

Diagnosis and Treatment of Hypersensitivity Pneumonitis: S2k Guideline of the German Respiratory Society and the German Society for Allergology and Clinical Immunology.

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German recommendations for the diagnosis of hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis (EAA), were last published in 2007 [1]. The current S2k Guideline for the Diagnosis and Treatment of Hypersensitivity Pneumonitis replaces these diagnostic recommendations. They were supplemented by the aspect of chronic, and in particular of the chronic fibrotic phenotype of HP, and also, as the first HP guideline, include treatment recommendations. Based on current scientific evidence and on expert opinion, 12 consensus recommendations were developed. They include important statements summarizing the diagnostic process, the treatment indication and therapeutic strategies for patients with HP. Particular emphasis was placed on the different clinical courses (acute and chronic) and their characteristics (inflammatory and/or fibrotic pattern), which present differential diagnostic challenges and ultimately result in different treatment approaches. In addition to general information (diagnosis, classification, clinical disease course, epidemiology, pathogenesis, risk factors, prognosis, and special aspects associated with occupational disease), the guideline will present the various clinical disease entities of HP, some in detail, others in tabular form. A major focus is on the various diagnostic steps and the different treatment approaches. The background information serves to provide a deeper understanding and inform the implementation of the recommendations. In particular, other current international guidelines for the diagnosis of HP as well as German guidelines for the diagnosis of interstitial lung diseases (ILDs) (Leitlinien zur Diagnostik interstitieller Lungenerkrankungen) in general and for the pharmacotherapy of fibrotic ILDs were integrated and considered in this guideline [2 – 6].

New definition of the classification of the clinical course as acute, as chronic non-fibrotic or as chronic fibrotic HP

Some of the recommendations explicitly differentiate between acute and chronic HP, especially chronic fibrotic HP

Presentation and listing of genetic findings that are risk factors for HP

Comprehensive table of syndromes in alphabetical order with the corresponding antigens and antigen sources of an HP, additionally sorted by antigen category

Notes regarding environmental diagnostics and biosampling

Recommendation to use a standardized questionnaire to identify a possible antigen source or triggering antigen

Recommendation to use specific IgG antibodies with published thresholds

Explanation of the HRCT features of HP, their distribution, and pathophysiological correlate

Categorization of the radiologic HRCT evaluation as inflammatory or fibrotic HP

Recommendation for the assessment and weighting of the inflammatory component in fibrotic HP in HRCT imaging

Recommendation to disregard the CD4/CD8 ratio in the bronchoalveolar lavage (BAL) analysis in the diagnostics of HP

Differentiated recommendation to obtain histological samples using transbronchial forceps or cryobiopsy, or surgical lung biopsy (SLB)

No recommendation for provocation testing in chronic HP

Separate diagnostic criteria for acute or non-fibrotic HP and chronic fibrotic HP

Differentiated recommendation for anti-inflammatory and/or antifibrotic drug therapy in chronic fibrotic HP

Presentation of various prognostic parameters of HP

Relevance of HP as an occupational disease

HP (also called extrinsic allergic alveolitis) is a lung disease characterized by an immune-mediated inflammatory response of the lung parenchyma and of the terminal bronchioles. The condition can manifest as a variety of clinical manifestations. The non-IgE-mediated allergic response is mainly the result of the inhalation of an inciting antigen by sensitized, predisposed individuals.

Antigens are predominantly high-molecular (glyco)proteins from microbial, animal or plant sources, and – less frequently – low-molecule chemical substances. The most common HP variants are bird fancier's lung and farmer's lung. The clinical presentation of the different types (acute or chronic HP, or non-fibrotic or fibrotic HP) is often noncharacteristic, giving rise to a variety of differential diagnoses.

Traditionally, HP was classified as acute, subacute, or chronic [7]. Since subacute HP was difficult to define in a cluster analysis of 168 HP patients, only an acute and a chronic type were differentiated later on [8]. Taking into account the progression of the disease, some authors in older publications also classified it as acute intermittent, acute progressive, chronic progressive and chronic non-progressive or chronic residual [9 – 11]. The clinical course generally depends on type of antigen, intensity of exposure, duration of exposure and frequency of exposure. Clinical courses may also overlap [12].

Currently, only a non-fibrotic phenotype is differentiated from a fibrotic clinical phenotype based on radiological and possibly histopathological findings since these findings can be objectively determined and are more relevant for the management and prognosis of the condition [3 , 13 , 14]. However, the fact that the term “acute HP” better describes typical “outbreaks” of HP in the occupational or home environment and that chronic HP may also be non-fibrotic speaks for maintaining the categories of acute and chronic HP (Fig. 1) [15].

Acute HP is characterized by the sudden onset of influenza-like symptoms with fever, chills, headache and arthralgia, shortness of breath with a non-productive cough, chest tightness, and fatigue 3–12 h after repeated and high-intensity antigen exposure. Inspiratory fine crackles are noticed on auscultation. After antigen avoidance, patients usually become symptom-free within 24–48 h, even without pharmacotherapy. The clinical severity of the symptoms often leads to hospitalization [16 – 18].

Chronic HP can be caused either by long-lasting, continuous, yet low-level antigen exposure (insidious and chronic HP), or by recurrent, undiagnosed acute/subacute courses (chronic recurrent HP). In chronic-insidious HP in particular, the clinical symptom is often only increasing dyspnea on exertion, and advanced pulmonary fibrosis may already be present when a patient first presents to a doctor [19]. The diagnostic differentiation from other chronic fibrotic lung diseases, especially idiopathic pulmonary fibrosis, may be difficult in this case. Clubbing is found in up to 50% of patients with chronic HP and is indicative of an unfavorable prognosis [20]. Chronic HP is frequently characterized by progressive fibrotic ILD [19]. Particularly in chronic farmer's lung, the development of emphysema can be the leading manifestation in some cases [21 , 22]. Question 1: Shall the clinical course of HP be categorized into acute and chronic or into non-fibrotic and fibrotic? Recommendation R1 1. HP should initially be categorized as an acute or chronic form, particularly from an occupational medicine point of view

Chronic HP should be furthered categorized into a fibrotic or non-fibrotic phenotype to reflect the implications of fibrosis on prognosis and treatment

The prevalence of HP depends on environmental factors such as antigen concentration, frequency and duration of antigen exposure, antigen solubility, particle size, weather conditions but also on social and cultural factors as well as smoking. Different data collection methods add to the challenge of drawing proper conclusions concerning the prevalence of HP.

Prevalence data from cross-sectional studies are usually based on questionnaires and possibly also on data from serological tests and clinical assessments and often lead to falsely high estimates of the prevalence as the clinical symptoms of HP are associated with a variety of differential diagnoses [23]. However, the prevalence of chronic HP is possibly underestimated as the differentiation from idiopathic ILD may be difficult [24].

HP usually manifests in adulthood, affecting men and women equally. Manifestations in childhood have been reported as case studies [25 , 26]. The mean age in a larger cohort was 52 years. 58% of patients were female, with men predominating at younger ages [27]. In contrast to other ILDs, HP manifests predominantly in non-smokers [28 , 29].

HP is a rare disease. The incidence of EAA in the UK population for the period 1991–2003 appears to be stable, with approximately 1 new case per 100,000 persons per year in the general population [28]. More recent data show a similar annual incidence of 1.16 new cases per 100,000 persons in Denmark for the period 1998–2010 and even 1.28–1.94 per 100,000 persons in the USA for the period 2004–2013 [27 , 30]. In registry studies of ILDs, data regarding HP vary significantly, ranging between 1.5 and 47.3% of patients [31 , 32].

With regard to the individual clinical variants of HP, most prevalence data are available for farmer's lung and bird fancier's lung. The prevalence of farmer's lung is estimated at 0.01–2% for the general population [33 , 34] and 0.25–10.4% for people working in agriculture [35 – 43]. The prevalence of budgerigar fancier's lung is 3.4% [44] and of pigeon fancier's lung even up to 21% [45 – 47].

The reported incidence of occupational HP in the UK is 1–2 cases per million workers per year. Nevertheless, case numbers may be significantly underreported [48].

Due to the fact that only a few subjects will develop HP following exposure, its development is assumed to be attributable to a genetic predisposition, among other factors. Table 1 provides a summary of key studies on genetic findings whose occurrence correlates with the development or prognosis of HP [49 – 59].

Selected key genetic findings identified as HP risk and/or prognostic factors

Since gene polymorphisms in HP patients are often simultaneously found in different genes, there is potentially an interaction of the various genetic changes [51]. Documented familial clustering also supports the hypothesis of a genetic predisposition [60 – 62].

Both common and rare gene variants have been described in HP. They are mainly located in the major histocompatibility complex including the TNF gene promoter region. HLA-DRB1 and HLA-DR3 variants have been described in bird fancier's lung, HLA-DQ3 in summer-type HP and variants in the HLA-A, -B, and -C loci in farmer's lung [54]. Similar to IPF, the minor T allele in the MUC5B polymorphism was identified more often in patients with chronic HP than in healthy controls [56]. Similar gene expressions were shown for IPF and chronic HP, for instance, in genes responsible for collagen formation [55]. Gene polymorphisms in the surfactant protein-coding genes (SFTPs), which are relevant in the biosynthesis of surfactant, are associated with a higher or lower risk of developing fibrotic HP vs. IPF [59]. Dysfunctional telomeres due to variants of the telomere genes TERT, RTEL, and PARN were also described in HP patients and are associated with an unfavorable prognosis and reduced tolerance to immunosuppressive therapy [57].

