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POSITION PAPER

Occupational hypersensitivity pneumonitis: an EAACI position paper

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Abstract

The aim of this document was to provide a critical review of the current knowledge on hypersensitivity pneumonitis caused by the occupational environment and to propose practical guidance for the diagnosis and management of this condition. Occupational hypersensitivity pneumonitis (OHP) is an immunologic lung disease resulting from lymphocytic and frequently granulomatous inflammation of the peripheral airways, alveoli, and surrounding interstitial tissue which develops as the result of a non-IgE-mediated allergic reaction to a variety of organic materials or low molecular weight agents that are present in the workplace. The offending agents can be classified into six broad categories that include bacteria, fungi, animal proteins, plant proteins, low molecular weight chemicals, and metals. The diagnosis of OHP requires a multidisciplinary approach and relies on a combination of diagnostic tests to ascertain the work relatedness of the disease. Both the clinical and the occupational history are keys to the diagnosis and often will lead to the initial suspicion. Diagnostic criteria adapted to OHP are proposed. The cornerstone of treatment is early removal from exposure to the eliciting antigen, although the disease may show an adverse outcome even after avoidance of exposure to the causal agent.

Abbreviations
BAL, Bronchoalveolar lavage; HRCT, High-resolution computed tomography; ICT, Inhalation challenge tests; ILD, Interstitial lung disease; IPF, Idiopathic pulmonary fibrosis; MWF, Metal working fluid; NSIP, Nonspecific interstitial pneumonia; OHP, Occupational hypersensitivity pneumonitis; UIP, Usual interstitial pneumonia.

Key messages

- OHP manifests with a variable spectrum of clinical and radiologic findings that may mimic a wide range of lung diseases. The possibility of OHP should be considered in all cases of interstitial lung disease of unknown etiology and in patients with relapsing respiratory and flu-like symptoms that are work related.
- Establishing the diagnosis of HP and the causal role of the workplace is based on a combination of diagnostic tests and requires a multidisciplinary approach.
- Identification of the offending agent/source of exposure is crucial for establishing a diagnosis of OHP and providing evidence of a causal relationship between the disease and the work environment.
- Removal from exposure to the causal workplace agent is the recommended treatment of OHP, although the possibility of an adverse outcome has been described even after avoidance of exposure.
- Diagnosing a case of OHP should prompt to survey the remaining workforce to identify other potentially affected workers.

The occurrence of severe respiratory and systemic symptoms has been associated with a variety of inhaled organic antigens and reported under various descriptive terms such as 'farmer's lung', 'pigeon breeder's lung', or 'bird fancier's lung'. In 1960, Pepys first demonstrated the presence of precipitating antibodies directed against antigens derived from moldy hay in the serum of patients affected with 'farmer's lung' disease (1) and introduced the term 'extrinsic allergic alveolitis' to describe conditions that occur after exposure to various organic antigens (2). Because the disease is not only confined to the alveoli, but also involves the bronchioles (i.e. alveolobronchiolitis), the term 'hypersensitivity pneumonitis' (HP) is more appropriate and is currently most commonly used (3).

This report focuses on the various aspects of HP in the specific context of an occupational etiology. The objectives of the Task Force were (i) to provide a critical review of our current knowledge on HP caused by the occupational environment, and (ii) to propose an updated definition and practical guidance for the diagnosis and management of occupational HP (OHP).

Methodology

The present document is the result of an expert consensus process based on a thorough review of the available literature conducted by an EAACI Task Force consisting of a panel of allergologists, occupational physicians, and pulmonologists. The online database PubMed was searched for published articles using the following terms: (work* OR occupation*) AND ("hypersensitivity pneumonitis" OR "extrinsic allergic alveolitis"). Data pertaining to the diverse aspects of OHP were critically reviewed, summarized, and discussed by the Task Force members. From the start, it was recognized that an evidence-based approach would not be possible because of the heterogeneous quality of published studies. Instead, a consensus was reached during two face-to-face meetings of the Task Force members and through an informal iterative process soliciting input from all panel members on draft documents.

Definition

Based on the key features of the disease that were outlined by previous authors (4–11) and the EAACI nomenclature for allergic diseases (12), the following consensus definition is proposed: 'OHP is an immunologic lung disease with variable clinical presentation and outcome resulting from lymphocytic and frequently granulomatous inflammation of the peripheral airways, alveoli, and surrounding interstitial tissue which develops as the result of a non-IgE-mediated allergic reaction to a variety of organic or low molecular weight agents that are present in the work environment'.

Classification

HP is a complex dynamic clinical disorder that varies in its initial presentation and clinical course. The clinical presentation of HP has classically been categorized as acute, subacute, and chronic depending on the condition of exposure and other clinical features (4). However, it is now widely acknowledged that there may be considerable overlap among these three clinical syndromes. The international HP Study Group performed a cluster analysis of 168 patients with HP (8, 13) and identified two phenotypes of patients. The patients in one cluster were characterized by more recurrent systemic symptoms (chills, body aches) and normal chest radiographs than those in the second cluster who showed significantly more clubbing, hypoxemia, a restrictive pattern on pulmonary function tests, and fibrosis on HRCT scan. Hence, this study demonstrates that subacute HP is particularly difficult to identify, and the classification of HP should be restricted to two phenotypes as summarized in Table 1.

