REVIEW
HYPERSENSITIVITY PNEUMONITIS

Exposure assessment in hypersensitivity pneumonitis: a comprehensive review and proposed screening questionnaire

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ABSTRACT Hypersensitivity pneumonitis is an immune-mediated inflammatory lung disease characterised by the inhalation of environmental antigens leading to acute and chronic lung injury. Along with suggestive clinical and radiological findings, history and timing of suspected antigen exposure are important elements for diagnostic confidence. Unfortunately, many diagnoses remain tentative and based on vague and imprecise environmental or material exposure histories. To date, there has not been a comprehensive report highlighting the frequency and type of environmental exposure that might lead to or support a more systematic approach to antigen identification. We performed a comprehensive literature review to identify and classify causative antigens and their associated environmental contexts or source materials, with emphasis on the extent of the supportive literature for each exposure type. Eligible publications were those that reported unique inciting antigens and their respective environments or contexts. A clinical questionnaire was then proposed based on this review to better support diagnosis of hypersensitivity pneumonitis when antigen testing or other clinical and radiological variables are inconclusive or incomplete.

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Exposure history in hypersensitivity pneumonitis may be thought of in terms of an inciting antigen or its exposure setting or source. An approach reflecting a comprehensive assessment of the published literature may improve diagnosis and management. https://bit.ly/2AJp5vr

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Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an immune-mediated inflammatory lung disease characterised by injury from the inhalation of mostly organic environmental antigens. Multidisciplinary discussion (MDD) of relevant exposure history, suggestive radiological findings and histopathology, when available, may be helpful in making a confident diagnosis, though there remains significant equipoise even among MDD-discussed cases [1, 2]. This may be due to overlapping findings as well as unclear and difficult to attain exposure history. For example, some occupational exposures that may increase risk of HP, including farming or hairdressing, have also been reported as epidemiologically associated with idiopathic pulmonary fibrosis (IPF) [3]. Regarding radiological findings, a fibrotic usual interstitial pneumonia (UIP) pattern on computed tomography (CT) may be suggestive of IPF in the absence of diagnosable secondary aetiologies, but a similar pattern may be found in approximately 10% of patients with biopsy-proven fibrotic HP [4]. Moreover, 40% of patients with IPF may have features of air trapping or mosaicism on CT imaging, which may also overlap with HP [5]. Serum-precipitating antibodies against specific antigens are often obtained and may suggest HP. However, sensitivity and specificity vary widely among screening studies and have not been established in terms of clinical utility. Positive precipitating antibodies have ranged between 39–78% of patients with interstitial findings [6–10], but have also been found in those without clinical or radiological disease. Among sausage industry workers for example, 37% may have positive precipitating antibodies, but no evidence of lung disease [11].

Given clinical overlap with other interstitial lung diseases (ILDs) and nonspecific findings on presentation, exposure history remains an important element for supporting HP diagnosis. Unfortunately, inadequate review of exposures or possible settings and materials may be a cause of frequent HP misdiagnosis [12]. There are currently more than 200 antigens reported as possible causative exposures. To the best of our knowledge, there have been few comprehensive assessments of the recent literature highlighting the specific array or frequency of environmental or occupational exposures and their inciting antigens, with the intent of generating a more concise or evidence-based review of systems or questionnaire for history-taking. Herein, we performed a literature review using Embase and Ovid/MEDLINE databases to identify and classify causative antigens and highlight the frequency and extent of supporting evidence for each exposure type.

Search strategy and literature review

We searched for publications in Embase and Ovid/MEDLINE database from November 1, 1999 to October 31, 2019, using the search terms "hypersensitivity pneumonitis" and "extrinsic allergic alveolitis". Eligible articles included clinical studies or case reports that described specific causative organisms or antigens through species-specific precipitating antibodies, positive inhalation provocation testing or lymphocyte proliferation testing. These were then reviewed for a description of the relevant or suspected environmental or occupational exposure history. Non-English-language articles, basic science or experimental animal studies and paediatric articles (age <18 years old) were excluded. References of included articles were also reviewed.

The search terms "hypersensitivity pneumonitis" and "extrinsic allergic alveolitis" yielded 5084 and 2062 articles, respectively. After exclusion based on language, article type and removal of duplicates, 1574 articles were screened. Of these, 1397 publications were excluded due to nonreporting or missing descriptions of suspected species-specific causative organisms or antigens. Final publications included 57 clinical studies and 120 case reports (figure 1).

Type of exposure

The included articles from this literature review identified 1596 cases with referenced antigen-positive testing (some patients were positive for more than one antigen). Negative antibody testing was reported in 427 patients but those with suspected exposures were still considered relevant HP diagnoses. Avian, fungal, bacterial, mycobacterial and other organic/inorganic exposures were identified, as described in tables 1 and 2.

