis; ILD = interstitial lung disease; IQR = interquartile range

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Chronic hypersensitivity pneumonitis (CHP) is an immune-mediated form of interstitial lung disease (ILD), caused by an inhalational exposure to an environmental antigen, resulting in parenchymal fibrosis.[1] By definition, a diagnosis of CHP assumes a history of antigen exposure, but only one-half of all patients eventually diagnosed with CHP will have one identified.[2] Failure to identify an exposure may lead to a delay in diagnosis, misdiagnosis, and appropriate treatment (part of which includes avoidance of the inciting agent).

Not only is antigen exposure identification important in the formulation of an accurate diagnosis, it has been shown to affect prognosis,[2] risk of relapse, and quality of life.[3] Survival is significantly longer in patients with CHP with an identified antigen (mean, 8.75 years) compared with those whose antigen remains unidentified (mean, 4.88 years).[2] In addition to enabling earlier diagnosis (and therefore earlier treatment), identification and avoidance of the antigen may improve prognosis.[4,5]

Consensus statements advise that a careful history should be taken to identify possible exposures in all patients suspected of possible CHP.[1,6,7] There are several published questionnaires and lists of exposures that clinicians might use to assess exposures.[1,8,9] However, none of these to our knowledge have been systematically developed or proven to be as effective or more effective than clinical history in practice. There is a clear need for a systematically developed and validated CHP exposure assessment instrument.

Methods

Identification of the Delphi Items

Potential exposure items for inclusion in an assessment instrument were identified through a systematic review of the literature. Electronic searches were performed though Medline, EMBASE, and the Cochrane Register of Controlled Trials from January 1, 1990, to April 30, 2019, using the following terms: "chronic hypersensitivity pneumonitis," "fibrotic hypersensitivity pneumonitis," "hypersensitivity pneumoni*," and "extrinsic allergic alveolitis." Two reviewers (H.B., and J.L.) screened all articles to identify papers that included incident cases of hypersensitivity pneumonitis with an exposure recorded. No restriction was placed on language. Exposures associated with five or more cases were included as Delphi items and categorized as microbial particulate matter; animal and plant proteins; and chemical exposures.[1] Factors which were used to confirm the clinical relevance of an exposure identified from the literature were also presented in the Delphi survey. Items presented in currently available questionnaires were also reviewed.[1,8-10]

Selection of the Delphi Panel

Forty international experts were invited to participate based on clinical expertise (>10 years' clinical experience), and publication record specific to interstitial lung disease (at least 30 publications), and respiratory and/or occupational health training, and recognition of ILD experience by holding a position of influence (eg, department head, expert committee panel member, journal editor). Experts were included from a wide range of countries to account for a variation in geographical exposure patterns and exposure assessment practices.

Delphi Survey Implementation

The Delphi survey was conducted in two rounds over 3 months. Experts were asked to complete demographic questions relating to their medical practice and experience. Experts were asked to rate the degree of importance that each exposure item be included in an exposure assessment tool for CHP. A 5-point Likert scale was used (1, strongly agree; 2, tend to agree; 3, neither agree nor disagree; 4, disagree; 5, strongly disagree). All questions were formatted as "forced responses," reducing the possibility of missing data. Surveys were completed anonymously online through the Qualtrics survey platform (Qualtrics, Provo, UT). Ethics approval was obtained from Monash University (institutional review board number 17069).

Consensus was defined as 80% or greater consensus to agree (strongly or tend to) or disagree (strongly or tend to).[11] To account for the possibility of a bimodal distribution of responses, a median and interquartile range (IQR) consensus method was also applied: in the first round, items with a median score ≤ 2 and an IQR $= 0$ were considered included. Items with a median score ≥ 4 and an IQR $= 0$ were removed. Items that did not achieve consensus in the first round were submitted to the experts in the second round, with the distribution of responses provided. In the second round, items with a median ≤ 2 and an IQR $= 1$ were placed on a list of "possible" items. Items were required to achieve consensus in both methods to be included. Each item was presented up to two times to aim to achieve consensus.

The Delphi survey also included qualitative questions whereby experts were asked to add exposures or items not listed that they determined were important factors in CHP. These responses were assessed using content analysis,[12,13] and relevant items were presented in subsequent rounds. Items that achieved consensus were included in a CHP clinical exposure assessment instrument.