Causal agents

A large number of occupational agents/antigens have been described as potential causative agents of HP in a wide variety of occupations. These offending agents can be classified into six broad categories that include bacteria, fungi, animal (glyco)proteins, plant (glyco)proteins, low molecular weight chemicals, and metals (Table 2). Using a quantitative structure–activity relationship (QSAR) model, it was found that chemicals causing OHP tend to have a higher predicted asthma hazard, are more lipophilic, and are more likely to be protein cross-linkers than those causing occupational asthma (14).

As working practices have changed, some causes of OHP have markedly declined (e.g. farmer's lung) while new agents/

Table 1 Proposed classification of occupational hypersensitivity pneumonitis

Characteristics	Acute/subacute OHP	Chronic OHP
Exposure to causal antigen at work	Intermittent high-level exposure (e.g. farmers)	Continuous low-level exposure (e.g. bird breeders)
Onset of symptoms	2–9 h after exposure; may evolve to gradually increasing symptoms over days to weeks	Insidious, over weeks to months
Nature of symptoms	Cough and dyspnea, but predominantly influenza-like symptoms	Progressive symptoms (dyspnea, cough, and weight loss), sometimes punctuated by intermittent attacks of symptoms or slowly increasing
Physical signs	Fever	Inspiratory crackles; cyanosis; digital clubbing; cor pulmonale
Outcome	Symptoms peak within 6–24 h after exposure; last hours to days; and recur on re-exposure; may progress to severe dyspnea	End-stage fibrotic disease and/or emphysema; exacerbations may occur despite avoidance of exposure

Classification derived and adapted from the cluster analysis of the HP Study Group (13).

exposures are emerging (15). In the last decades, metal working fluids (MWF) have been frequently implicated as a causative agent of HP among machine operators (16, 17). Mycobacterium immunogenum has been identified as the presumed etiological agent in a number of HP due to MWF, but in most instances the causative agent(s) remained uncertain (16, 17). Aerosolized water containing various species of bacteria, mycobacteria, and fungi generated by ultrasonic humidifiers, air conditioners, hot tubs, steam irons, water-damaged offices, and water-related pursuits in general (e.g. swimming pools, hydroponic cultivation) has been increasingly implicated as causing OHP (15). Awareness of new causal agents is important in helping clinicians to suspect possible causes of OHP.

Epidemiology

The burden of OHP in the general population is unknown, but HP in general is considered a rare disease with an estimated incidence of ~0.9 cases per 100 000 person-years for the period 1991–2003 (18). Population-based registries reported that HP accounted for 1.5–12% of incident cases of interstitial lung diseases (ILDs) during the 1990s (19).

The reported prevalence rates for OHP have been greatly affected by the diagnostic criteria used for defining the disease (5). The prevalence estimates derived from questionnaires were 3–6 times higher than the figures based on a questionnaire combined with the presence of specific IgG antibodies among farmers (20, 21) and pigeon breeders (22, 23). A case definition based on the predictive value of symptoms and results of diagnostic procedures has been recently developed and may be useful for assessing workers with suspected OHP (24).

A number of cross-sectional surveys have assessed the prevalence of OHP in various high-risk occupations. The estimated prevalence rates of OHP ranged from 1.3% to 12.9% (20, 21, 25–27) among farmers and from 8.0% to 10.4% among pigeon breeders (22, 23). The few published cohort studies of OHP reported incidence rates of 2–5 cases per 10 000 farmers per year during the 1980s (28, 29). Cross-sectional studies provided prevalence estimates in various high-risk workforces, such as workers exposed to tobacco (5.2%) (30), mollusk shells (23%) (31), isocyanates (0.9–4.7%) (32, 33), contaminated air conditioner (15%) (34), swimming pools (27%) (35), and MWF (5.6%) (16). These figures, however, usually come from reports of outbreak investigations, and it should be borne in mind that this condition often occurs in time- and place-limited 'epidemics'.

There is a lack of recent data on the incidence of OHP. Data from the German statutory accident insurance institutions covering approximately 40 million active workers show that an average of 14 new cases of OHP were recognized annually over the period 2000–2013. The etiological agents were molds and fungi in 45.9% of the cases, plant-derived materials (15.6%), animal hair and feathers (15.7%), bacteria, bacterial components, and other microorganisms (10.8%), unspecified organic dusts (1.6%), isocyanates (0.5%), and miscellaneous products (10.4%) (M. Raulf, personal communication). In France (~30.5 million active workers), an average of 29 new cases of OHP were allowed compensation annually over the period 2005–2012, of whom 80% were self-employed workers, mainly from the agricultural sector (J.C. Dalphin and J.J. Laplante, personal communication). In Finland (~2.45 million active workers), an average of 30 new cases of OHP were compensated annually and reported to the Finnish Register of Occupational Diseases over the same period (H. Suojalehto, personal communication). Ninety-eight percent of these cases were attributed to molds.