Animal protein exposure

Bird or avian protein exposure was the most commonly reported form of HP, namely "bird fancier's" or "pigeon breeder's" disease. Repeated inhalation of avian proteins through bird droppings or feathers precipitated the majority of lung injury. We identified 31 publications providing specific antibody or precipitation testing against avian antigens. Most reported cases were exposed through keeping birds as pets in the home or breeding them as hobbies or professions. Goose or duck feather and down-containing duvets, pillows, coats or jackets were also a significant source of environmental exposure when there was no reported history of live bird exposure [13–19]. Notably, suspected HP cases related directly to domestic chicken or turkey exposure have not been reported or published, despite their relative ubiquity.

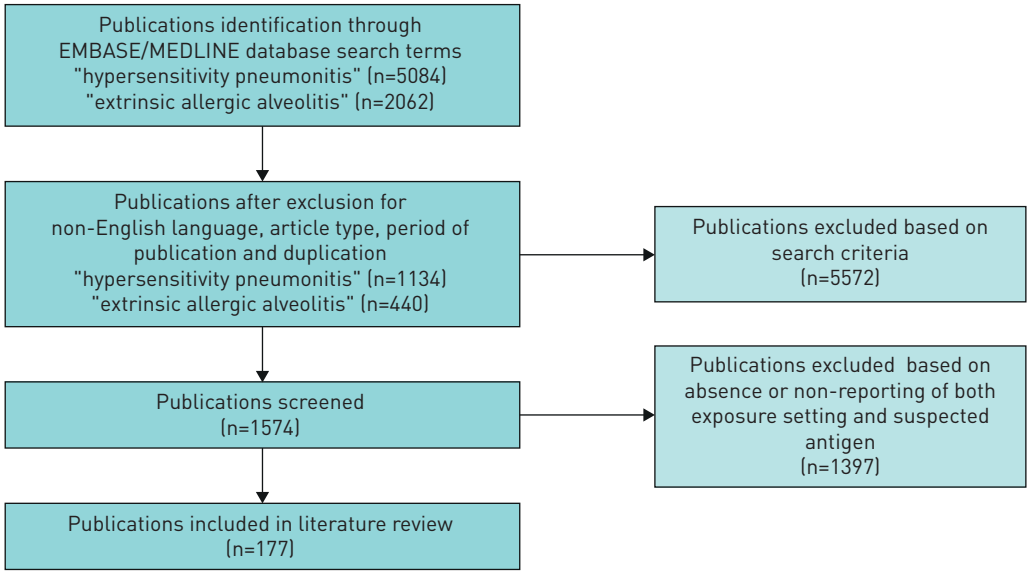

FIGURE 1 Literature search strategy.

Indirect exposure to avian antigens has also been reported. Three patients developed lung disease despite never having had direct bird exposure as a result of existing antigens in their homes from previous bird owners [20–22]. In another case, a mushroom worker developed suspected bird-related HP due to exposure to work-related poultry manure [23]. Given the high number of published HP cases and possible exposure settings, enquiring about direct and indirect exposure to bird protein through bird ownership or breeding, down or feather-containing items and droppings or faeces, is of high relevance and yield.

HP has been reported with protein exposure to two other animal species, chinchillas and flour mites. Recurrent episodes of HP in a French farmer were confirmed by positive testing for precipitating antibodies to chinchilla fur [24]. Removal of the chinchilla resulted in clinical improvement. Flour mite antigens were believed to have precipitated HP in a French baker [25].

Fungal exposure

Fungi are found in nearly every environment and are a second leading reported cause of HP. Environments or materials with water damage or moisture often support increased fungal growth and

TABLE 1 Specific antigens by type

Type of antigens	Specific antigens			
1. Animal protein	Bird protein, chinchilla, flour mite			
2. Fungi	*Trichosporon* spp.	*Aspergillus* spp.	*Penicillium* spp.	*Wallemia sebi*
	Eurotium amstelodami	*Fusarium* spp.	*Lichtheimia corymbifera*	*Cladosporium* spp.
	Cryptococcus spp.	*Candida* spp.	*Rhizopus* spp.	*Chrysonilia sitophila*
	Absidia corymbifera	*Mucor* spp.	*Scopulariopsis* spp.	*Paecilomyces* spp.
	Alternaria spp.	*Aureobasidium pullulans*	*Cephalosporium acremonium*	*Neurospora crassa*
	Exophiala spp.	*Phoma* spp.	*Rhodotorula* spp.	*Trichoderma* spp.
	Bjerkandera adusta	*Curvularia lunata*	*Humicola fuscoatra*	*Peziza domiciliana*
	Sphaerotheca fuliginea	*Ulocladium botrytis*		
3. Bacteria	*Thermoactinomyces* spp.	*Saccharopolyspora rectivirgula*	*Saccharomonospora viridis*	*Bacillus* spp.
	Streptomyces spp.	*Acinitobacter* spp.	*Pseudomonas* spp.	*Stenotrophomonas* spp.
	Ochrobactrum spp.	*Staphylococcus* spp.	*Arthrobacter* spp.	*Paenibacillus* spp.
	Brevibacterium spp.	*Sphingobacterium spiritivorum*	*Enterobacter* spp.	*Rhanella* spp.
	Pantoea agglomerans			
4. Mycobacteria	*Mycobacterium avium* complex	*M. immunogenum*	*M. chelonae*	*M. fortuitum*
	M. mucogenicum	*M. gordonae*		
5. Other antigens	Mushroom spores	Hay/damp straw/silage	Isocyanates	Water from humidifiers
	Cork	Metalwork fluid	Corn	Wheat/flour
	Sausage dust	Wood products	Bacilli Calmette–Guérin	Argan
	Catechin	Phytase	Proteolytic enzyme	Tiger nut