Exposure Assessment Instrument Validation

People with ILD were recruited from University of California, San Francisco. Participants engaged in one-on-one and small group sessions with the facilitator (H.B.) to review the CHP clinical exposure assessment instrument. Cognitive interviews were performed to ensure that each item was clearly understood, relevant, not redundant, and reflected the concept which they were intended to measure. Participants were asked about readability, clarity of instructions, appropriate literacy level, questions that they were unwilling to answer, and whether they understood the terms used for exposures considering their geographical and cultural context. Interviews were audio-recorded and transcribed verbatim. The instrument was revised according to the themes presented at each session, and were continued until saturation (ie, the point at which no new information resulting in changes to the instrument was identified through additional interviews).[14] Ethics approval was obtained through the University of California, San Francisco, institutional review board (number 19-28068).

Results

Systematic Literature Review

The systematic literature search yielded 38,001 citations; after screening, 922 citations were included in the final analysis (Fig 1). The most common reasons for exclusion included not involving HP patients, no exposure assessment performed or reported, and no cases presented (review or editorial). The review identified 60 unique exposures, of which 24 had more than five citations, and these were presented in the Delphi survey. An additional five exposure items were identified by experts and presented in subsequent rounds.

Delphi Panel Participants and Expertise

Thirty-six experts from 15 different countries completed both rounds of the Delphi survey; three failed to respond to the invitation and 1 declined to participate. Experts had an average of 19 years clinical training (SD, 9), including an average of 14 years in a dedicated ILD service (SD, 7) and 54 publications. The majority attended an ILD multidisciplinary meeting once per week (95%), and they saw an average of 51 ILD consults and 12 CHP consults per month.

Experts agreed that it is important to ask about clinically relevant exposures in the clinical assessment of CHP, including domestic, occupational and lifestyle, and hobby-related exposures. Just over 50% currently use a questionnaire or published list of exposures in their clinic as a guide to history-taking, including seven locally adapted questionnaires.

Delphi Survey Results

The Delphi survey identified 18 exposures with consensus or inclusion in an exposure assessment tool (Fig 2). Seven items failed to meet consensus. There was no consensus disagreement for any of the items.

Experts agreed that a temporal relationship between the exposure and onset of symptoms (92% agreement; median = 1, IQR = 0), and symptoms that improve with avoidance of the exposure (97% agreement; median = 1, IQR = 0) would increase the likelihood an identified exposure is clinically significant. Experts agreed the duration of exposure was important (86% agreement; median = 2, IQR = 1); however, no clear consensus was achieved about the minimum duration of exposure required. There was a lack of consensus on whether symptoms improved with corticosteroids (33% agreement, 33% disagreement; median = 3, IQR = 2), whether others in the workplace/family environment/similar environment experienced similar symptoms after the same exposure (72% agreement; median = 2, IQR = 2), and proximity of the exposure to the patient (66% agreement; median = 2, IQR = 1) (see e-Appendix 1).

Based on the Delphi survey results, a provisional CHP exposure assessment instrument was synthesized. The provisional instrument consisted of two parts. Part A asked patients whether they have had contact with any of the 18 exposures identified by expert consensus, using a simple yes/no, and a free text query. Part B asked the patient questions related to key qualifiers identified by the Delphi panel.

Patient Validation

Twelve patients participated. All participants found the provisional exposure assessment instrument instructions easy to understand, although some participants were unsure if their minor exposure was relevant, so the term "regular basis" was included in the instructions, which improved participants' ability to complete the questions