Risk factors

Epidemiological studies have documented a relationship between exposure to organic antigens—most often assessed qualitatively—and the level of serum-specific IgG antibodies against these antigens (22, 23, 36, 37) and/or the prevalence of HP (22, 26, 38). Nevertheless, it remains uncertain why only a small proportion of exposed workers develop HP. Genetic susceptibility to HP has been associated with the

Table 2 Principal agents causing occupational hypersensitivity pneumonitis

Categories	Agents	Examples of jobs and occupational exposures
Bacteria	*Thermophilic actinomycetes*	Farmers; bagasse workers; mushroom workers, potato riddlers, compost workers, ventilation systems
	Lichtheimia corymbifera	Farmers
	Acinetobacter, Ochrobactrum	Metal working fluids
	Streptomyces albus	Compost workers
	Klebsiella oxytoca	Humidifiers
	Bacillus subtilis enzymes	Detergent industry
	Mycobacterium avium complex and other nontuberculous mycobacteria	Spa workers
	Mycobacterium immunogenum	Metal working fluids, machine operators
Fungi	*Alternaria alternata*	Humidifiers, wood workers
	Aspergillus spp.	Stucco workers, tobacco growers, malt workers
	Trichosporon cutaneum	Summer-type HP
	Penicillium glabrum	Cork workers
	Pencillium roqueforti	Cheese workers
	Penicillium verrucosum	Food processors
	Penicillium camemberti	Food processors
	Penicillium citreonigrum	Peat moss processing workers
	Cryptostroma corticale	Maple bark strippers, florists
	Botrytis cinerea	Wine makers
	Mucor stolonifer	Paprika slicers
	Rhodotorula	Humidifiers
	Various mushrooms: *Shiitaki, Bunashimeji, Pleurotus, Pholiota, Shimeji, Agaricus*	Mushroom workers
Enzymes	Phytase, subtilisin	Animal feeding, cleaners
Animal & insect proteins	Avian serum and feather proteins	Bird breeders
	Rat serum proteins	Laboratory workers
	Pearl	Pearl industry
	Mollusk shell	Nacre industry
	Silk	Textile workers
	Carmine	Food and cosmetic industry
	Sitophilus granarius	Farmers
Plant proteins	Tiger nut	Food processors
	Legumes (e.g. soy)	Food processors
	Malt	Food processors
	Alginate	Seaweed workers
	Woods: ramin, pine	Wood workers
	Esparto dust	Stucco workers
Low molecular weight chemicals	Diisocyanates	Chemical and polyurethane industry, painters
	Acid anhydrides	Plastic workers, aircraft industry
	Acrylate compounds	Dental technicians
	Triglycidyl isocyanurate	Painters (powder paint)
	Pharmaceutical agents: penicillins, cephalosporins	Pharmaceutical industry
	Dimethyl phthalate and styrene	Yacht manufacturing
Metals	Cobalt	Hard-metal workers
	Zinc	Smelters
	Zirconium	Ceramic workers

following: (i) polymorphisms of the major histocompatibility complex (MHC) class II molecules HLA-DR and DQ; (ii) the promoter region in the TNF-alpha gene; (iii) the immunoproteasome catalytic subunit PSMB8 which participates in the degradation of proteins into peptides for presentation by the MHC class I molecules; and (iv) the transporter associated with antigen processing (TAP)-1 gene for MHC class I molecules, whereas polymorphisms in the tissue inhibitor of metalloproteinase (TIMP)-3 promoter region may protect against the development of HP as reviewed in (10). Conversely, smoking has been consistently associated with a lower prevalence of specific IgG antibodies to organic antigens and clinical HP as compared to nonsmokers (20, 26). This protective effect of smoking has been attributed to nicotine which may affect macrophage and lymphocyte function. A promoting role of extrinsic cofactors, such as a viral infec-

tion (39), lipopolysaccharides LPS (40), or exposure to pesticides (27) has also been suggested.

Pathophysiology

In its simplest form, HP is a delayed immune response to an inhaled antigen, usually a protein, to which the subject had been previously sensitized. The immune mechanism is a Th1 response as opposed to asthma which is a Th2 response. As for any immune response, the inflammation in HP involves many cell types and a plethora of inflammatory mediators released mostly by activated lymphocytes and alveolar macrophages (41). The lymphocyte is the predominant cell found in the lungs of HP patients as observed by bronchoalveolar lavage (BAL) (42). It has been proposed that the ratio of CD4+/CD8+ is lower in HP than in sarcoidosis, although this notion has been contradicted, and a recent study suggests that the CD 103+ cell could offer a better differentiation (43). Regulatory T cells (Treg) lose their normal function in the disease (44). While lymphocytes are the predominant cells in well-established HP, during an acute exposure neutrophils are also activated (45). Dendritic cells become mature and acquire an enhanced capacity to present the antigen to the lymphoid cells (46). Activated B lymphocytes release IgG antibodies specific to the causative antigen. It is still unclear whether these antibodies are a marker of exposure or whether they actively participate in the disease *per se* (47). What we know is that many individuals exposed to HP antigens develop these specific antibodies (precipitins) without ever having active HP (48). Also, it remains largely unknown why some patients with HP evolve toward fibrosis or emphysema. Fibrocytes are clearly implicated in the fibrotic process (49). Interleukin-17 was found to be essential in the pathogenesis of lung fibrosis in a murine model of HP (50). Multiple cytokines and pro-inflammatory proteins are increased in BAL of both idiopathic pulmonary fibrosis (IPF) and HP (51).

Diagnosis

The diagnosis of HP in general remains often challenging as there is no gold standard test and the diagnosis is made from a combination of procedures. In addition, the diagnosis of OHP requires ascertaining the work relatedness of the disease with a high level of confidence. A multidisciplinary approach, including clinicians, radiologists, pathologists, and occupational physicians/hygienists, is strongly recommended to improve the diagnosis of OHP, as demonstrated for IPF (52).

Clinical and occupational history

As with most occupational diseases, both the clinical and the occupational history are keys to the diagnosis and often will lead to the initial suspicion of an occupational cause. In some occupations, there may be a high level of awareness among workers of the possibility of HP, for example, knowledge of the existence of farmers' lung among farmers or MWF lung among machine operators. Conversely, the worker who develops HP from a less common cause will likely have no personal suspicion of the diagnosis, and if presenting with acute symptoms is more likely to receive a diagnosis of an acute respiratory infection.