TABLE 2 Epidemiology of specific antigens by frequency of reported cases

Specific antigens	Number of patients	Number of unique publications	Setting	Selected references
1. Avian exposure	**381**	**31**		
	187	19	Keeping or breeding birds	[13, 14, 98]
	111	7	Use of duck or goose down jackets, duvets or pillows	[13–19]
	77	4	Direct contact with birds in the environment	[14]
	3	3	Indirect contact with bird-contaminated items or environment	[20–22]
	2	1	Exposure to droppings	[23]
	1	1	Working in duck or goose farms	[99]
2. *Trichosporon* spp.	**145**	**15**		
T. asahii	140	14	Summer-type HP, domestic fungal contamination	[100–102]
T. mucoides	2	1	Summer-type HP	[102]
T. japonicum	1	1	Domestic fungal contamination	[103]
Trichosporon spp.	2	1	Farm environment	[42]
3. *Thermoactinomyces* spp.	**113**	**10**		
T. vulgaris	104	10	Farm environment, metalwork fluid, esparto grass, garbage exposure, domestic bacterial contamination	[28, 61, 95, 104, 105]
T. candidus	8	1	Metalwork fluid	[95]
T. sacchari	1	1	Domestic bacterial contamination	[28]
4. *Aspergillus* spp.	**109**	**32**		
A. fumigatus	21	8	Cork factory, esparto grass, corn, bark mulch, garbage exposure, domestic fungal contamination	[21, 28, 39, 52, 60, 61, 104]
A. niger	11	5	Domestic fungal contamination, onion	[28, 40]
A. flavus	2	2	Domestic fungal contamination	[28]
A. oryzae	1	1	Koji brewer	[106]
A. versicolor	1	1	Domestic fungal contamination	[21]
Aspergillus spp.	73	20	Farm environment, domestic fungal contamination, dry sausage dust, metalwork fluid, dug wells, salami, flour, endogenous exposure from aspergilloma, nosocomial exposure, feed store and compost production	[25, 27, 42, 49, 50, 58, 95, 107–112]
5. *Saccharopolyspora rectivirgula*	**92**	**12**	Farm environment, esparto grass, garbage worker, summer-type HP	[42, 44, 45, 61, 104, 113]
6. Nontuberculous mycobacterium	**68**	**20**		
M. avium complex	47	16	Hot tub, sauna	[13, 63, 64]
M. immunogenum	18	2	Metalwork fluid	[70, 71]
M. chelonae	1	1	Bassoon musical instrument	[57]
M. fortuitum	1	1	Hot tub	[69]
M. mucogenicum	1	1	Hot tub	[68]
M. gordonae	1	1	Home humidifier	[114]
7. *Penicillium* spp.	**58**	**17**		
P. frequentans	12	2	Cork factory, mushroom worker	[47, 52]
P. glabrum	9	1	Cork factory	[51]
P. citrinum	6	2	Mushroom worker	[46, 115]
P. chrysogenum	2	1	Garbage exposure	[104]
P. camemberti	1	1	Salami production	[116]
P. notatum	1	1	Corn	[39]
Penicillium spp.	27	9	Farm environment, dry sausage dust, metalwork fluid, onion and potato processing, salami production, feed store, domestic fungal contamination	[41, 42, 49, 50, 95, 112, 117]
8. *Wallemia sebi*	**46**	**5**	Farm environment	[43–45, 48]
9. Mushroom spores	**36**	**5**	Mushroom workers: *Bunashimeji, Shimeji, Shitake, Eryngi*	[79, 80, 84, 94, 118]
10. *Eurotium amstelodami*	**29**	**4**	Farm environment	[43–45]
11. *Fusarium* spp.	**24**	**10**		
F. oxysporum	9	1	Farm environment	[45]
F. vasinfectum	8	3	Domestic fungal contamination	[26, 29, 31]
F. solani	2	2	Metalwork fluid, onion and potato processing	[41, 70]
F. napiforme	1	1	Domestic fungal contamination	[30]
Fusarium spp.	4	3	Metalwork fluid, bassoon musical instrument	[57, 71]