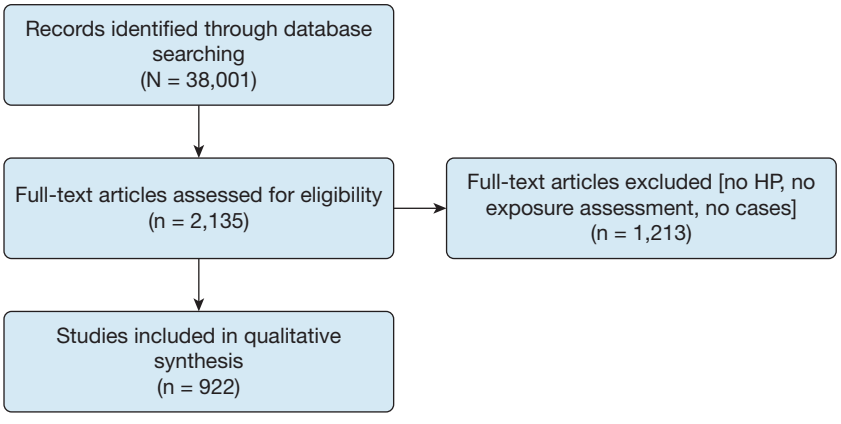

Figure 1 – *PRISMA diagram for literature search.*

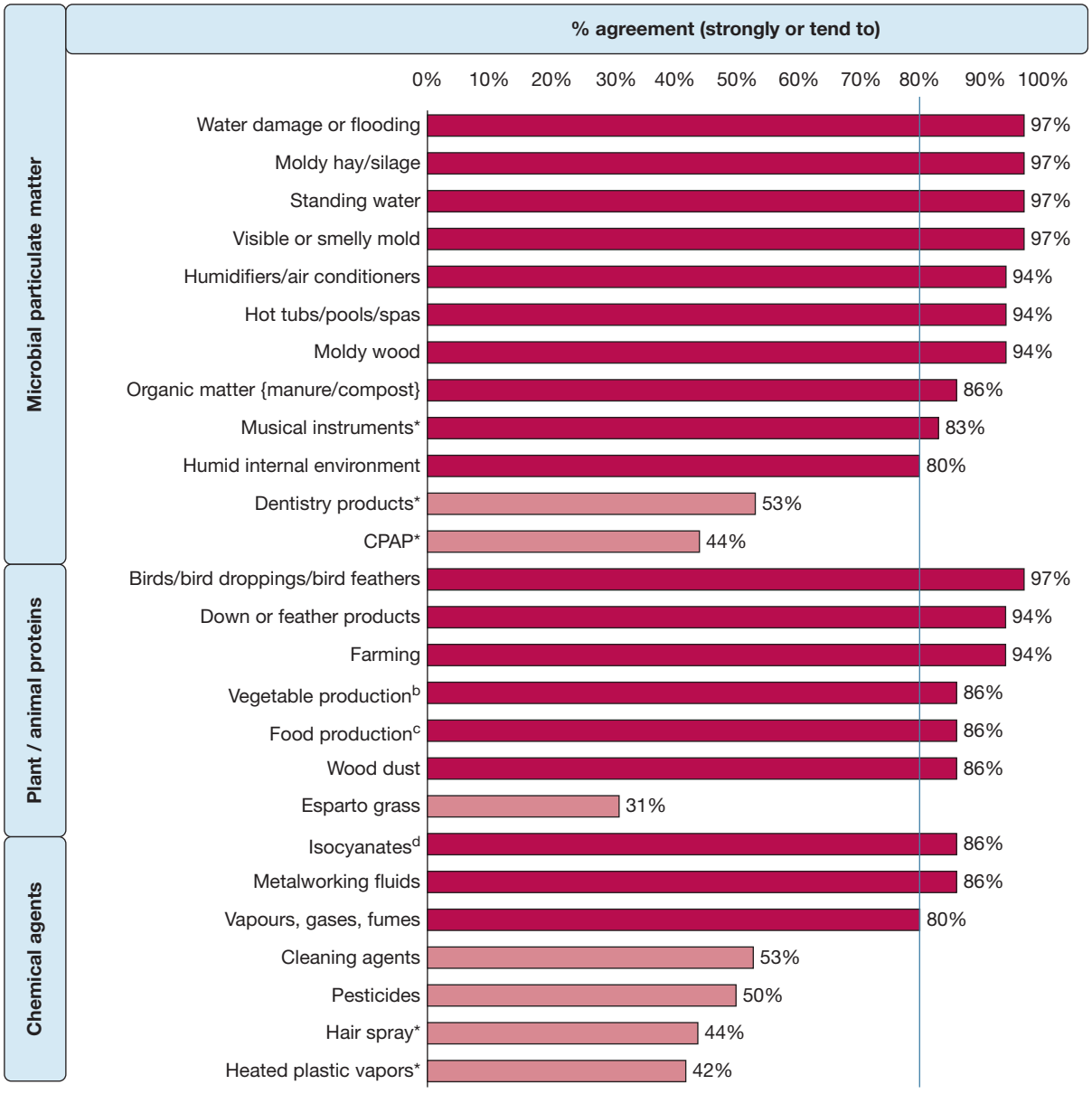

Figure 2 – *Exposures are listed with their corresponding agreement; 80% agree or strongly agree is marked as the a priori cutoff.* [a]*Includes trombone, saxophone, bagpipes.* [b]*Includes working with mushrooms, onions, potatoes, others.* [c]*Includes salami washers, cheese washers, wheat, sugarcane, malt, others.* [d]*Includes spraying pain, adhesives, polyurethane foam.* **Additional exposures suggested by experts.*