The symptoms of HP whether due to an occupational or another environmental cause are the same, but the timing of symptoms may be different with the occupational setting. In addition to respiratory symptoms (i.e. dyspnea, cough, chest tightness/discomfort, and less commonly wheezing), there may be systemic symptoms, such as fever and malaise especially in acute episodes of HP, and weight loss especially in chronic HP. In acute episodes, symptoms typically start 6–8 h after the relevant exposure and may clear 24–48 h after cessation of exposure (13, 53). Therefore, when triggered by a workplace antigen, acute symptoms typically start toward the end of a work shift or following a work shift and improve near the end of a weekend off work. In contrast, chronic HP related to a workplace antigen may have no clear pattern related to short periods off work. A detailed history of the occupation and the exposures is important to enable suspicion of an occupational cause, but some cases of HP may only be detected on histologic changes (54).

Lung function tests

Lung function tests support the diagnosis of ILD but are not helpful to differentiate HP from other ILDs. The most common pattern of physiological abnormalities in HP is a restrictive ventilatory defect associated with impaired gas exchange (decreased diffusing capacity for carbon monoxide [DLco] and/or hypoxemia on exercise). Noteworthy, lung function parameters are normal in a substantial proportion (10–17%) of the patients, particularly between episodes of acute HP (53, 55, 56). DLco is the most frequently affected lung function parameter, but may be normal in up to 22% of affected patients (53, 56). On the other hand, impaired DLco is the only abnormal finding in about 10% of the patients (55). The FEV_1/FVC ratio is often decreased in HP, suggesting some degree of airflow obstruction that has been related to bronchiolitis and emphysema. An obstructive or mixed pattern of ventilatory impairment has been described in 0.5–33% of the patients in large series of HP (53, 55–58).

Radiology

Chest radiograph

Chest radiograph findings in HP are nonspecific (i.e. ground-glass opacities, airspace consolidation, micronodules, reticular or linear interstitial opacities, and honeycombing) (53). Nevertheless, clinicians should be aware that the chest radiograph may be normal in a substantial proportion (~20%) of patients with HP (53, 59, 60).

High-resolution computed tomography (HRCT)

HRCT is more sensitive than standard chest radiographs in detecting changes in the lung interstitium (60) and is now acknowledged as a key procedure in the evaluation of HP and ILDs in general. Nevertheless, clinicians should be aware

Table 3 High-resolution computerized tomography features of HP

CT findings	Characteristics	Pathologic correlations
Ground-glass opacities	• Patchy or diffuse, bilateral, and symmetric • Predominantly in the lower lung zones in acute farmer's lung	• Diffuse lymphocytic interstitial pneumonitis • Minor degrees of organizing pneumonia
Centrilobular nodules	• Small (<5 mm), poorly defined • Widespread uniform distribution	• Cellular bronchiolitis • Predominantly peribronchiolar interstitial pneumonitis • Focal areas of organizing pneumonia (usually irregular nodules >10 mm in diameter)
Areas of decreased attenuation (mosaic perfusion) and expiratory air trapping	• Most often in a lobular distribution • Patchy air trapping on expiratory CT images	• Small-airway obstruction by cellular bronchiolitis and shunting of blood away from poorly ventilated regions of the lung • Constrictive bronchiolitis (less commonly)
Reticulation and parenchymal distortion	• Irregular linear or reticular opacities associated with traction bronchiectasis and honeycombing • Patchy or random or showing a predominantly subpleural and peribronchovascular distribution • Relative sparing of the lung bases • Superimposed on findings of acute or subacute HP	• Fibrosis
Airspace Consolidation		• Organizing pneumonia • Superimposed complication such as infection • Less commonly, acute exacerbation with diffuse alveolar damage
Cysts	• Few thin-walled cysts • Size ranging from 3 to 25 mm • Usually associated with ground-glass opacities	• Presumably resulting from partial bronchiolar obstruction by the peribronchiolar lymphocytic infiltrate
Emphysema	• No detailed description	• Unknown mechanism

that HRCT may be normal in a substantial proportion (8–18%) of patients with proven HP (53, 59). The predominant HRCT abnormalities that can be found in HP are summarized in Table 3 together with their—often presumed—pathologic correlations (53, 55, 59–67). The predominant HRCT findings in acute and subacute HP are ground-glass opacities, poorly defined small centrilobular nodules, mosaic attenuation (patchwork of regions of differing attenuation) on inspiratory images, and gas trapping on expiratory CT images (67). Chronic HP is characterized by the presence of reticulation and parenchymal distortion due to fibrosis superimposed on findings of subacute HP. Thin-walled cysts have been described in a substantial percentage (13–39%) of patients with subacute and chronic HP (66, 68). Emphysema can be seen in about 20% of nonsmoking patients with chronic HP, particularly in patients with farmer's lung (63, 69, 70). Mediastinal lymphadenopathy has been occasionally reported in HP (63).

Environmental sampling

Identification of the offending antigen source at work is important for the determination of antigen-specific IgG antibodies. Collecting material from the workplace environment, for example, like settled dust or using personal or stationary airborne sampling equipment, is required when the suspected antigen is not commercially available or when the source of a hidden antigen has to be detected (71). Extracts from these material sources can be used as test antigens for direct IgG measurement or as the inhibitor phase in specific IgG inhibition tests (72). When fungi or other microorganisms are the suspected antigenic source, microbiological analysis of the sampled material may be important to document the causal role of the workplace but should be completed by the determination of antigenic activity by antigen-specific IgG inhibition tests (73).