Continued

TABLE 2 Continued

Specific antigens	Number of patients	Number of unique publications	Setting	Selected references
12. *Lichtheimia corymbifera*	**23**	**2**	Farm environment	[44, 45]
13. *Saccharomonospora viridis*	**22**	**3**	Metalwork fluid, farm environment, hot tub	[45, 95, 119]
14. *Cladosporium* spp.	**21**	**10**		
C. sphaerospermum	12	5	Farm environment, mushroom worker, salami production	[47–49]
C. herbarum	7	4	Domestic fungal contamination, farmer's lung disease	[21, 37, 39]
C. cladosporioides	1	1	Contaminated air conditioner	[37]
15. *Cryptococcus* spp.	**21**	**2**		
C. albidus	17	1	Summer-type HP	[120]
C. uzbekistanesis	4	1	Domestic fungal contamination	[102]
16. Hay	**21**	**3**	Farm environment	[44]
17. *Streptomyces* spp.	**14**	**4**	Farm environment	[43–45]
18. *Candida spp.*	**14**	**6**		
C. albicans	11	3	Metalwork fluid, swimming pool, endogenous exposure	[59, 95, 121]
C. guilliermondii	1	1	Home humidifier	[35]
C. famata	1	1	Home humidifier	[34]
Candida spp.	1	1	Garbage exposure	[104]
19. Isocyanates	**12**	**5**	Paint sprayer, plastic welder, car repair shop, powder-coating factory	[75–77]
20. *Rhizopus* spp.	**11**	**3**		
R. microsporus	7	1	Sawmill worker	[122]
R. nigricans	4	2	Cork factory, dry sausage dust	[50, 52]
21. *Bacillus* spp.	**10**	**3**	Metal work fluid, ultrasonic misting fountain	[33, 71]
22. *Chrysonilia sitophila*	**9**	**1**	Cork factory	[51]
23. *Absidia corymbifera*	**9**	**1**	Farm environment	[43]
24. Water from humidifier	**9**	**1**	Contaminated water from humidifier, unclear antigen (suspect bacterial endotoxin)	[33]
25. *Acinitobacter* spp.	**8**	**2**		
A. calcoaceticus	1	1	No identified exposure or setting	[123]
Acinitobacter spp.	7	1	Metal work fluid	[96]
26. *Pseudomonas* spp.	**7**	**3**	Home humidifier, facial streamer in beauty shop	[33, 68]
27. Cork	**7**	**1**	Cork factory	[52]
28. *Mucor* spp.	**6**	**3**		
M. mucedo	1	1	Cork factory	[52]
Mucor spp.	5	2	Home humidifier, dry sausage dust	[33, 50]
29. *Scopulariopsis* spp.	**6**	**2**	Mushroom worker (Shimeji)	[47]
30. *Paecilomyces* spp.	**6**	**4**		
P. lilacinus	2	2	Bassoon and tenor horn musical instrument	[56, 57]
P. nivea	1	1	Oil fan heater	[36]
P. variotii	1	1	Oil fan heater	[36]
Paecilomyces spp.	2	1	Hardwood processing plant	[124]
31. Metalwork fluid	**5**	**2**	Metalwork fluid	[96, 125]
32. *Alternaria alternata*	**4**	**4**	Mushroom worker (Shitake), farm environment	[39, 53]
33. *Aureobasidium pullulans*	**4**	**2**	Domestic fungal contamination	[29, 113]
34. *Cephalosporium acremonium*	**4**	**2**	Domestic fungal contamination	[29, 126]
35. *Stenotrophomonas* spp.	**4**	**1**	Ultrasonic misting fountain	[33]
36. *Ochrobactrum* spp.	**3**	**1**	Metal work fluid	[96]
37. *Neurospora crassa*	**3**	**2**	Domestic fungal contamination, hardwood processing plant	[29, 124]
38. *Exophiala* spp.	**2**	**2**		
E. jeanselmei	1	1	Sauna	[127]
E. phaeomuriformis	1	1	Bagpipe musical instrument	[54]
39. *Phoma* spp.	**2**	**2**	Saxophone and bassoon musical instrument	[55, 57]
40. *Rhodotorula* spp.	**2**	**2**	Bassoon musical instrument	[57]
41. *Trichoderma* spp.	**2**	**2**		
T. viride	1	1	No identified exposure or setting	[29]
Trichoderma spp.	1	1	Farm environment	[48]

Continued

TABLE 2 Continued

Specific antigens	Number of patients	Number of unique publications	Setting	Selected references
42. Corn, oat	**2**	**2**	Exposure to corn, bakery setting	[25, 39]
43. Bacilli Calmette–Guérin	**2**	**2**	Intravesicular therapy in bladder cancer	[83]
44. Wheat/flour	**2**	**2**	Exposure to wheat/flour	[126]
45. Argan	**2**	**1**	Cosmetic factory	[128]
46. Catechin	**2**	**2**	Green tea production, catechin inhalation therapy	[85, 129]
47. Wood dust	**2**	**2**	Wood processing plant	[130]
48. Flour mite	**1**	**1**	Bakery setting	[25]
49. Proteolytic enzyme	**1**	**1**	Surgical instrument cleaning	[131]
50. Tiger nut	**1**	**1**	Horchata production factory	[132]
51. Konjak flour	**1**	**1**	Konnyaku production factory	[86]
52. Phytase	**1**	**1**	Cattle feed factory	[133]
53. Chinchilla	**1**	**1**	Pet chinchilla	[24]
54. Shrimp shell powder	**1**	**1**	Seafood factory	[134]
55. Sausage dust	**1**	**1**	Sausage production factory	[50]
56. Miscellaneous organisms	**1**	**1**	Water reservoir of steam iron	[62]
Sphingobacterium spiritivorum				
Sphaerotheca fuliginea	1	1	Greenhouse	[126]
Pantoea agglomerans	1	1	Herbal factory	[135]
Ulocladium botrytis	1	1	Saxophone musical instrument	[55]
Humicola fuscoatra	1	1	Domestic fungal contamination	[136]
Bjerkandera adusta	1	1	Domestic fungal contamination	[137]
Peziza domiciliana	1	1	Domestic fungal contamination	[32]
57. No identified setting				
Staphylococcus spp., *Arthrobacter* spp., Enterobacteriaceae, *Paenibacillus* spp., *Rhanella* spp. and *Curvularia lunata*				