In addition to genetic variants, other risk factors are also being debated. A 2007 study showed that fetal microchimerisms is associated with a severe course of HP [63]. In addition, data suggest that intense antigen exposure can lead to worsening of an existing HP [64]. Moreover, viral upper respiratory tract infections pose an increased risk of developing pulmonary fibrosis [65]. They trigger an increased expression of MHC class II proteins, which in turn induce the production of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and inter-feron-gamma, resulting in inflammation and alveolar cell damage [66]. Pesticides can also lead to increased inflammation caused by the cytokines TNF- α , IL-2, and IL-4 and, thus, may be a risk factor for the development of HP [67].

Smoking is associated with a lower risk of developing HP. This is believed to be due to the immunosuppressive properties of smoking, especially of inhaled nicotine, on the function of alveolar macrophages, resulting in the reduced formation of the proinflammatory cytokine TNF- α or reduced expression of B7 costimulatory molecules (CD80, CD86) [68]. Studies show that smokers had lower measurable levels of specific antibodies in their blood after high antigen exposure than non-smokers [29 , 69 , 70]. However, chronic fibrotic HP is more often associated with smoking [71 – 73]. Risk factors for a severe, potentially fatal progression of chronic HP are older age, male sex, and the presence of a UIP pattern on the HRCT [74].

The pathogenesis of HP is not yet fully understood. HP is described as a complex immune disease with a combination of humoral (type III) and cell-mediated (type IV) mechanism following exposure by inhalation of antigens with a particle size $<5\text{ }\mu\text{m}$. Toll-like receptors (TLR), in particular TLR2, are responsible for recognition of the various antigens and subsequently initiating the inflammatory response [75].

In the first 48 h following antigen exposure, an IL-8-mediated neutrophilic alveolitis can be demonstrated by BAL [76 – 78]. Later, the Th1 immune response dominates in acute HP. Activated alveolar macrophages secrete proinflammatory cytokines, which in turn stimulate Th1 lymphocytes to produce TNF- α , which is required for formation of granulomas in the lung parenchyma. Th1 cytokines (TNF- α , INF- γ , IL-12, IL-18) ultimately lead to the predominant infiltration of CD8+ lymphocytes [77 , 79]. Accordingly, HP is characterized by a marked

lymphocytic alveolitis in BAL 48–72 h after antigen exposure.

In addition to the Th1 immune response, Th17 lymphocytes also play a role in HP pathogenesis and are probably associated with disease severity [77 , 80]. Functionally compromised regulatory T cells (Treg lymphocytes) can be detected in HP patients and may be associated with antigen tolerance in asymptomatic exposed individuals [81].

Specific IgG antibodies formed by activated B lymphocytes are considered to be markers of exposure. Their actual role in the pathogenesis is not yet fully understood as they are also normally found in exposed but healthy individuals [82].

It is also not clear why some patients develop chronic HP with pulmonary fibrosis. In chronic HP, there is a switch to a Th2 immune response, which also dominates in IPF [83]. A dominant Th2 immune response was found in lung tissue, particularly in patients with chronic HP and histologic evidence of a UIP pattern [84]. This Th2 immune response was confirmed by the BAL lymphocyte profile in patients with chronic HP [85]. In addition to IL-17, excessive apoptosis of epithelial cells and increased fibroblast activity seem to play a significant role in the pathogenesis of pulmonary fibrosis in HP [86 – 88].

In a considerable percentage of HP patients, a triggering antigen cannot be identified despite comprehensive screening, and disease manifestations radiologically and histomorphologically consistent with fibrotic HP are also reported in familial pulmonary fibrosis. In such cases, it is often assumed that the triggering antigen has not been found. Alternatively, the clinical findings of a foremost chronic fibrotic HP without triggering antigen may be mimicked as a result of genetic factors (see Risk Factors section). English literature suggests using the term cryptogenic hypersensitivity pneumonitis for this [3].

Common variants of HP are bird fancier's lung, farmer's lung, and humidifier lung and, in an occupational context, metal worker's lung. Major variants are briefly described below. A large number of other potentially causal antigens and/or antigen sources of HP have been described and may define other variants of HP. A selection of disease variants (in alphabetical order) and the corresponding antigens and antigen sources in HP are shown in Table 2 , and antigen categories with antigens and the corresponding antigen sources as well as selection of disease variants of HP are shown in Table 3 (both modified and expanded based on [2 , 89 , 90]).

Selection of disease variants (in alphabetical order) and the corresponding antigens and antigen sources in HP (modified and expanded based on [2 , 89 , 90])

Antigen categories with antigens and the corresponding antigen sources as well as selection of disease variants of HP (modified and expanded based on [2 , 89 , 90])

(modified and expanded based on [2 , 89 , 90]) (Tables 2 , 3). More information on antigen identification in cases of known exposure or HP case reports for known antigens are available on the www.hplung.com online platform [91]. Many of these antigens cannot be tested with commercially available serological test extracts.

HP caused by avian antigens is usually the result of exposure to pigeons, budgerigars, other parakeets or parrots. However, exposure to other bird species (including wild birds) can also cause HP [92 – 94]. This entity, generally referred to as bird fancier's lung or bird breeder's lung or more specifically as pigeon fancier's lung, pigeon breeder's lung, or budgerigar fancier's lung, is probably the most common form of HP worldwide.

Protein-containing bird dust from bird droppings or feathers and bird serum were identified as causal antigens. In terms of bird feathers, the down feathers beneath a bird's coat of contour feathers probably play the critical role as they produce feather dust insulating the birds against

moisture and protecting them from heat loss [95]. Indirect exposure to birds can also cause bird fancier's lung [96 – 98]. Avian antigens were still detectable in house dust up to 18 months after the removal of all birds [99], and a Japanese study showed that the amount of avian antigens in a home influences the progression of chronic avian lung disease after the removal of all birds [100].

A special type of HP caused by avian antigens is feather duvet alveolitis. This trigger seems to play an increasingly important role in HP in recent years. Contact with goose feathers or duck down in adolescence and the use of non-industrially produced down duvets often stand out in patient history [101]. A Spanish study found feather duvet alveolitis to be the cause in 26% of 127 patients diagnosed with HP, with the reported prevalence being 6.2/100,000 in people exposed to down feathers versus 54.6/100,000 in bird fanciers [102]. The identification of specific IgG antibodies against goose and duck feathers is particularly important in laboratory diagnostics and can be helpful for the differentiation of bird fancier's lung [103].

Cross-reactions with other avian antigens need to be taken into consideration, and patients with bird fancier's lung should always remove any down feather pillows/beds and clothing as part of antigen avoidance [101 , 103]. In addition, it has been found that HP can also be caused by indirect exposure to avian antigens. Avian antigens should therefore be considered ubiquitous antigens to which anyone can be exposed [104].

Farmer's lung was a common form of HP in Europe, caused by repeated exposure to moist hay and straw. Its incidence has decreased in recent decades due to changes in storage conditions and feeding techniques. Thermophilic actinomycetes which are gram-positive bacteria find optimal growth conditions in stored hay due to moisture and to fermentation processes leading to an increase in temperature (temperatures between 40°C and 60°C), and are among the main antigens of farmer's lung disease. They include, without being limited to *Saccharopolyspora rectivirgula* (previously called *Micropolyspora faeni*), *Thermoactinomyces vulgaris* , *Thermoactinomyces viridis* , *Laceyella sacchari* , and *Thermoactinomyces sacchari* [105 , 106]. Accordingly, there is a correlation with weather conditions as an increased incidence of the disease is recorded in areas with high precipitations, especially during the time of harvest.

Mold fungi, mainly *Aspergillus*, but also *Alternaria*, *Lichtheimia* (formerly *Absidia*) *corymbifera* , and *Botrytis* , find ideal growth conditions in the warm and humid environment of a barn where they release fungal spores. When feed and bedding is brought into the barn and during feeding, fungal spores are dispersed through the air [107 , 108].

Humidifier lung was initially predominantly an occupational disease caused by air conditioning and humidification systems in joineries, bookbinderies and print shops [109 – 111]. The incidence of humidifier lung in the workplace was significantly reduced by appropriate hygiene measures implemented by the statutory accident insurance.

In recent years, however, the popularity of ultra-sound-based misting fountains in private homes and medical offices has led to the development of a special type of humidifier lung called misting fountain alveolitis [112 , 113].

Machine operator's lung is a condition potentially affecting people who come into contact with metalworking fluid (MWF) at their place of work as these may be contaminated with microorganisms [114 – 116]. MWFs are used in metal processing to reduce friction between tools and components, dissipate heat, and remove chips when working metal. The resulting aerosol formation can expose workers to microbial components. A current registry study from Great Britain showed that occupational exposure was the cause of the disease in 50 of 206 HP patients. In these patients, the most frequent definitely occupational trigger was microbial contamination of MWFs, which was responsible for 36 of the total number of 50 occupational HP cases [117].

Typical microorganisms in MWFs, which were also identified as triggers of EEA, include bacteria such as: *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Pseudomonas oleovorans*, *Pseudomonas alcaligenes*, *Ochrobactrum anthropi*, *Acinetobacter lwoffii*, non-tuberculous mycobacteria, such as *Mycobacterium immunogenum*, *Mycobacterium chelonae*, *Mycobacterium gordonae*, but also molds such as *Fusarium solani*, *Fusarium oxysporum*, *Fusarium verticillioides*, *Aspergillus fumigatus*, and *Aureobasidium pullulans*. Among these, pseudomonas and mycobacteria antigens were most frequently identified as the dominant antigens in MWF [2 , 118].