Laboratory tests

The determination of antigen-specific IgG antibodies is an important step in the diagnosis of OHP as it makes it possible to identify the causal workplace agent. An elevated titer of antigen-specific IgG antibodies associated with consistent clinical and HRCT features is strongly supportive of HP. Conversely, a decrease in the concentration of specific IgG after antigen avoidance may also support a diagnosis of HP (74). However, the presence of specific IgG antibodies is not *per se* a marker of disease (31, 48, 75, 76), while the absence of specific IgG antibodies does not exclude the diagnosis of HP. A multicentre study of patients with ILDs identified the presence of precipitins as a significant predictor of HP with an odds ratio of 5.3 (95% confidence interval (CI): 2.7–10.4)

(53). Fenoglio et al. (77) found that the assessment of specific IgG against a panel of locally relevant antigens yielded a sensitivity of 76% (95% CI: 60–92%) and a specificity of 82% (95% CI: 74–90%) in mold-induced HP.

Different methods for qualitative (e.g. precipitation/Ouchterlony technique, immunoelectrophoresis) and quantitative (ELISA, ImmunoCAP, Immulite) determination of specific IgG antibodies are available, but the results often differ considerably (78). Quantitative evaluation of antigen-specific IgG (expressed in mgA/l) requires that cutoff values should be established for each antigen using a suitable nonexposed, healthy reference population. The interpretation of specific IgG antibodies determination should take into account the known antigenic cross-reactivity, between different fungal (79) and bird species (80). Whether the determination of specific IgG antibodies against recombinant antigens for the serodiagnosis of OHP, for instance in farmer's lung disease, increases the diagnostic performance compared with existing techniques requires further investigation (81). The major limitation of specific IgG measurement is the unavailability of validated antigen preparations for most agents causing HP. Nevertheless, new antigens can be prepared using biotinylation and coupling to Streptavidin ImmunoCAP (82, 83). In addition, inhibition testing with the patient serum can be used as a detection tool for identifying the offending antigen source (73). Lymphocyte proliferation tests with the suspected antigen cannot be used in routine practice as the method has not been standardized, but in selected cases, for example using BAL cells from patients with acute bird-related HP, this test may be a useful diagnostic tool and highlight the important role of cellular immunity in the onset of bird-related HP (84).

Bronchoscopy and pathology

Bronchoscopy with bronchoalveolar lavage (BAL) is a supportive diagnostic tool in patients with suspected HP. An increase in total cell count in BAL with marked lymphocytosis, often greater than 50% and usually with a relative predominance of CD8+ T cells (low CD4+/CD8+ ratio), is an important and characteristic feature of acute and subacute HP (85). In chronic fibrotic diseases, lymphocytes may be only mildly elevated with increased CD4+/CD8+ ratio (86, 87). Therefore, a normal or elevated CD4/CD8 ratio does not rule out the diagnosis of HP and depends on the clinical course and the offending antigen (88). The absence of lymphocytosis in BAL makes the diagnosis of HP highly unlikely but is possible within the first 48 h after intense antigen exposure or in residual diseases where neutrophils may be predominant (89, 90). Asymptomatic, exposed individuals may also show BAL lymphocytosis without any adverse prognostic value, and therefore, lymphocytosis alone does not confirm the diagnosis of HP (48).

Transbronchial lung biopsy is of limited usefulness for the diagnosis of HP (91), and a surgical lung biopsy is rarely indicated in acute or subacute HP. Transbronchial lung cryobiopsy is a novel technique to obtain larger biopsy samples with a high diagnostic yield in ILDs and, therefore, might be considered a valid alternative to surgical lung biopsies in chronic HP (92). The pathologic pattern in HP is well characterized with the triads of interstitial lymphocytic bronchiolocentric pneumonitis, poorly formed and loosely arranged, small non-necrotizing granulomas and a BOOP pattern in acute/subacute forms (93). In chronic HP, the histopathological findings of surgical specimens can mimic a UIP-like or a nonspecific interstitial pneumonia (NSIP)-like pattern with characteristic bronchiolocentric distribution, sometimes with areas of organizing pneumonia and limited granuloma formation. Important findings for chronic HP are an additional subacute pattern, interstitial giant cells with cholesterol clefts, granulomas, Schaumann bodies, and centrilobular and bridging fibrosis with an upper lobe predominance, but in some cases lung specimens are indistinguishable from IPF (94–96).

The potential side-effects of endoscopic and surgical examinations are to be mentioned to the patient (especially the risk of pneumothorax). Patient's signed agreement is required after all necessary information will be given.

Inhalation challenges

Inhalation challenge tests (ICT) can be conducted either with the suspected agent in the laboratory or at the subject's workplace (56, 97–100). The safety requirements and the protocol of exposure are similar to those applied for ICT in occupational asthma (101). These tests should be conducted only in specialized centers with expertise in ICT procedures. Important barriers to the routine use of ICT in the laboratory for the investigation of OHP include (i) the unavailability of appropriate facilities, (ii) the lack of standardized antigen preparations, and (iii) the absence of validated criteria for defining a positive response (Table 4) (56, 97–100, 102).