HP: hypersensitivity pneumonitis.

therefore increased risk of antigen exposure. We identified 82 publications with 568 antigen-positive tests. Approximately 30 species of fungi have been reported as causative agents, described in tables 1 and 2. *Trichosporon asahii* is the most common in terms of number of reported cases, presenting as summer-type HP in Japan, followed by cases involving *Aspergillus*, *Penicillium*, *Wallemia sebi* and *Eurotium amstelodami*, in descending order, respectively.

T. asahii was found in the homes of affected patients with prior water damage and wood decay or in the trapped moisture of straw mats. *T. asahii* spores are often released more intensely in the summer months, causing seasonal outbreaks and the descriptive diagnosis of "summer-type HP". Outside of Japan, a variety of other fungal species have been reported in contaminated homes, including more commonly *Aspergillus* and *Fusarium* from Europe and North America, followed by *Penicillium*, *Cladosporium*, *Cryptococcus*, *Aureobasidium pullulans, Peziza domiciliana* and *Cephalosporium acremonium* [21, 26–32]. Fungal contamination may also occur through a variety of moisture containing or trapping domestic items, including humidifiers, air purifiers, heating units, air conditioners and ventilation ducts [33–37].

The farm environment is a commonly reported setting for both fungal and bacterial antigen exposure, resulting in so-called "farmer's lung". Both types of organism may be found in moist hay or straw, grain bins, animal feed, silage and manure, as well as on contaminated crops such as onion, potato and corn [38–41]. Reported causative fungal organisms have included *W. sebi*, *Aspergillus*, *E. amstelodami*, *Penicillium*, *Lichtheimia corymbifera*, *Fusarium*, *Absidia corymbifera*, *Cladosporium*, *Alternaria alternata* and *Trichosporon*, in decreasing frequency [39, 42–48].

Sites of food production have also been reported as sources of fungal antigen exposure, particularly in Europe. *Aspergillus* and *Penicillium* were reported as fungal contaminants in salami and dry sausage dust, leading to HP. Additional reported species include *Rhizopus, Mucor* and *Cladosporium* from salami production [49, 50]. Other work environments that reported potential fungal contaminants include cork factories, mushroom farms and sawmills. Cork material has been reported as contaminated with

Aspergillus, *Penicillium*, *Rhizopus* and *Mucor*, leading to a specific type of HP termed "suberosis" [51, 52]. Mushroom farms have also been the setting for HP, with reported precipitating antigens related to *Penicillium*, *Cladosporium, Scopulariopsis* and *A. alternata* [46, 47, 53].

Wind and brass musical instruments have recently been reported as associated with inciting fungal antigens. Identified species, taken specifically from a bagpipe, bassoon, saxophone and tenor horn, have included *Fusarium*, *Paecilomyces*, *Exophiala phaeomuriformis*, *Phoma* species, *Purpureocillium lilacinum* and *Ulocladium botrytis* [54–57].

Finally, endogenous antigens associated with clinical infection may also induce HP. Yoshimoto *et al.* [58] reported a case of HP precipitated by *Aspergillus* from an infectious aspergilloma, while Schreiber *et al.* [59] described a case of HP caused by endogenous *Candida albicans*.

Bacterial and nontuberculous mycobacterial exposure

Bacteria and nontuberculous mycobacteria (NTM) as inciting agents of HP have been reported less commonly compared to fungal antigens. We identified 46 publications reporting 353 antigen-positive tests. The most commonly reported environmental exposure was farm or grain dust, with two thermophilic filamentous and spore-forming bacteria *Thermoactinomyces vulgaris* and *Saccharopolyspora rectivirgula* being the most common. Although both have been found in multiple locations on farms, they have also been isolated from esparto grass or esparto fibre, a type of material used in the production of ropes and canvas [60, 61].

Water reservoirs have been reported as contaminated with bacteria believed to be associated with HP. *Bacillus*, *Pseudomonas*, *Stenotrophomonas* and *Sphingobacterium spiritivorum* species have been isolated from mist fountains and steam irons as possible HP antigens [33, 62]. Moreover, bacterial endotoxin itself, as detected in high levels of used wastewater, has also been proposed as possibly leading to hypersensitivity lung injury [33].