Specific IgG antibodies against *M. immunogenum* were successfully identified using ELISA and electrophoresis methods and can help differentiate between healthy exposed persons and affected patients [119]. The diagnostic spectrum for the detection of HP has, meanwhile, been expanded, and at least one pseudomonas antigen plus *M. immunogenum* should always be tested for. In the case of potential exposure to mold, it is recommended to include these antigens in the test panel [120].

Patients in the USA were first described in 1997 as having developed lung disease after using whirlpool-like hot tubs in which mycobacteria of the *Mycobacterium avium* complex were found in the water [121 , 122]. Some of the clinical findings pointed at an infectious process, while others spoke of an immunological disease. For example, the *M. avium* complex was cultured from sputum, BAL or lung biopsies, but the condition often fully resolved when appropriate precautions were taken or corticosteroids were added, without antimycobacterial drug therapy. The term hot tub lung was introduced to describe this condition.

In addition to whirlpools, a shower and a private indoor swimming pool were also described as exposure sources [123 , 124]. For HP associated with swimming pool use, other triggering antigens must also be considered, such as *A. pullulans* [125], *S. rectivirgula*, and *Neurospora sitophila* [126] as well as *Candida albicans* [127].

In 1 patient, hot tub lung was also described as an occupational disease, with occupational health studies showing that pool cleaners in particular had a significantly increased risk of respiratory problems (OR 9.6) and that the cleaning of water filtration systems in particular was associated with the highest risk [128 , 129].

Potential antigen exposure in the patient's history is an essential element in the differential diagnosis of ILDs. In a large prospective registry study from India, for example, 75% of all patients with HP, which was the most common ILD at 47%, had a history of antigen exposure. This information was obtained using a structured questionnaire [32]. In another prospective multicenter study, the most powerful of six clinical predictors for the diagnosis of HP (OR 38.8) was evidence of apparent exposure to an antigen or antigen source in the patient's medical history [18]. Data from a retrospective study showed that exposure to birds or bed feathers in the patient history, along with age and characteristic HRCT features, is one of three diagnostic criteria for chronic HP, with a specificity of 90% and a sensitivity of 48% [130].

In acute forms of HP, the temporal relationship between exposure and symptoms needs to be considered in addition to identification of a potential inciting antigen. This criterion fails in primarily chronic forms of the disease [4]. In a relevant number of patients (up to 50%) with chronic HP, no causative antigen can be identified, and this is associated with increased mortality [72 , 131]. A structured collection of information regarding potential risks is advisable [132].

The role of questionnaires to assess a potential exposure and/or identify the causative antigen is currently not fully understood. In two observational studies, the inciting antigen was identified in 59% and 100% of cases using such a questionnaire, although the small case numbers of 19 and 46 patients, respectively, meant that conclusiveness was limited. A questionnaire was more likely to identify the inciting antigen than the medical history (RR 3.80; 95% CI 1.79–8.06) or the testing of specific IgG antibodies (RR 1.58; 95% CI 1.12–2.23), although not more likely than the combination

of specific IgG antibodies and inhalation provocation testing (RR 0.90; 95% CI 0.65–1.24) [24 , 133]. Questionnaires should consider regional, cultural as well as seasonal aspects. The sensitivity of structured questionnaires also depends on the type of inciting antigen. In addition to exposure per se, factors that may be significant for exposure to be relevant are also collected [134]. Indirect antigen contact, e.g., via clothing or materials originating from other people, should also be taken into account [132]. Recently, a German questionnaire for the differential diagnosis of ILDs was published, which also covers a variety of potential antigen sources of HP [135]. Question 2: Shall a detailed medical history be obtained, also using a standardized questionnaire, from patients newly diagnosed with ILD and suspected of having HP to identify potential HP-relevant exposures regardless of an obvious antigen exposure? Recommendation R2 1. A comprehensive medical history shall be obtained to identify possible antigen exposure in patients' homes or work environment for all patients newly diagnosed with ILD and suspected of having HP

A standardized questionnaire to identify a possible antigen source or a potentially inciting antigen should be used but does not replace the collection of the patient's medical history

Numerous substances/antigens were described as potentially causing HP. The relevant inciting substances can be roughly subdivided into six categories: bacteria, fungi, animal (glyco)proteins, plant (glyco)proteins, low molecular weight chemicals, and metals. A quantitative structure-effect relationship model showed that chemicals causing occupational HP tend to have a stronger predicted asthma hazard are more lipophilic and have greater potential for protein cross-linking than substances causing occupational asthma "only" [136]. This publication identified a total of ten chemicals potentially causing chemical worker ' s lung , including various specific di-isocyanates, which were also found to trigger occupational asthma, as well as pyromellitic anhydride from the acid anhydride group.

Sampling from the Patient's Environment . To determine antigen-specific IgG antibodies, it is necessary to identify the corresponding antigen source, e.g., at the workplace or in a patient's home environment [2]. If the suspected antigen is not commercially available or if the source of a hidden antigen needs to be detected, material, e.g., settled dust, is to be collected from the place of work; wearable or stationary air sampling devices can be used for this purpose [137]. Extracts from these workplace samples can be used as test antigens for direct IgG testing [138] or used as inhibitors in an IgG inhibition assay [98]. If the suspected inciting antigen is a fungus or another microorganism, microbiological analysis of the collected material may be important to document the association with exposure at the workplace. This analysis should, however, be complemented by determining the antigenic activity using an antigen-specific IgG inhibition assay [139]. In addition to identifying specific bacteria in contaminated MWF-samples and using the isolates as antigen source, the direct processing and use of a MWF-sample from the workplace as an antigen source to identify the IgG antibody concentration can also assist in determining the presence of HP caused by MWF [118 , 120]. Such biosampling or environmental assessment can, in principle, also be done in cases of presumed non-occupational HP without a clearly identifiable inciting antigen, although the costs in this case are not covered by accident insurance and usually also not by health insurance.

The core of laboratory tests in HP is the detection of elevated levels of specific IgG antibodies against suspected antigens. However, a positive IgG antibody test only indicates exposure and, in isolation, does not confirm a HP diagnosis.

Various commercially available qualitative and quantitative test methods are on the market to determine specific IgG antibodies, each with different specificities and sensitivities. The number of potential HP antigens that can be used in these tests is limited [4].

IgG antibodies were originally detected by Ouchterlony double immunodiffusion or immunoelectrophoresis. These methods have been replaced in recent years by more sensitive enzyme immunoassays, some developed by individual laboratories themselves. Commercially available assays complement the options. It is difficult to compare the results across laboratories

because all these assays used different, arbitrarily chosen quantitative units, and the applied antigen preparations were not standardized. Automated systems are meanwhile available for the quantitative determination of specific IgG antibodies (expressed in mg A /L) [140].

Only a small number of studies are available on the clinical significance of determining antibodies of the IgG subclasses (especially IgG2) in HP. A recommendation in this regard can therefore not be provided [141].

In addition, the interpretation of the data is complicated by the fact that there is no agreement on the cut-off values, i.e., what is the “normal range” for healthy individuals and what are “pathological” values indicating the presence of HP. In contrast to the assessment of specific IgE concentrations (for which a cut-off >0.35 kU/L is established), the cut-off values for different IgG antigens and different methods are inconsistent, spanning a wide range depending on the antigen [142]. It is therefore advisable to always use the same method for serial measurements during the follow-up of patients. Hence, cut-off values need to be defined for each antigen and each method based on a corresponding non-exposed, healthy reference population. Since the formation of antigen-specific IgG antibodies is a physiological process influenced both by exposure to – often ubiquitous – antigens and the patient’s immune status, “normal” and “abnormal” values will inevitably overlap when cut-off values are determined. Even significantly elevated IgG concentrations are not conclusive evidence of the presence of HP, even if a correlation exists between IgG titer level and the probability of disease [143 – 145]. The published data on normal ranges for antigen-specific IgG antibody concentrations vary significantly for some antigens, which may be partly due to regional differences in antigen exposure [90 , 103 , 146 – 149]. However, a questionnaire is not a reliable tool to rule out overlooked exposure to ubiquitous antigens such as aspergilli in control subjects.

In addition, at times significant cross-reactivity between some antigens must be taken into account as well as nonspecific assay reactions (such as those referred to as “background activity” by the FEIA system manufacturer). This should be considered a possibility, in particular if the specific IgGs are elevated for all antigens tested [103 , 149 , 150].

For patients with clinically suspected HP, the presence of specific IgG antibodies has a high predictive value (OR 5.3) [18]. In the differentiation to other ILDs, however, a sensitivity of only 83% and specificity of 68% is reported for the detection of specific IgG antibodies, whereas, in the differentiation to other exposed, non-diseased persons, the sensitivity is 90% and 91%, respectively, and with regard to non-exposed, non-diseased persons even 93% and 100%, respectively [3 , 151].

Allergen avoidance after HP diagnosis often leads to a decrease in antibody levels within 6–12 months, but only 50% of patients experience normalization [152]. A decrease in elevated specific IgG antibodies after antigen avoidance may also support a HP diagnosis [144]. Therapy with systemic steroids leads to a decrease in total serum IgG levels [153 , 154]. However, to our knowledge, there are no published studies on the influence of systemic steroids on the specific IgG antibodies.