on subsequent rounds. This term was chosen because there was no consensus from Delphi experts as to what constituted a sufficiently regular basis. Wording for some exposures was refined and combined based on participant feedback. Participants found it difficult to determine the estimated duration of exposure, but when an estimated date of onset field was suggested, it was easier for participants to complete. The average duration to complete the instrument was 7 min, and overall participants found it reasonably easy to complete. Based on the patient validation process, a revised and final version of a CHP clinical exposure assessment instrument was developed (see e-Appendix 1).

Discussion

Through a systematic literature review, Delphi consensus of ILD experts, and patient validation process, we have developed an exposure assessment instrument for CHP containing a short, meaningful, and manageable list of exposures. This represents a systematic and methodologically robust approach to

developing such an instrument, including theorization of a conceptual network and item development, adjustment of the conceptual network, authentication of the framework/pretesting and refinement of the items, assembly and interpretation of the data, and adaptation of the instrument to patient use.[15]

At the core of our methodology is the Delphi technique, a well-established technique used in guidelines and consensus documents.[6] It allows, in the absence of a higher level of evidence, the development of consensus amongst expert opinion. Contrary to usual research and guideline development, the Delphi technique is anonymous, allowing each expert to contribute equal weight to the consensus, and can be performed without the need for face-to-face meetings, thus enabling expert opinion from around the world.

Engagement with users in testing and validating any instrument is crucial to determine readability and understanding of the items in the instrument.[15] It is important to determine that items are clearly understood, relevant, not redundant, and reflect the concept which they are intended to measure. Among tools developed for exposure assessment in CHP, we believe our instrument is unique in incorporating such validation.

This exposure assessment instrument has been designed specifically for the clinical assessment of exposures in CHP. It is not intended to replace the entire clinical history, nor is it designed to screen for other relevant factors in ILD or other respiratory diseases. Its application is designed to assist the clinician to determine whether there is a relevant exposure that may render the diagnosis of CHP more likely. Its use may also assist in the ability to determine ongoing exposures in actively exposed patients for which identification and remediation is essential to their management.

Although specific steps were taken to include a wide range of geographical locations and cultural contexts (including articles in languages other than English, recruiting ILD experts from around the world), clinical utility of this exposure assessment instrument may be affected by different local prevalence patterns. The future of exposure assessment may include engagement with users in more geographically diverse settings, validation of clinical utility in diverse local settings, and translation and further validation in other languages.

Critical to understanding this issue will be studies of the instrument's performance characteristics in different clinics, communities, and countries. Future research should focus on testing this exposure assessment instrument and other diagnostic tests in geographically diverse clinical settings to determine if they affect the frequency, confidence, and accuracy of a CHP diagnosis. This will involve determination of the sensitivity, specificity, and likelihood ratios of each approach, and an understanding of how findings affect the prevalence-dependent pretest probability in patients with various clinical presentations. Ultimately, tools such as this exposure assessment instrument need to be tested in the real world to demonstrate improvements in patient-centered outcomes (eg, dyspnea, functional status, survival time) and health-care value (eg, reduced utilization, improved management, lower costs). It is also clear from the Delphi responses that further research is required to determine the frequency, duration, and other factors that would increase the likelihood an identified exposure is clinically significant.

Conclusion

This Delphi survey provides items that ILD experts agree are important to ask in all patients presenting with suspected CHP and provides a basis for a systematically derived CHP exposure assessment instrument. Ongoing research is required to validate these items in the clinical setting.

Acknowledgments

Author contributions: H. B. led the project, ethics adherence, data analysis, and manuscript preparation. All authors contributed to the concept and design of the project, data interpretation, manuscript synthesis, and revisions. H. B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional Information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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