NTM mycobacteria, particularly *Mycobacterium avium complex* (MAC) have been reported as inciting antigens in a particular type of inflammatory lung disease known as "hot-tub lung", which some have proposed is a form of HP [63–65]. MAC isolated from either sputum or the bronchoalveolar lavage of those affected were the same genotypic species isolated from culprit hot tubs or showers [63, 66, 67]. Other NTM species, including *M. fortuitum* and *M. mucogenicum* have been reported in hot-tub lung [68, 69]. *Mycobacterium* in metalwork fluid, used in machine operation for automobile and aircraft manufacturing have been reported as culprit antigens for HP. *M. immunogenum* has been widely found and believed to cause a specific type of HP known as "machine operator's lung" [70, 71].

Organic and inorganic material exposure

Organic and inorganic chemical compounds have been reported as causative antigens in HP, including isocyanates, acid anhydrides, chloroethylenes and acrylate compounds [72–77]. We identified 39 reports with 123 antigen-positive tests. Again, reported methods used to identify specific antigens included direct measurement of precipitating circulating antibodies, inhalational challenge and lymphocyte stimulation, using samples taken directly from suspected environmental sources (mushroom, hay, corn and metalwork fluid) [78–80].

Other rare or uncommon sources of exposure leading to HP are further highlighted. Mushroom spores were the most commonly reported organic antigen causing HP outside of other fungal and bacterial species [47, 79, 80]. Precipitating antibodies against hay have also been reported [44]. Isocyanates are the only cited chemical compound with positive IgG antibody testing supporting an HP-like response [75–77, 81]. Diisocyanate, the most common form of isocyanate, is found in plastic or foam material often exposed to during manufacturing. Commercial paint and varnishes, which often involve the use of sprayers for aerosolised exposure, also contain diisocyanates and are commonly found in automobile manufacturing and repair garages [82]. Intravesicular Bacilli Calmette–Guérin (BCG) therapy for bladder cancer was reported as precipitating HP in one case study, with specific IgG against BCG confirmed by precipitating antibody testing [83]. Antibodies against extracted hay antigen, sausage dust and cork have also been reported in patients with HP. However, for these specific antigens, it may be difficult to exclude other undetected contaminating organisms (mould or bacteria) as the more clinically relevant antigen [44, 50, 52]. Other rare but reported organic and inorganic compounds include corn, oat, argan tree plant oil found in many cosmetic products, catechin phenol compounds found in green tea, pine sawdust and proteolytic enzymes used in the cleaning of surgical instruments. Tiger nut from horchata factories, Konjak flour from a Konnyaku factory, phytase used in cattle feed and shrimp shell powder found in seafood processing are additional rare but reported inciting antigens (see table 2).

Hypersensitivity pneumonitis according to region

Epidemiology of HP may vary depending on climate, geographic conditions, availability of culprit environments and occupational or industrial practices (see supplemental tables 1–3). We classified reports into four main geographical groups according to the frequency of publication. These were Europe, East Asia (dominated by Japan), North America and a conglomerate of "others". Sixty-eight publications represented European locations followed by 59 reports from Japan, North America (40 publications) and other combined regions (10 publications). Publications from those designated as combined or "other" regions included reports from India, Mexico, South Korea, Taiwan and New Zealand. Highlighting specific exposures according to geography may be helpful in delineating patterns of presentation, though publication bias is likely based on the availability of local academic or clinical institutions able to track them. In that regard, a lack of specific reports for a region does not necessarily reflect the absence of that type of exposure or disease but perhaps more the absence of review and reporting.

Bird-related HP was the most common type of published HP in Europe and North America. Although summer-type HP was the most common type in Japan, bird-related HP was also commonly reported. However, the type of exposure or setting appeared to differ according to the described region. Bird antigen exposure with the use of down or feather-containing products appeared to be less reported in Europe compared to Japan and North America, as described in supplemental tables 1–3.

In Europe, the farm environment, metalwork fluid exposure, cork manufacturing, salami and sausage production, esparto grass and musical instruments were frequently reported as occupation or hobby-related exposure types. Although home-related HP cases were noted, they were reported less frequently than occupation-related sources of exposure.

In Japan, domestic antigen exposure was the most commonly published type of HP (summer-type HP), followed by bird-related and other occupational exposures. Japan also had the highest number of publications regarding mushroom worker's lung disease, including several specific species *bunashimeji, shimeji, shitake, enoki* and *eryngi* [46, 53, 79, 80, 84]. Unique industries in Japan, such as green tea and Konnyaku manufacturing, might suggest geographically specific work exposures for HP [85, 86].

In North America, hot-tub lung diseases associated with NTM was the most commonly reported type of HP. HP related to metalwork fluid was also common. Home-related HP associated with water damage or mould-contaminated homes was the next most commonly reported subtype, followed by HP related to the farm environment [87], with a lower number of identifiable causative antigens.