The absence of elevated specific IgG antibodies does not, however, rule out HP. “Seronegative” HP without elevated specific IgG antibodies is possible. In most cases the triggering antigen has not (yet) been identified [155]. In the chronic fibrotic form, in particular, no obvious antigen source can be identified in up to 50% of cases, making specific IgG testing challenging [14]. In this regard, a so-called cryptogenic HP, e.g., in the context of familial ILD, is debated [3]. There are also findings indicating that compared to acute cases, chronic bird fancier’s lung disease is associated with significantly lower specific IgG antibodies based on quantitative ELISA results. Nevertheless, they are still significantly higher in patients with chronic HP than in IPF patients [156]. It should also be noted that significantly lower specific IgG antibodies are seen in smokers, although these will increase after smoking cessation [155 , 157]. In general, it may be helpful to determine a panel of specific IgG antibodies against common potential allergens for HP in patients with suspected HP [

151 , 158]. In individual cases, inhibition testing can be helpful to identify the source of allergen [139].

In asymptomatic subjects with antigen exposure, the presence of elevated specific IgG antibodies only indicates exposure induced sensitization and not a disease. For example, typical specific IgG antibodies are detected in 10% of asymptomatic farmers and 40% of asymptomatic bird breeders [159]. The detection of elevated specific IgG antibody levels in these asymptomatic exposed farmers is of no prognostic significance for the development of HP [160]. Question 3: Shall specific IgG testing against potential antigens associated with HP be done in patients with newly diagnosed ILD and suspected HP? Recommendations R3 1. Specific IgG testing against potential antigens shall be done in all patients with newly diagnosed ILD and the differential diagnosis of acute or chronic HP

The method used should be one for which published threshold values in a control population are available

The measurement of specific IgG antibodies should either be determined by the suspected antigen source (e.g., bird keeping, agriculture, mold exposure) or based on a selection of potential common antigens (e.g., bird dusts including goose feathers, molds and thermophilic actinomycetes)

The evidence supporting lymphocyte proliferation testing for antigen detection is very low. These assays are therefore not recommended [4]. In acute HP, nonspecific signs of inflammation such as leukocytosis, elevated C-reactive protein levels and accelerated erythrocyte sedimentation rates may be detected in serum [95].

In addition, an increase in total IgG and a positive rheumatoid factor may be seen, contributing to the potential misdiagnosis of rheumatoid arthritis (RA)-associated with ILD [161]. Positive antinuclear antibody titers were found in 43–58% of HP patients and were associated with accelerated disease progression [162 , 163].

While levels of YKL-40, a chitinase-like protein, were higher in HP patient serum samples than in those of control subjects, they seem to be lower than in other ILDs. YKL-40 therefore seems to be a promising marker to discriminate between HP and other ILDs [164 , 165]. Other biomarkers such as KL-6 ("Krebs von den Lungen-6" [lung cancer-6]), SP-D (surfactant protein D) and apolipoproteins had promising results in some studies and may have the potential to be implemented in real-life practice. As research progresses, additional biomarkers are expected to become new and successful tools that complement the currently available diagnostic methods [165].

HP is characterized by a restrictive lung function and, consistent with gas-exchange impairment, a reduced diffusing capacity and/or resting or exercise-induced hypoxemia as seen in blood gas analysis [18 , 166 – 168]. Ergospirometry including measurement of the alveolar-arterial oxygen gradient (AaDO₂) is the more sensitive method for detecting a diffusion disorder also in HP. Here, increased dead-space ventilation and a restricted breathing reserve reflect ventilatory limitation [169]. It is important to note that nonspecific bronchial hyperresponsiveness can be detected in up to 50% of patients with acute HP. This must not lead to misdiagnosing the condition as bronchial asthma [170].

Chronic HP usually shows a restrictive ventilatory impairment, and rarely also an obstructive pattern. The role of pulmonary emphysema needs to be considered in this context and should not be taken as an argument against the presence of chronic HP [171]. Several studies showed the co-existence of pulmonary emphysema in patients with HP from agricultural or avian antigens, between 17% and 33% across all groups and between 18% and 36% in the group of never-smokers [21 , 22 , 168 , 172 – 174].

Lung function has no role in the diagnostic differentiation between HP and other ILDs. As with other ILDs, clinical parameters and lung function should be monitored every 3–6 months in patients with chronic HP [5]. Lung function testing serves to assess the functional implications of the condition, verify the effectiveness of antigen avoidance or drug therapy, identify a progressive fibrotic disease, predict prognosis in chronic forms and is also essential for forming an expert opinion, e.g., regarding a patient's ability to work.

The historically common chest X-ray has lost its importance in patients suspected to suffer from HP. Both, in the presence of an unremarkable chest X-ray that does not explain the clinical findings, as well as in the case of an abnormal chest radiographic finding, additional chest CT should be performed for differential diagnosis (see Chest X-Ray section).

Thin-section chest CT acquired in a volumetric mode provides overlay-free, high-resolution images of the fine pulmonary structures and has become the imaging modality of choice for any ILD, thus replacing projection radiography. Consequentially, it serves as a mainstay in the current guidelines for diagnosing HP.

In patients with acute symptoms, chest X-ray was in the past rather used for ruling out other possible causes than for diagnosing HP [175]. Chest radiograph is unremarkable in 20% of cases [176]. In “positive” chest X-rays, ill-defined nodular opacities (according to ILO: small rounded opacities p / q / r) were reported in a small number of patients. Rarely, consolidation was detectable. The distribution of the nodular opacities was diffuse with relative basal sparing [177 , 178].

In patients with chronic symptoms, early fibrosis cannot be ruled out by chest X-ray. Subtle changes are underestimated by projection radiography. Reticular opacities (small irregular opacities s/ t / u according to ILO) representing fibrotic changes can only be detected in advanced fibrotic remodeling. These may be combined with or superimposed by nodular changes from the acute phase. The distribution is variable [178].

In any ILD, as in cases of suspected HP, the imaging modality of choice is a non-enhanced thin-section volumetric CT of the chest (also referred to as HR (high-resolution CT) acquired with a thin collimation at sustained end-inspiration. To assess the lung parenchyma, an edge-enhancing high reconstruction kernel should be used for optimum spatial resolution. To assess the soft-tissues, a smoothing, low reconstruction kernel should be used to create optimum contrast resolution. Slice thickness shall not exceed 1.5 mm. A 30% slice overlap is recommended. Regardless of the direction of acquisition, images should always be sorted craniocaudally. In addition to axial orientation, multi-planar reconstructions with a maximum slice thickness of 1.5 mm are required in the sagittal and coronal planes. Minimum-intensity projections (minIP) are optional. A low dose protocol (low dose; LD-HRCT) is especially recommended for follow-up scans. If needed, additional images may be acquired at end-expiration or in prone position. For this, either single scans or spiral computed tomography, both in low dose technique, may be used [179].

Thin-section volumetric CT has replaced chest X-ray as the radiological standard in the diagnosis of HP due to superior specificity and sensitivity. Two current international guidelines defined probability levels for the diagnosis of HP based on HRCT criteria (“typical”, “compatible,” or “indeterminate,” whereby even a classification as “indeterminate” does not rule out HP [3 , 4]). According to the international guideline published in Chest in 2021, HRCT plays a key role in the diagnostic algorithm [4]. Immediately after the exposure history and antigen specification have been assessed, the further diagnostic workup is determined by the HRCT category. In Germany, the above-mentioned HRCT categorization based on probability levels has not yet become established in clinical practice due to its complexity.

In some literature [15] as well as in this guideline, HP is clinically categorized according to the course of disease over time in an “acute” and “chronic” form and further on in a “chronic

non-fibrotic” and “chronic fibrotic” form. Referring to these clinical categories, we recommend from a radiology perspective that a pragmatic distinction be made in the HRCT assessment between a purely inflammatory type and a fibrotic type. Of note, HRCT signs of “inflammatory HP” can occur both in clinically acute HP as well as in the clinically chronic phenotype. The HRCT analysis follows a systematic description based on signs and their distribution (Tables 2 , 3 , 4).

HRCT features, distribution, and correlating pathophysiology of HP

The following findings can be present in non-fibrotic HP. Signs

Ground-glass opacities (Fig. 2): the dominant feature of acute/subacute disease are ground-glass opacities (in addition to ground-glass nodules, see below). They reflect the acute inflammation of the parenchyma. Ground-glass opacities can be confluent or multilocular.

Ground-glass nodules (Fig. 3): ground-glass nodules are ill-defined and have a maximum diameter of 5 mm (“cotton wool”-like). They are the HRCT morphological correlate of bronchiolitis.

Consolidation (Fig. 4): consolidation can be present, but is much rarer than ground-glass opacities. Like ground-glass opacities, it is indicative of inflammation and the histological pattern often corresponds to that of organizing pneumonia (OP). When consolidation occurs, it is usually multilocular.

Air trapping (Fig. 2 – 4): air trapping produces a mosaic pattern. A mosaic pattern can principally have various causes. If caused by air trapping, the typical polygonally shaped “dark” areas are the pathological substrate of focal hyperinflation due to the obstructive component in HP. Vessel calibers are reduced within the hyperinflated areas due to secondary hypoxic pulmonary vasoconstriction (previously known as “Euler-Liljestrand mechanism”) (Fig. 5).