ICT should be considered in patients with suspected OHP when (i) alternative procedures have failed to identify with sufficient accuracy either the diagnosis of HP or a specific causal exposure and (ii) the suspected causal agent has not been formerly described as causing OHP. Few studies have assessed the diagnostic performance of ICT in HP (Table 4) (56, 97–100, 103). Overall, ICT with a specific occupational agent in the laboratory is confirmatory when there is a clear response, while failure to develop a positive response to a workplace ICT under the patient's usual exposure conditions argues strongly against the diagnosis of OHP.

Anyhow, complete information must be given to the worker if ICT is proposed and always before it is performed. In that last situation, the patient's agreement is required. A specific agreement form including all necessary information as well as the patient's and the responsible doctor's signatures will be required.

As an alternative to ICT, an 'antigen avoidance test' may be useful to support a diagnosis of OHP. Tsutsui et al. (104) recently reported the changes in physiological parameters and biomarkers after a 2-week antigen avoidance test in 196 patients with chronic HP (mostly related to bird antigens) and a control group of 43 patients with other ILDs. The optimal cutoff value for each parameter was determined

Table 4 Criteria for interpreting inhalation challenges

References	Patients	Antigen	Criteria for a positive response	Validity of the criteria
Hendrick (97)	144 ICT in 29 suspected HP (18 proved HP); 2 controls	Avian antigens	**1** Rise in body T° >37.2°C **2** Increase in blood neutrophils >2500/mm^3 **3** Decrease in FVC >15% **4** Decrease in DLco >15%	• Equivocal result: 15/144 • Sensitivity: 78% (criteria 1); 68% (criteria 2); 48% (criteria 3); 17% (criteria 4) • Specificity: >95% for all criteria
Ramirez-Venegas (98)	17 chronic HP; 17 other ILD; 5 controls	Avian antigens	At least one of the following criteria: **1** Decrease in FVC >16% **2** Decrease in PaO_2 >3 mmHg **3** Decrease in SaO_2 >3% **4** Rise in body temperature >0.5°C	• Equivocal result: 3/39 • Sensitivity: 76-100% • Specificity: 82-86%
Ohtani (99)	11 chronic HP; 6 controls	Avian antigens	Three or more of the following criteria: **1** Increased radiologic abnormalities **2** Increase in P(A-a) O_2 >10 mm Hg and/or a decrease of DLco >20% **3** Decrease in FVC >15% **4** Increase in blood leukocyte count >30% **5** Increase in C-Reactive Protein >1.0 mg/dl **6** Increase in body T° >1.0°C and/or systemic symptoms **7** Respiratory symptoms	• Equivocal result: 3/11 • Sensitivity: 73% • Specificity: 100%
Morell (56)	59 HP; 30 healthy pigeon keepers; 20 other ILD;	Avian antigens	**1** FVC decrease >15% or DLco decrease >20% **2** 10–15% FVC decrease plus at least one of the following criteria: **a)** White blood cell increase ≥20% **b)** Decrease in SaO_2 >3% **c)** Significant radiologic changes **d)** Rise in body temperature >0.5° C **e)** Clinical symptoms (e.g. cough, dyspnea) **3** FVC decrease <10% plus ≥3 abovementioned criteria	• Equivocal result: 5/59 • Sensitivity: 92% • Specificity: 100%
Ishizuka (103)	28 HP; 19 other ILD;	Avian antigens	Two or more of the following criteria: **1** Increased radiologic abnormalities **2** Increase in the alveolar–arterial oxygen pressure difference (P[A-a]O_2) by more than 10 mm Hg and/or a decrease of DLco by more than 20% **3** Decrease in FVC > 15% **4** Increase in the peripheral white blood cell count by more than 30% **5** Increase in C-Reactive Protein > 1.0 mg/dl **6** Increase in body T° >1.0°C and/or the development of systemic manifestations, including chills and general fatigue **7** Development of respiratory symptoms (cough and dyspnea)	• Equivocal result: 7/47 • Sensitivity: 79%† • Specificity: 95%

HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; PaO_2, partial pressure of oxygen in arterial blood; P(A-a)O_2, alveolar–arterial oxygen pressure difference; SaO_2, transcutaneous oxygen saturation.
†Sensitivity and specificity increases to 93% and 95% when peripheral white blood cells count and P(A-a)O_2 are included as monitoring parameters for the test.

using ROC analysis. Positivity of two or more of the following criteria: (i) >3% increase in FVC, (ii) >13% decrease in the serum level of Krebs von den Lungen-6 (KL-6), and (iii) >3% decrease in white blood cell count yielded a sensitivity of 51% and a specificity of 81%.

Diagnostic criteria

A number of diagnostic criteria based on different constellations of clinical, laboratory, functional, radiologic, and pathologic findings have been published, although none of these

criteria have been validated (4, 105–107). These diagnostic criteria may be valid for the acute/subacute forms of the disease but are less appropriate for chronic HP (108). Using logistic regression analysis, a large cohort study of 116 patients with HP compared with 284 subjects with other ILDs (53) identified six significant predictors: (i) exposure to a known offending antigen, (ii) positive specific IgG (precipitating) antibodies to the offending antigen, (iii) recurrent episodes of symptoms, (iv) inspiratory crackles, (v) symptoms occurring 4–8 h after exposure, and (vi) weight loss. The association of the six above-quoted criteria provided a probability of 98% of having HP.

Based on previously published criteria for acute/subacute (53) and chronic HP (108) and a consensus among Task Force members, operational criteria for diagnosing OHP are proposed in Table 5, although this approach requires further clinical validation.