A proposed screening questionnaire for HP exposure

Previous reports suggest that HP may be underdiagnosed or misdiagnosed due to failure or inability to identify causative exposures [1, 12, 29, 78]. A large report from the United States suggested that nearly 40% of patients with suspected HP did not have an identifiable antigen or exposure setting [87]. Antigen identification may also be associated with prognosis [88], where suspected exposure identification and removal of the offending antigen may play a key role in management. Currently, there is no widely accepted review based on comprehensive or systemic reporting from the literature to guide screening for suspected exposures in patients presenting with parenchymal lung disease. Vasakova *et al.* [1] recently proposed a questionnaire to screen for all causes of ILD, which included common HP exposures, but was not specific to HP. For general use, we proposed a comprehensive screening questionnaire to cover the majority of specific antigens and their culprit exposures as reported in our literature review (table 3).

Discussion

Antigen exposure history is important in the diagnosis and management of HP, as presenting clinical and radiological findings may be fleeting or overlap with other ILD and be challenging to diagnose. In the absence of widely accepted diagnostic criteria, particularly for fibrotic HP cases, a balance of contributing factors appears to increase diagnostic confidence.

Relevant exposure history for many clinicians is a leading factor in suspected diagnosis, though may prove difficult to accurately assess, exclude or confirm. When present it may support HP diagnosis even when clinical, radiological or serological findings are equivocal, but be absent when the latter is strongly suggestive and cast doubt on the suspected diagnosis. The degree to which exposure history is convincing one way or another may also be dependent on the presenting stage or subtype of HP. For example, in some cases of acute or subacute HP with typical or suggestive radiological findings, a relevant and timely exposure history may be sufficient to make a diagnosis without additional serological or histopathological testing. In contrast, patients presenting with UIP-like radiological features (traction bronchiectasis with honeycombing) might strongly suggest IPF unless a particularly strong and solicited exposure history is noted [89]. Solicited exposure history may also be considered inconclusive or incidental if the overriding

TABLE 3 Evidence-based exposure screening questionnaire

			Number of published cases	Number of publications
1. Have you been exposed to birds or feather/down-containing items?				
☐ YES	☐ NO	Bird: Pet birds (tropical), pigeon breeding or other birds in your environment? (duck and geese)	243	26
☐ YES	☐ NO	Feather/down-containing items (duck or goose down-containing jackets, pillows, blankets or feather dusters)?	111	7
☐ YES	☐ NO	Exposure to bird droppings in a farm, factory, or home setting (droppings in an attic, barn, porch or yard)?	2	1
2. Have you had any of the following in your home or work environment?				
☐ YES	☐ NO	Humidifiers or mist fountains	17	5
☐ YES	☐ NO	Mould or mildew	13	10
☐ YES	☐ NO	Moist or decayed wood	9	6
☐ YES	☐ NO	Flood/water damage	4	4
☐ YES	☐ NO	Straw mats	2	1
☐ YES	☐ NO	Window or single unit air conditioners	1	1
☐ YES	☐ NO	Oil fan heater	1	1
☐ YES	☐ NO	Steam iron	1	1
3. Do you frequently use a hot tub, jacuzzi or sauna?			58	17
☐ YES	☐ NO			
4. Have you had any of the following occupations or hobbies or worked in any of the following locations?				
☐ YES	☐ NO	Farm/greenhouse worker	295	20
☐ YES	☐ NO	Machine operator	48	5
☐ YES	☐ NO	Mushroom worker or worker in mushroom factories	42	8
☐ YES	☐ NO	Carpenter/sawmill worker or worked in a hardwood processing plant	16	5
☐ YES	☐ NO	Wind or brass musical instrument (*e.g.* saxophone, bassoon, tenor horn, bagpipe)	5	4
☐ YES	☐ NO	Painter or paint sprayer	5	2
☐ YES	☐ NO	Garbage collector	5	2
☐ YES	☐ NO	Well digger	5	1
☐ YES	☐ NO	Baker	3	2
☐ YES	☐ NO	Working with plaster	1	1
☐ YES	☐ NO	Plastic welder	1	1
☐ YES	☐ NO	Food production or processing: salami, dry sausage, green tea, onion, potato, flour, wheat, seafood	17	9
☐ YES	☐ NO	Cork factory	17	2
☐ YES	☐ NO	Repair garage or aircraft manufacturing	10	4
☐ YES	☐ NO	Esparto fibre factory	10	2
☐ YES	☐ NO	Cosmetic production	2	1
☐ YES	☐ NO	Warehouses	1	1
☐ YES	☐ NO	Feeding stores/factory	1	1

clinical concern for IPF and its poorer prognosis is high, particularly in the absence of other supportive findings like histopathology. Clinical improvement or stability after antigen avoidance might support an HP diagnosis, though fibrotic HP cases may still progress despite suspected antigen avoidance.

In practice, exposure history may be thought of as comprising two related elements: the suspected and relevant inciting antigen (*e.g.* avian, mould, bacterial, mushroom spore) and its source or environmental context (*e.g.* occupation, farm environment, water damage, feather duvets or blankets, showerheads). Clinicians may equate the two as part of a working diagnosis; however, it is not uncommon to suspect a culprit environment or occupation without a specific antigen or vice versa (positive antibody testing for one or more antigens on screening but no identifiable exposure or occupational history). When only one or the other is present, diagnostic confidence may remain low without the support of other suggestive radiological or histopathological findings.