Air trapping may be visible on inspiratory images, but it is easier to recognize on expiratory images due to the lack of volume decrease and of density increase compared to inspiratory images. Minimum-intensity reconstructions provide an even more impressive visualization because hypodense areas are accentuated. Pointing to the heterogeneity of the generic term “mosaic pattern,” some authors only use the term “air trapping” if the finding is confirmed in expiration [180 , 181] (Fig. 2 , 3).

Three-density pattern (Fig. 4): the three-density pattern (formerly known as head cheese sign) is created by the combination of three attenuation levels in the lung parenchyma on inspiratory scans (air trapping, normal lung, areas of ground-glass opacity/consolidation) and is indicative of a mixed infiltrative and obstructive process which, while not pathognomonic, is highly suggestive of HP [182].

Cysts (Fig. 6): parenchymal cysts are found in up to 13% of inflammatory HP cases. The thin-walled cysts range in size from a few millimeters to 1.5 cm [183].

Inflammatory HP is usually bilateral and symmetric with a diffuse distribution in the axial and coronal plane. However, there can be a predominance in the middle or lower lung zones or in the peribronchovascular regions. The ground-glass nodules are found in a centrilobular location. The cysts are located within ground-glass opacities but otherwise show no preference in terms of location (Fig. 2 , 3 , 6).

Inflammatory HP (non-enhanced HRCT; lung window; MPR, axial plane in inspiration (a), expiration (b)). Signs: ground-glass opacity and air trapping (the geographically shaped areas show increasing density differences in expiration). Distribution: diffuse, no preference.

Inflammatory HP with centrilobular ground-glass nodules (non-enhanced HRCT, lung window, MPR axial in inspiration (a), expiration (b)). Signs: ground-glass nodules and air trapping (the geographically shaped areas show increasing density differences in expiration). Mosaic pattern already recognizable in inspiration: no scan in expiration necessary. Distribution: ground-glass nodules: centrilobular; air trapping: random.

Three-density pattern (non-enhanced HRCT; lung window; MPR axial in inspiration; without (a) and with (b) marked borders). Combination of ground-glass opacity/consolidation (dashed border), air trapping (dark areas, uninterrupted border), and normal parenchyma (dotted border).

Systematic image analysis in mosaic pattern (from [184]).

Cysts in inflammatory HP. (Native HRCT; lung window; axial MPR in inspiration). Signs: Ground-glass opacity, ground-glass nodules, thin-walled cysts in the lingula. Distribution: ground-glass opacity diffuse, ground-glass nodules centrilobular, cysts within the ground-glass opacity.

Not all listed findings have to be present simultaneously. Instead, typically a selection of the above-mentioned features are present in different combinations and with different weighting. Even one typical HRCT sign alone (e.g., ground-glass nodules) in a characteristic (centrilobular) distribution can be highly suggestive of an (inflammatory) HP diagnosis. As a general rule, the probability of HP is higher if more characteristic features are found. Of note, in approximately 8% of cases of inflammatory HP, the HRCT may be unremarkable [18].

Ground-glass opacities and consolidation are potentially reversible. However, ground-glass opacities can persist over a long period of time (Fig. 7). From a radiology perspective, this finding correlates with the clinical form of chronic non-fibrotic HP. Nevertheless, radiology cannot definitely determine if chronic ground-glass opacity is true inflammation or rather represents fine fibrotic changes [185].

Persistent ground-glass opacity in HP (non-enhanced HRCT; lung window; axial MPR in inspiration; baseline (a), after 1 year (b)). a , b Diffuse ground-glass opacities and a mosaic pattern (consistent with air trapping). Usually ground-glass opacity is considered to represent the inflammatory component of HP. However, with basically unchanged extent of ground-glass opacities over the course of 1 year, it cannot be ruled out that fine fibrosis is the underlying pathology although there are no distinct signs of fibrosis (like traction bronchiectasis, honeycomb cysts, irregular reticulation).

The following findings can be present in fibrotic HP. Signs

Fibrosis (Fig. 8 – 10): any sign of fibrosis may be found, including coarse and/or fine irregular reticulation, traction bronchiectasis and traction bronchiolectasis, architectural distortion, honeycombing, and volume reduction of affected lung areas. These signs of fibrosis alone are not pathognomonic for fibrotic HP.

The presence of cysts is described in up to 39% of cases of fibrotic HP.

Pulmonary emphysema: as a late consequence of HP, some patients may develop pulmonary emphysema, mostly centrilobular, either alone or in combination with ILD, as described above. This is, in particular, seen in patients with “farmer's lung.” Emphysema was described in 48% of these patients, which was more prominent than the fibrotic changes [186]. Other types of pulmonary emphysema (paraseptal, bullous emphysema) are also possible [21 , 187 , 188]. Bronchiolar inflammation and obstruction is considered to be the main culprit in terms of pathophysiology. Patient history is crucial in these cases as they present with emphysema regardless of smoking history.

Fibrosis (Fig. 8 – 10): fibrosis is usually seen in a multilobar distribution both in axial and in coronal plane, and can involve all lobes. It can also be asymmetric. Some patients show characteristics that are helpful for the differential diagnosis: in about 10% of patients, the upper lobes are predominantly affected, about 20% of patients show a predominant peribronchovascular distribution, and in 20–40% the costophrenic angles are relatively spared.

Cysts: the cysts are located within ground-glass opacities.

Emphysema: variable distribution and upper-lobe predominance are possible.

Fibrotic HP with significant inflammation (non-enhanced HRCT; lung window; MPR in inspiration axial (a), coronal (b)). Signs: irregular reticulation, traction bronchiectasis, and honeycombing – fibrosis. Ground-glass opacity and centrilobular ground-glass nodules even outside of fibrosis – inflammation. Distribution: axial and coronal: fibrosis: upper lobe, inflammation: diffuse.

Fibrotic HP with little inflammation (non-enhanced HRCT; lung window; MPR in inspiration axial (a), coronal (b), coronal (c) minIP (minimum-intensity projection)). Signs: fine reticulation with traction bronchiolectasis (uninterrupted arrows) – fibrosis; ground-glass opacity predominantly within obvious fibrosis – presumably consistent with fine fibrosis; mosaic attenuation with multilobar geographically configured hypodense areas which exhibit decreased vessel calibers (dashed arrows) – air trapping with secondary mosaic perfusion. Mosaic pattern already clearly recognizable in inspiration: no scan in expiration necessary. Distribution: axial and coronal: random, without central or peripheral predominance, partly peribronchovascular (uninterrupted arrows), air trapping >5% per lobe.

Fibrotic HP without inflammation (non-enhanced HRCT; lung window; MPR in inspiration axial (a), coronal (b)). Signs: irregular reticulation with traction bronchiectasis = fibrosis. No ground-glass opacity, no ground-glass nodules = no inflammation. Distribution: axial and coronal: significant upper-lobe involvement, peribronchovascular predominance (arrows).

The following parameters are helpful for differential diagnosis. Signs of the inflammatory stage are frequently present. This combination of fibrosis, which may not be classified based on HRCT morphology, and signs of inflammation (ground-glass opacity, ground-glass nodules) as well as air trapping and/or the three-density pattern is very helpful for the differential diagnosis and increases the probability of a fibrotic HP. The following should be noted:

The respective percentage of inflammation and fibrosis should be weighted semi-quantitatively in the radiological report. Only ground-glass opacity without obvious fibrosis should be classified as inflammation (Fig. 8 , 10).

Similarly, air trapping should only be considered a sign of obstruction primarily originating from the airways when there is no obvious fibrosis. Within fibrosis of any origin, architectural distortion can lead to valve phenomena leading to secondary air trapping (Fig. 9).

The quantitative extent of air trapping is important to recognize the probability of fibrotic HP increases if air trapping is found in >3 lobes, or if >5% of the lung parenchyma is involved as (currently) determined by visual assessment (Fig. 9) [189].

Honeycombing is not the predominant fibrotic lesion.

An unusually pronounced mosaic pattern and the three-density pattern in particular suggest fibrotic HP [130 , 180 , 190]. The three-density pattern has a specificity of >90% for the presence of fibrotic HP but is also seen in other conditions (e.g., sarcoidosis and DIP) (sensitivity of just below 50%) (Fig. 5 , 9) [191].

Fibrosis in HP can also manifest as NSIP or UIP pattern, and then cannot be differentiated radiologically from such patterns of other etiologies. According to current literature, a UIP pattern is seen in almost 50% of fibrotic HP [192].

HRCT Features of Acute Exacerbation in HP . New ground-glass opacities and/or consolidation on HRCT may indicate an acute exacerbation in fibrotic ILDs and, hence, also in fibrotic HP [193 – 195]. In a Japanese cohort, acute exacerbation was found less often in fibrotic HP (3% after 1 year; 10% after 3 years) than in IPF (8% and 20%). The HRCT criteria of “progressive pulmonary fibrosis” were not a predictor of acute exacerbation [196].

HRCT Features of Pulmonary Hypertension in HP . A fibrotic HRCT pattern in patients with HP is one of the predictors of pulmonary hypertension [197 – 199]. Non-enhanced HRCT may provide indirect evidence of pulmonary hypertension. This includes dilatation of the central and peripheral pulmonary arteries (central: main pulmonary artery ≥ 29 mm in men and ≥ 27 mm in women) with a main pulmonary artery-to-ascending aorta ratio of >1 . These criteria, however, vary significantly, in particular depending on age, gender and weight. A normal pulmonary artery caliber does not rule out pulmonary hypertension. The Fleischner Society has, therefore, drafted risk-based cut-off values based on clinical context. The above cut-off values can only be used in relation to a high-risk population, such as in fibrotic HP, depending on the extent of fibrosis [200].