Table 5 Diagnostic criteria for acute/subacute and chronic occupational hypersensitivity pneumonitis

Acute/subacute occupational hypersensitivity pneumonitis (OHP)
The diagnosis of acute/subacute OHP can be established if the following diagnostic features are fulfilled:
1. Exposure to a potentially offending antigen source at the workplace
2. Recurrent episodes of symptoms, occurring 4–8 h after occupational exposure
3. Elevated titer of specific IgG (precipitating) antibodies to an occupational antigen†
4. Inspiratory crackles on physical examination
5. HRCT pattern compatible with acute/subacute HP

If all these features are not fulfilled, one of the following criteria can act as a substitute:
6. Bronchoalveolar lavage lymphocytosis
7. Pathology of lung specimen consistent with acute/subacute HP
8. Positive ICT in the laboratory or positive workplace challenge or improvement after avoidance of the suspected occupational exposure†

Chronic occupational hypersensitivity pneumonitis (OHP)
The diagnosis of chronic OHP can be established if four or more of the following criteria are fulfilled:
1. Exposure to a potentially offending antigen source at the workplace
2. Elevated titer of specific IgG (precipitating) antibodies to an occupational antigen†

Or:

Bronchoalveolar lavage lymphocytosis
3. Reduced carbon monoxide diffusing capacity (DLco) and/or hypoxemia at rest or exercise
4. HRCT pattern compatible with chronic HP
5. Pathology of lung specimen compatible with chronic HP
6. Positive ICT in the laboratory or positive workplace challenge or improvement after avoidance of the suspected occupational exposure†

HRCT, high-resolution computed tomography; ICT, inhalation challenge test.
†These tests provide objective evidence supporting the causal relationship with the workplace environment, although in some specific settings (e.g. MWF exposed workers, farmers), documentation of exposure to a potentially offending source at the workplace can be considered sufficient evidence of the occupational etiology of OHP.

Differential diagnosis

Depending on the clinical presentation, several syndromes should be considered in the differential diagnosis when evaluating patients with suspected OHP. For acute HP, these include infectious respiratory diseases and acute neutrophilic pulmonary responses associated with transient flu-like symptoms that have been described after exposure to a variety of organic dusts and bioaerosols contaminated with multiple bacterial and fungal species (7). The nonspecific symptoms of the '*sick-building syndrome'* may also mimic some features of HP (109).

The differential diagnosis of chronic HP includes a large spectrum of disorders that cause ILDs. In this setting, it is important to carefully rule out the occupation as a cause of the patient's ILD. The clinical, radiologic, and histopathological features of IPF and chronic HP can be indistinguishable (94, 110). A recent study showed that almost half of patients diagnosed with IPF were subsequently diagnosed with chronic HP, and most of these cases were attributed to occult exposure to avian antigens (111). The authors highlight the importance of investigating the possibility of chronic HP caused by subtle exposures to avian antigens or other environmental factors in patients suspected to have IPF. However, in most ILD centers a high proportion of those labelled with chronic HP have no identified cause of their disease, and the aforementioned study (111) report is very unusual in this respect.

BAL lymphocytosis >30% should raise the suspicion of chronic HP in patients with a usual interstitial pneumonia (UIP)-like pattern on HRCT (112). The HRCT findings that best differentiate chronic HP from NSIP and IPF include the presence of lobular areas with decreased attenuation and vascularity, centrilobular nodules, and lack of lower zone predominance of abnormalities (66). Interestingly, it has been recently suggested that high FeNO levels could help to differentiate chronic HP from other types of pulmonary fibrosis (113). HP should also be considered in patients diagnosed with NSIP, as a NSIP pattern without granulomas can be the only pathologic finding of HP (114). The differential diagnosis of chronic HP also includes granulomatous ILDs, such as sarcoidosis and chronic beryllium disease (7, 115).

Outcome and management

Acute OHP usually resolves spontaneously after removal from the triggering antigen (116), but if severe may require supportive treatment with supplemental oxygen and/or a short period of treatment with corticosteroids (117). Less acute or chronic manifestations of HP are commonly treated at least initially with corticosteroids although such treatment is not a substitute for removal from exposure (118, 119), and its long-term efficacy has not been evaluated in prospective clinical trials. Treatment continues until no further improvement in physiological abnormalities is observed. The corticosteroid schedule suggested by some is similar to that in sarcoidosis and other ILD (119, 120). There is very limited

evidence supporting the use of inhaled steroids as a replacement for systemic corticosteroids in HP (7, 121). In chronic, progressive HP, immunosuppressants may be added as corticosteroid sparing agents (119, 122), and lung transplantation is an option for severe disease with possibly better outcome when performed for HP than for IPF (54). Although B lymphocytes are involved in the pathogenesis of HP and their degree of activation somehow reflects the extent of the inflammation of HP (123), anti-B-cell therapy cannot be recommended.

Every effort should be made to completely remove the patient from further exposure to the causative antigen, as there has been consensus that this option offers the best outcome of disease (7, 9, 10). Although there are few comparative studies on the effects of avoidance *vs* persistence of exposure (118), recurrent acute episodes (reflecting relapsing exposure) have been associated with worse diffusing capacity compared with a single acute episode (58). A recent Japanese study of 23 subjects with chronic bird-related HP followed for 1 year showed that the levels of exposure to avian antigen were related to disease progression, estimated by a FVC decline over 6 months ≥10% predicted (124).