Additionally, environmental exposure history may be insufficient to conclude an inciting culprit antigen as multiple antigens may be involved in various settings in the same patient. A variety of methods are available as screening or directed testing to confirm specific antigen sensitivity, including the measurement of precipitating antibodies, inhalational challenge and lymphocyte proliferation [78, 90]. Confirmation of precipitating antigens using a panel of more commonly encountered mould or avian antigens may be useful when there is no apparent history of suspected exposure or more than one potential precipitating antigen

may be involved. Identification of suspected antigens may also be critical to management as antigen avoidance can reduce further lung injury. Although unidentified antigens were reported as an independent risk factor for poorer outcome [88], the exact prognostic role of antigen identification remains controversial, with other reports suggesting opposing results, particularly in those with fibrotic disease [91–93].

Soliciting a possible environmental setting or source of known exposure may be the only available step in avoiding antigen exposure. While serologic testing might support a specific organism or antigen, such testing may not be readily available or be unable to test all possible culprit antigens. Instead, a useful review of exposures to relevant environments or materials may better assist clinicians in the efficient use of specific serological studies. For example, living on a farm is a commonly solicited but nonspecific setting that may involve exposure to avian, fungal and bacterial antigens. Additional testing to confirm hypersensitivity to relevant antigens such as *T. vulgaris*, *S. rectivirgula*, *W. sebi*, *Aspergillus* and *E. amstelodami* may be helpful for potentially excluding more commonly inciting antigens if negative [42–45, 94]. Otherwise, a history of farm exposure on its own may be insufficient to confirm HP diagnosis or assist in antigen avoidance. The domestic or residential environment is another example of multiple sources of possible contamination and antigen exposure in one environment. Fungal exposure may involve trapped moisture in water-damaged structures, heaters or air conditioners, with contamination of both bacteria and fungi in the water reservoirs of humidifiers and steam irons. Colonisation of mycobacteria in showerheads or hot tubs is a commonly solicited source of potential antigen exposure in the United States [33, 65]. Patients working in commercial garages might be exposed to metalwork fluid used in machine operation as well as diisocyanates found in some commercial paints [70, 76, 95, 96]. Proving antigen hypersensitivity may be nearly impossible in these settings, other than to empirically avoid exposure, which for some may mean potential loss of livelihoods or property when exposure does not necessarily mean related disease.

Despite the abundance of available literature, there has been little agreement on the merit or significance of which exposures should be more specifically sought out during history-taking and which may be of less relevance. Barnes *et al.* [97] recently completed a Delphi assessment of 36 international experts and found agreement on 18 items for clinical review of exposures in fibrotic or chronic HP. The five with highest agreement (97%, with inclusion cut-off of 80%) included exposure to mouldy hay or silage, standing water, water damage or flooding, visible mould or a mouldy smell and bird or avian protein exposure. An in-depth literature review was pursued prior to the Delphi process to provide a comprehensive list of exposure items, with final suggested exposure items more or less reflecting agreement between the extent of reported cases and expert clinical experience. This is an important first step in unifying a history-taking approach, particularly in fibrotic HP, though the authors note that future studies are needed to support prospective utility.

In summary, our review suggests that bird protein exposure was the most frequently reported setting or exposure type, followed by specific exposures in the farm environment, home or domestic fungal or bacterial contamination, occupational metalwork fluid exposure and mushroom spores, respectively. However, we included a majority of studies reporting both a specific antigen and its suspected environmental setting or source, which may not be reflective of how real-world HP diagnoses are made as often one or both of these components may be missing in typically diagnosed cases. Sensitivity of serum IgG antibodies to suspected antigens in fibrotic HP has been reported as often absent or lower than in nonfibrotic or more acute cases, which might also lead to the inclusion of less fibrotic HP studies in our review [7]. In contrast, we also reviewed and included less commonly solicited or reported antigens that may be regionally or geographically differentiated or prove more incidental to specific occupations or hobbies. Rare or novel precipitating exposures, which have yet to be confirmed or supported by antigen-detecting studies such as precipitating serum antibodies or inhalational challenge testing, were not included in our review. Indeed, the use of such confirmatory or supportive antigen studies varies among institutions and is hindered by lack of standardisation. Finally, while we proposed a comprehensive screening questionnaire covering the majority of causative antigens and their culprit environments based on a systematic review of the published literature, the actual epidemiology of particular organisms and clinical validation of this or any other questionnaire requires further study and may lead to additional customisation based on institutional need, geography and population demographics.

Conclusion

In summary, identification of specific antigens and their exposure source in patients with suspected HP remains challenging. Not only is the identification of suspected antigens and their sources helpful in HP diagnosis but may also play a role in antigen avoidance, which may affect prognosis and outcome. Bird antigen exposure was the most frequently reported cause of HP from the literature, followed by fungal, bacterial and organic or inorganic antigens. After a comprehensive review of reported antigens and their

associated exposure source, we proposed a directed questionnaire to screen for suspected exposures in patients presenting with undifferentiated parenchymal lung disease.

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