Respiratory Bronchiolitis . Centrilobular ground-glass nodules and ground-glass opacities are a feature of both smoking-associated respiratory bronchiolitis (RB) and inflammatory HP. However, the distribution in RB differs from that in inflammatory HP. While in HP the distribution is diffuse, RB is characterized by an upper-lobe predominance of lesions. Air trapping is seen in both conditions, but air trapping in RB is associated with large airway disease presenting as bronchial wall thickening, which is not a sign of HP.

Infectious Bronchiolitis . It can present as centrilobular ground-glass nodules on HRCT. In contrast to HP, however, the distribution is almost never diffuse, but usually multilobar. A typical sign of infectious bronchiolitis is the accompanying inflammatory thickening of the bronchial wall, sometimes with bronchial obstruction. A tree-in-bud pattern consistent with an inflammatory retention of bronchial and alveolar secretions is not found in HP. In addition, a more rapid change in findings in follow-ups suggests infectious bronchiolitis rather than HP.

Lymphocytic Interstitial Pneumonia . In theory, the much rarer lymphocytic interstitial pneumonia (LIP) can be quite similar in appearance to HP, presenting with centrilobular ground-glass nodules, ground-glass opacities and cysts. However, cysts are more frequent, more numerous and usually larger in LIP compared to HP. Air trapping is not a characteristic feature of LIP. The association with an autoimmune disease (especially Sjögren’s syndrome) is also helpful for the diagnosis of LIP.

Idiopathic Pulmonary Fibrosis . Idiopathic pulmonary fibrosis (IPF) is the most important differential diagnosis. In typical cases, the distribution of the UIP pattern is the key differentiation factor as it is characterized by subpleural and dorsobasal predominance in contrast to the relative sparing of costophrenic recessus in up to 40% of HP cases. Moreover, in some patients, fibrotic HP predominantly affects the upper and middle zone as well as the peribronchovascular region [201].

A recent study describes a coarse mesh-like pattern of reticulation in fibrotic HP as a “hexagonal pattern” [202], defining it as interlobular septal thickening, possibly extending from the subpleural to the central region through two or more layers of pulmonary lobules (Fig. 11). This pattern was significantly more common (70%) in fibrotic HP than in IPF (32%).

“Hexagonal pattern” (non-enhanced HRCT; lung window; MPR in inspiration axial (a), sagittal (b)). Irregular thickening of the interlobular septa in the lower lung zones, extending through several layers from subpleural to central.

Honeycomb cysts are less common in HP and appear at a much later stage of disease [203]. In a small number of cases, fibrotic HP may present as a typical UIP pattern. In a Portuguese study of 63 patients with HP-, UIP-, or a UIP-like pattern was found on HRCT in 46% of cases [192].

In these cases, synchronous signs of inflammation (centrilobular nodules) and/or the three-density pattern are [3 , 180 , 204] indicative of HP as the cause of fibrosis. In this regard, the three-density pattern has the highest specificity for distinguishing fibrotic HP from IPF [180]. The specificity of air trapping increases with increasing severity (Fig. 12).

Histomorphology of Hypersensitivity Pneumonitis (HP). a Low-power view of a transbronchial lung biopsy, demonstrating a reduction in air-filled alveolar spaces in favor of increased interstitial tissue (H&E, scale bar = 1,000 μ m). b Higher magnification reveals alveolar interstitium expanded by a dense lymphocytic infiltrate, consistent with interstitial pneumonitis, which is accentuated in a bronchiolocentric pattern in initial stages of EAA (H&E, scale bar = 100 μ m). c Subsequent immunohistochemical analysis reveals a predominantly T-cellular lymphocytic infiltrate (CD3-positive). Lymphoid follicle formation is typically not observed (CD3, scale bar = 50 μ m). d Transbronchial lung biopsy showing an ill-defined, epithelioid cell granuloma without necrosis adjacent to inflamed alveolar septa on the left side of the image (H&E, scale bar = 250 μ m). e Higher magnification reveals centrally located plump epithelioid cells (arrow) surrounded by loose lymphocytic aggregates (H&E, scale bar = 50 μ m). f EAA granulomas may also contain multinucleated giant cells, in this example ordered multinucleated giant cells. The granulomas are generally loosely demarcated from the adjacent tissue (H&E, scale bar = 50 μ m). g Multinucleated giant cells may show cytoplasmic inclusions, exemplified here by a cholesterol cleft (asterisk). Additionally, an intra-alveolar polypoid myofibroblastic bud (arrow) is visible at the lower image border, surrounded by desquamated macrophages and lymphocytes. In conjunction with the adjacent interstitial pneumonitis, this corresponds to a focus of organizing pneumonia. Thus, this transbronchial biopsy demonstrates the three pathognomonic injury patterns of EAA: interstitial pneumonitis, epithelioid cell granulomas, and foci of organizing pneumonia (H&E, scale bar = 100 μ m). h Intra-alveolar myofibroblast proliferations of organizing pneumonia may present more prominently as braid-like formations (asterisk) lining large areas of alveolar spaces (H&E, scale bar = 100 μ m). i Transbronchial biopsy showing heterogeneous interstitial fibrosis (asterisk) adjacent to cellularly broadened alveolar septa in the context of interstitial pneumonitis. This may indicate transition to the fibrotic form of EAA. A polypoid myofibroblast bud of organizing pneumonia (arrow) is also visible (H&E, scale bar = 100 μ m).

In a retrospective study from Spain, profound mosaic attenuation/air trapping was described as an important distinguishing feature of fibrotic ILDs in 83 cases with lung biopsy being the gold standard. Evidence of mosaic attenuation/air trapping in more than three lobes outside of fibrotic areas spoke against UIP and suggested fibrotic HP or CTD-ILD (61% in non-UIP versus 20% in UIP) [181]. In a Canadian study, air trapping involving >5% of the lung parenchyma on expiratory scans allowed for differentiation of fibrotic HP from other fibrotic ILDs with a sensitivity of 91% and a specificity of 77% [189].

Pulmonary ossifications can occur in fibrotic ILDs. They are mostly seen in IPF and SSc-ILD (IPF 31%; SSc-ILD 29%). They can also occur in fibrotic HP, but significantly less frequently (19%) [205].

ILD with NSIP Pattern . The morphology of NSIP pattern in HRCT is highly variable. Discrete air trapping may also be found in rare cases. However, the NSIP pattern rarely has centrilobular nodules, and it affects the lung parenchyma more homogeneously than fibrotic HP. Moreover, NSIP is characterized by basal and peripheral predominance. Relative subpleural sparing as found in the NSIP pattern in some cases is uncommon in fibrotic HP. However, fibrotic HP can also manifest as a typical NSIP pattern and then cannot be distinguished radiologically from other etiologies of this pattern (see above).

Asbestosis . It is histopathologically similar to fibrotic HP as it is also characterized by bronchiolocentric pathogenesis. In HRCT, however, asbestosis predominantly affects the dorsobasal lower lobes, similar to IPF. Lower-lobe predominance is found in only one third of fibrotic HP cases with the tendency to relatively spare the costophrenic recesses. This distribution was confirmed in a retrospective study from China (204 patients with asbestosis; 74 patients with fHP), as was the upper-lobe predominance for fibrotic HP. Asbestos-exposed patients had significantly more numerous and more characteristic pleural changes than the HP patients. Among the fibrotic changes, subpleural intralobular nodules, so-called “early fibrosis,” were the key characteristic of asbestosis, albeit with a moderate sensitivity (specificity 86%, sensitivity 57%, PPV 92%, NPV 42%). Exposure dose units were not assessed in this study. Interestingly, mosaic attenuation and three-density patterns were also seen in more than half of the asbestosis cases, and were not significantly different from those of fibrotic HP [206]. This may be attributable to asbestos-induced small airway disease affecting the respiratory bronchioles, which rarely can lead to an obstructive ventilatory disorder in asbestosis [207 , 208].

In conclusion, the radiology of HP can be summarized as follows: 1. A chest X-ray is not appropriate to diagnose HP due to low sensitivity and specificity. Thin-section HRCT using multidetector volumetric acquisition, possibly with images in expiration as needed, is the modality of choice.

In contrast to the highly complex radiological classification criteria based on degrees of probability as presented in the 2020 international ATS/JRS/ALAT guideline, we propose a “pragmatic” radiological classification. Based on HRCT features, a purely inflammatory and a fibrotic type of HP can be distinguished. In both types, the HRCT features reflect the two disease components of “parenchymal infiltration” and small airway disease.

The inflammatory features are potentially reversible. Whether persistent ground-glass opacity is indicative of fine fibrosis cannot be resolved by HRCT morphology.

In the challenging diagnosis of “fibrotic HP”, the combination of fibrosis criteria (of any pattern) and synchronous features of the inflammatory phenotype – especially the three-density pattern – is highly suggestive of fibrotic HP. In addition, the variable coronal and axial distribution in fibrotic HP is important for differential diagnosis.

Occupational HP has the same HRCT morphology as described above. In the case of possible co-exposure to inorganic dust, features of other types of pneumoconioses need to be considered, and the classification according to ICOERD has to be performed as part of an expert assessment.