Reduction of exposure by the use of personal respiratory protective devices has not been clearly shown to be an effective strategy and has not been recommended, although there is some suggestion that reduced exposure may be effective for acute OHP in preventing further episodes (125). A few 'natural' challenge studies have shown that personal dust respirators have a protective effect on the clinical and functional manifestations of HP induced by short-term exposures due to birds and moldy hay (126, 127). Wearing protective masks over several months has also been associated with a reduction in the level of specific IgG antibodies against pigeon antigens (128). The long-term effect of respiratory protection on the development of chronic HP remains, however, unknown.

Methods to achieve avoidance of exposure vary with the responsible occupational cause. It may be feasible to completely remove the antigen from the work environment, for example, removal of identified fungal contamination in a work area or substitution of a product, for example, heated methylene diphenyl diisocyanate. When the suspected cause relates to MWF, even without identification of a specific etiologic agent, changes including enclosure of selected MWF machining operations, elimination of mist cooling, exhausting of water-based industrial processes, increased ventilation, worker training, and reduced microorganisms in sump fluid can permit return to work of a large proportion of affected workers (129).

OHP can lead to lung fibrosis, emphysema, or a combination of both. Bird breeder's lung may evolve toward fibrosis with a poor prognosis (130), while farmer's lung can lead to emphysema in up to 20% of patients (63, 64, 69). Whether these different outcomes are due to the different antigens or exposure profiles remains unknown. Mortality in farmers' lung has been estimated as 0.7% on average 8 years after diagnosis (131). The factors that have been associated with a worse outcome are summarized in Table 6 (57, 63, 64, 67, 70, 75, 96, 132–141). Cohort studies of patients with HP have consistently shown that the presence of fibrosis as evidenced by crackles on auscultation and reticulation on chest radiograph (136), lung biopsy specimens, or HRCT is associated with higher mortality (132, 135, 137). Patients with chronic HP may develop acute exacerbations that are associated with a poor outcome without further exposure to the inhaled antigens (140, 141). These acute exacerbations are characterized by worsening dyspnea over 1–2 months, new radiographic opacities, and absence of apparent infection, heart disease, or other identifiable cause. An increased risk of lung cancer has been suggested in one study, but needs further evidence (142).

As for other occupational diseases, support should be provided to the patient for an appropriate workers' compensation claim. The socioeconomic impact of OHP has not been systematically reported, but can be expected to be at least as significant as for occupational asthma. For farmers who may be unable to continue farming, the economic impact can be crippling.

Prevention

Primary prevention should be based on avoidance/reduction of exposure and health and safety education. There are, however, almost no prospective studies that have investigated the efficacy of preventive interventions on the incidence of OHP. Historical cohort studies have documented a decline in the rate of OHP among farmers after the introduction of modern techniques of hay and silage making (e.g. efficient drying of hay and cereals before storage) (143). Another example of successful avoidance measures has been described for MWF

Table 6 Factors associated with a worse outcome of HP

Characteristic	References
Delayed diagnosis and/or long-term exposure after onset of symptoms	Schmidt (75); de Gracia (57); Cormier (63)
Smoking	Ohtsuka (133); Fernandez Perez (132)
Recurrent acute attacks (*vs* single episode)	Braun (134); Erkinjuntti-Pekkanen (70); Malinen (64)
Crackles on auscultation	Hanak (135); Mooney (136)
Fibrosis at the time of diagnosis on lung biopsy or HRCT	Vourlekis (137); Churg (96); Gaxiola (138); Tateishi (67); Fernandez Perez (132)
Pulmonary artery hypertension	Koschel (139)
Acute exacerbations of chronic HP	Miyazaki (140); Olson (141)

HRCT, high-resolution computed tomography.

after changes in engineering (e.g. enclosing machines and improving ventilation), increasing awareness about appropriate work practices, and better maintenance of MWFs to decrease bacterial contamination (16, 17, 129, 144).

In the field of secondary prevention, diagnosing a case of HP should prompt a review of the workplace with risk assessment and a survey of the remaining workforce to identify other affected workers (145). Workforce surveys that were conducted after a sentinel case of HP had been diagnosed have most often identified additional cases, indicating that OHP may remain underdiagnosed unless actively detected (35, 146, 147). Tertiary prevention consists of appropriate medical management of identified cases as discussed above in the treatment section.

Research needs

Research on OHP would greatly benefit from the establishment of international multicenter cohorts of cases as was done for the American Thoracic Society HP study group (53). Nevertheless, it is very important to continue to report cases from different environments to increase awareness of clinicians to include HP in the differential diagnosis of occupational lung diseases. The multiple causative agents and environments need to be continuously updated and made available through international organizations. Research efforts are needed to help improving the diagnosis and treatment of HP, to identify the factors that determine the development of fibrosis and emphysema, and to evaluate the effectiveness of abatement procedures. In this regard, it is a high priority for research using much more rigorous epidemiological methods than have been employed before, and to reach a consensus definition among ILD specialists to agree on the proper identification and diagnosis of chronic HP.

The antigens causing OHP should be further characterized and antigenic preparations that can be used for the *in vitro* assessment of specific IgG antibodies and for the performance of inhalation challenges in the laboratory need to be developed and standardized. These antigens should be made widely available to clinicians in order to improve the diagnosis of OHP. Occupational health compensation committees need guidance to not only make the diagnosis but also standardize compensatory benefits and professional rehabilitation.

Conflicts of interest

All authors declare that they do not have any relevant conflict of interests regarding this paper.

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