In evaluating the HRCT morphology of ILD, radiologists shall determine if the characteristic signs and distribution of inflammatory or fibrotic HP are present. In fibrotic HP, the assessment shall state whether or not an inflammatory component is present as well as how the weighting of fibrosis and inflammation is

BAL is a key component of the diagnostic workup of patients with suspected HP [5]. A lymphocytic alveolitis in BAL is a characteristic and highly sensitive finding [15].

HP has the highest total cell counts of all ILDs and the highest degree of lymphocytosis, with often greater than 50% of total cells. The probability of HP increases with increasing percentage of lymphocytes. Absence of lymphocytosis makes acute HP highly unlikely [209].

In acute, non-fibrotic HP, the lymphocyte percentage is higher (46%; 20–80%) than in chronic fibrotic HP (19%; 11–41%) [210]. A meta-analysis, however, found no difference in the BAL lymphocyte count between chronic HP in general (43%) and the subgroup with chronic fibrotic HP as defined by radiology/histology [211].

In chronic fibrotic HP, only a mild or no lymphocytosis with elevated neutrophil levels may also be found [19 , 159 , 209 , 212 – 214]. A lymphocyte level of >30% was suggested as a useful threshold to discriminate chronic fibrotic HP from IPF [215]. A meta-analysis in the context of the international HP guideline showed that a cut-off of >30% of lymphocytes can distinguish fibrotic HP from IPF with a specificity of 80% and a sensitivity of 55%, and non-fibrotic HP from IPF with a sensitivity of even 88% and the same specificity of 80% [216]. At a lower separation threshold of 20% lymphocytes to differentiate between chronic HP and IPF, specificity is lower in favor of a higher sensitivity (specificity 72.7%, sensitivity 68.1%, PPV 56.9%, NPV 81.1%), and vice versa at a higher separation threshold of 50% lymphocytes (specificity 95.1%, sensitivity 30.9%, PPV 77.6%, NPV 71.6%) [211]. In general, higher BAL lymphocytosis thresholds would be better suited for routine clinical practice to distinguish HP from IPF due to higher specificity [211 , 216 – 218].

It should be noted, however, that a neutrophilic alveolitis may be detectable in acute HP within the first 48 h of antigen exposure [219]. This time window needs to be considered if BAL is performed following inhalation provocation testing.

In the evaluation of the lymphocyte subtypes, an increase in CD8 + T lymphocytes and, hence, a decreased CD4 + /CD8 + ratio was considered typical of HP [220]. However, it has been increasingly shown that the CD4 + /CD8 + ratio only plays a minor role in the differentiation between HP and sarcoidosis [209 , 221]. A normal or elevated CD4 + /CD8 + ratio in no way excludes HP. The variability may depend on the type of inciting antigen, the time of last antigen exposure and the clinical progression as increased ratios are found particularly in chronic fibrotic cases [85 , 222].

Other features of BAL in HP may include elevation in the counts of eosinophils, mast cells, plasma cells, and foamy macrophages (foam cells) [223 , 224]. In asymptomatic exposed persons (e.g., farmers), the detection of a lymphocytic BAL is of no prognostic significance, analogous to the detection of elevated specific IgG antibodies against potential antigens, and is described as subclinical lymphocytic alveolitis [160]. Question 5: Shall a BAL cell analysis be recommended for patients with newly diagnosed ILD who are suspected of having HP based on clinical symptoms? Recommendation R5 1. BAL differential cell counts shall be done in patients with newly diagnosed ILD suspected of having HP

Elevated lymphocyte counts (>30%) in BAL in patients with ILD should prompt further diagnostic workup with regard to the diagnosis of HP.

CD4/CD8 ratios in the BAL analysis shall not be used to diagnose HP

With regard to the value of lung biopsy in patients with HP, it first needs to be determined if the condition is acute/chronic and if the chronic type is fibrotic/non-fibrotic, or if another lung disease is suspected that would need clarification by lung biopsy.

If lung biopsy is indicated, the available options are two bronchoscopy procedures, transbronchial lung forceps biopsy (TBLB) and transbronchial lung cryobiopsy (TBLC), as well as SLB. The diagnostic accuracy or yield is generally lower with TBLB than with TBLC in all ILDs. This is due to the insufficient accessibility of subpleural lung areas in particular, the smaller size of the tissue samples, as well as crush artifacts. Evidence to support the diagnostic accuracy or yield of TBLB in HP patients is limited. In the acute or non-fibrotic-type, characteristic HP findings are seen in approximately 50% of patients. When including patients with acute or non-fibrotic HP and those with chronic fibrotic HP, the diagnostic yield is only 40% [210 , 225 , 226].

TBLC has meanwhile become an established diagnostic tool in ILDs [5]. A meta-analysis comparing diagnostic yield and complication rates of TBLB and TBLC in patients with HP clearly confirmed the superiority of TBLC with 82% (95% CI, 78–86) vs. TBLB with 37% (95% CI, 32–42), with a slightly higher complication rate for TBLC in terms of bleeding and pneumothorax [227]. In a

prospective multicenter study comparing TBLC and SLB in 65 patients with ILD, a consensus diagnosis of chronic HP based on histopathology was established in a first step using TBLC in 15% and SLB in 23% of cases and, after MDD, in 23% and 28% of cases, respectively. A high degree of agreement between the two biopsy methods was seen in the cases ultimately classified as definite HP (95%) [228]. Overall, SLB can be avoided in 82–91% of patients by using TBLC [3].

The evidence supporting the value of SLB in HP patients, usually for those with a chronic fibrotic type, is also limited: Of 46 patients with initial IPF diagnosis, 20 patients were ultimately diagnosed with chronic HP after re-evaluation with additional serologic tests and environmental analysis. In 16 of these 20 patients, pre-defined features of a chronic fibrotic disease could be confirmed by SLB [24]. In patients with unclear ILD, the suspected HP diagnosis initially was 24% based on CT findings and 32% based on histopathology using SLB. Ultimately, however, only 21% were diagnosed with HP, taking into account all the available information including CT and histopathology findings [229]. Especially in patients with initially unclassifiable ILD, SLB can result in the final diagnosis of an HP [230].

In the differential diagnosis versus IPF, in HP patients the histopathologic characteristics of HP are evident in 67% of all SLB samples [231]. An international guideline for the diagnosis of HP assessed the diagnostic yield of SLB in known or suspected HP as 96%. In 91% of cases, the histopathological findings from SLB confirmed the HP diagnosis, and in 9% an alternative diagnosis was made [3]. With regard to the complication rates of the different biopsy methods, see the German guideline for diagnosis of ILDs [5]. Question 6: Shall TBLB, TBLC, or SLB be used in patients with suspected HP requiring lung biopsy? Recommendation R6 1. If lung biopsy is necessary to diagnose acute or chronic non-fibrotic HP, TBLB, or TBLC should be performed

If lung biopsy is necessary to diagnose chronic fibrotic HP, TBLC shall be performed

If lung biopsy is necessary to diagnose chronic fibrotic HP, and a previous TBLC failed to result in meaningful findings or if TBLC is not possible, SLB should be performed

In general, the adequate interpretation of histopathology findings and the diagnosis of HP in particular always require clinical information and context. Histopathologic changes in the lung tissue of patients with non-fibrotic HP differ significantly from those seen in fibrotic HP [3 , 232]. The distinction between acute or chronic non-fibrotic HP is only possible through multidisciplinary discussion in a specialist ILD board meeting. The differentiation below, therefore, only provides a histopathologic distinction between non-fibrotic and fibrotic HP (Table 5 , 6).

HRCT signs and distribution of purely inflammatory HP

HRCT signs and distribution of fibrotic HP

Non-Fibrotic HP . The following triad of features is characteristic of non-fibrotic HP [3 , 233 , 234].
1. Cellular inflammatory interstitial infiltration (lymphocytes, partly plasma cells) with a bronchiolocentric distribution,

Loosely formed, nonnecrotizing epithelioid cell granulomas with irregular distribution within the peribronchiolar interstitium,

Lymphocytic, partly plasma-cellular bronchiolitis with OP pattern.

While lymphocytic infiltration is usually always present, granulomas are seen in two-thirds of the cases only and an OP pattern in half of the cases. It should be noted that the granulomatous inflammatory component in HP is usually ill-defined, embedded in the lymphocytic infiltrates and, therefore, easily overlooked. The OP pattern in HP usually features a more heterogeneous distribution and is less extensive than, for example, in pulmonary infection. The HP diagnosis is

considered “typical” if all three above-described histological features are detected, “probable” if two features are found, and “possible” or “indeterminate” if only one feature is seen (see Table 7) [3 , 233 , 234].

Histopathology of non-fibrotic HP (modified based on [3])

Lymphocyte-predominant (lymphocytes > plasma cells)

IL-defined, loose clusters of epithelioid cells and/or multinucleated giant cells

Located mainly in the peribronchiolar interstitium

Features which are inconsistent with the histopathological diagnosis of HP and suggest an alternative diagnosis

Numerous, well-formed sarcoidal granulomas or necrotizing granulomas

OP is quite a nonspecific pattern of damage that can be associated with a number of conditions. If an OP pattern is the sole finding, other entities possibly going along with an OP pattern (e.g., drug-induced pneumonitis, cryptogenic OP) need to be considered in the differential diagnosis [234].

Sarcoidosis is another important granulomatous ILD to be differentiated from HP. In sarcoidosis, the granulomatous inflammation is much more prominent, presenting with larger, well-formed granulomas, some of them confluent, and is located mainly along the lymphatic ducts of the bronchovascular bundles, the interlobular septa, and the visceral pleura [235].

Additional histopathologic differential diagnoses may include aspiration-induced bronchiolocentric inflammation, RB in smokers, pneumoconiosis (e.g., berylliosis), connective tissue disease-associated ILD, drug-induced injury, granulomatous ILD associated with immunodeficiency disorders or granulomatous infections (e.g., caused by mycobacteria or fungi) [4]. An infectious origin of the pathology, therefore, needs to be ruled out in the (initial) diagnosis of a granulomatous disease using appropriate techniques (e.g., Ziehl-Neelsen staining, auramine staining with subsequent fluorescence microscopic examination, Grocott staining, mycobacterial or fungal PCR, etc.). The results of these examinations should always be correlated with the radiological findings as well as (conventional) microbiological test results and the clinical findings (e.g., immunosuppression?).

Fibrotic HP . Fibrotic HP is characterized by interstitial fibrosis. In most cases, only isolated granulomas can be detected, which means a case may still qualify as HP depending on clinical findings, but the diagnosis can be much more challenging than in the case of acute HP. Centrilobular or bronchiolocentric fibrosis, as well as bridging fibrosis, suggest the presence of HP. The latter is characterized by uninterrupted fibrosis between the centrilobular and the perilobular regions (subpleural or near the interlobular septa). Additional histopathological features of fibrotic HP can be unique areas of acute damage as seen in non-fibrotic HP as well as giant-cell reactions with cholesterol-like clefts or oxalate crystals. The latter, in particular, can be easily misinterpreted as aspiration-related [231 , 236 – 238].

Depending on clinical progression or the disease stage, the predominant or sole histopathological pattern of cellular or fibrotic NSIP or of UIP may be detectable [231 , 236 – 238]. An autopsy study showed that granulomas, in particular, may also be completely absent in fibrotic HP. Compared to IPF, with the histopathologic hallmark of a UIP pattern, fibrotic HP also has lung areas with honeycombing in the lower lobes; in fibrotic HP, however, these are also found in the upper lobes and often are rather asymmetrically distributed [239]. Ultimately, distinguishing chronic fibrotic HP from other fibrosing lung diseases can be challenging. Particularly helpful is the detection of a

fibrotic NSIP pattern in combination with airway-centered fibrosis and features of non-fibrotic HP, especially granulomas [3].

If all these features are present, this is considered typical fibrotic HP. Without evidence of granulomas, this combination qualifies as probable fibrotic HP. If only fibrotic interstitial pneumonia, in particular fibrotic NSIP, is present, this is considered indeterminate for HP, while fibrotic HP is still a possibility (see Table 8) [3]. In principle, the differential diagnosis with regard to other fibrotic ILDs with a fibrotic NSIP pattern or UIP pattern may be difficult, especially if clinical or radiologic information is insufficient or not available at all. Question 7: Shall patients with newly diagnosed ILD and suspected HP be categorized into the “non-fibrotic” and “fibrotic” HP phenotype in the context of lung tissue histopathology? Recommendation R7 1. The histopathology assessment of ILD should provide information on whether characteristic features of non-fibrotic or fibrotic HP are present and whether these would be considered typical or probable pattern of non-fibrotic or fibrotic HP.

In fibrotic HP, the assessment should include the weighting between non-fibrotic and fibrotic HP features

Histopathology of fibrotic HP (modified based on [3])

Architectural distortion, fibroblastic foci±honeycombing (also in the upper lobes, often asymmetrical)

±Peribronchiolar metaplasia (syn. Lambertosis)

±Bridging fibrosis (fibrosis that spans centrilobular and perilobular regions)

Patchy poorly formed nonnecrotizing granulomas

Features that should not be found as they may suggest an alternative diagnosis, are

Numerous, well-formed sarcoidal granulomas or necrotizing granulomas

Inhalation provocation testing is usually not necessary in clinical practice. Inhalation provocation testing may be indicated if the diagnosis of HP cannot be established with certainty using other diagnostic tests, if costly antigen avoidance, e.g., change of residence or place of work, would be necessary, and for drawing up an expert opinion (occupational disease) or for research reasons (confirmation of a new antigen or antigen source) [240]. Inhalation provocation tests are performed as follows [240 , 241]: 1. In the form of re-exposure under actual, real-life conditions (e.g., at the workplace);

In the form of life- or workplace-like provocation in the laboratory (e.g., using hay provided by the farmer) or

As provocation with extracts of the suspected substances in the laboratory (e.g., with *A. fumigatus*)

In the largest retrospective study investigating inhaled provocation testing with various inciting antigens, sensitivity was reported at 73%, specificity at 84%, PPV at 94% and NPV at 47% [242]. In another retrospective study by the same working group, which only included patients with suspected HP caused by bird dust, sensitivity was as high as 92%, specificity was 100%, PPV 100% and NPV 80%. However, the specific inhalation test itself had in some cases been used to diagnose HP [168]. In another smaller retrospective study from Japan, a sensitivity of 93% and a specificity of 95% were established [243]. A negative test result, therefore, does not definitely rule out HP and a positive result provides very strong evidence of HP. Most experience with hay dust

provocation is available for acute HP [240 , 244]. However, provocation testing can also be done in chronic HP [245 , 246]. Sustained severe negative effects on the progression of HP were not observed; in some cases, an oral corticosteroid or oxygen had to be administered temporarily when a positive response developed [168 , 243 , 245 – 247]. For chronic bird fancier's lung, a history of keeping or breeding birds or obvious exposure to birds were strong predictors of a positive provocation test result. A drop in the FVC by >16% and in oxygen saturation (SpO₂) by 3% or in partial pressure of oxygen (PaO₂) by 3 mm Hg and an increase in body temperature of >0.5°C are reliable indicators of a positive provocation result [245 , 247].

In patients with acute HP and a newly suspected source of antigen, the diagnosis of HP and of the antigen source could be confirmed by inhalation provocation testing [112]. It should be noted that, in addition to a typical late response with general symptoms, a restrictive ventilation and diffusion disorder consistent with HP, a sole obstructive ("asthmatic") immediate response as well as a combined "asthmatic and alveolitic" reaction may be possible in the context of hay dust provocation testing [248]. It is also possible that only a systemic reaction (ODTS-like) will occur [240].

Due to procedure- and assessment-related complexity as well as the duration of the over time, inhalation provocation testing should not be done in an outpatient setting, but only as an in-hospital procedure at a sufficiently experienced institution.

There are no standardized or validated inhalation provocation tests [168 , 241 , 242 , 245 , 246 , 249]. Due to the lack of standardization and validation of the antigen preparations and lack of a standardized provocation method, the American guideline does not recommend inhalation provocation testing for the diagnosis of HP [4]. In Germany, an S2k guideline describing workplace-related inhalation testing provides information on the test procedure [250]. Question 8: Shall inhalation provocation testing be performed in patients with suspected HP? Recommendation R8 1. If the patient has clinical symptoms indicative of acute HP and an obvious antigen source or antigen has been identified, inhalation provocation testing can be performed in centers experienced in this test, if the diagnosis cannot be confirmed with the other steps of the diagnostic process, e.g., also for the first time confirmation of a new antigen source or a new antigen

Provocation testing should not be performed if there is a clinical suspicion of chronic, and in particular of chronic fibrotic HP and an obvious antigen source or antigen has been identified

Antigen avoidance is an option if a specific antigen or antigen source is suspected of inciting the condition. Following an elimination period with avoidance of a possible place of exposure (e.g., workplace, home) and the associated normalization of initially pathological parameters, the patient can be re-exposed to the suspected environment under controlled conditions (avoidance and re-exposure test).

If antigen sources are obvious, e.g., birds, indoor misting fountains or down feathers, re-exposure is not necessary, and documentation of the normalized parameters is sufficient [89]. However, only retrospective study data are available regarding the value of antigen avoidance. Most of these studies investigated the development of lung function under antigen avoidance [64 , 251 – 253]. One study reported a sensitivity of 51% and a specificity of 81% after 2 weeks of antigen avoidance in patients with chronic HP [64]. Others studies reported improved clinical symptoms under antigen avoidance alone [152 , 253 – 255]. Clinical improvement was observed in 41% of cases of chronic fibrotic HP and in 52–100% of cases of acute or non-fibrotic HP. Question 9: Shall antigen avoidance testing be performed in patients with suspected HP? Recommendation R9 1. If a patient has clinical symptoms indicative of acute HP and an antigen source or antigen is obvious, antigen avoidance testing should be done for diagnosis, if the antigen (source) has not been confirmed in the other steps of the diagnostic process

Clinical and/or functional improvement under antigen avoidance should be considered in making a HP diagnosis, whereby the relevance in patients with suspected acute or non-fibrotic HP is higher

than in those with chronic or fibrotic HP

Lack of clinical and/or functional improvement under antigen avoidance alone does not exclude the diagnosis of HP.

The diagnosis of HP is based on evidence of exposure (medical history), sensitization (specific IgG antibodies and/or BAL lymphocytosis), and presence of ILD (characteristic morphology in HRCT and/or biopsy). The diagnosis is, therefore, made using a combination of diagnostic criteria as no single finding is able to prove the diagnosis of HP beyond doubt. These diagnostic criteria were not prospectively validated. Their diagnostic accuracy, therefore, remains undetermined.

In acute HP, individual criteria were examined for their predictive value. The probability of HP in patients with obvious antigen exposure (e.g., farmers, bird fanciers), for example, who have a typical medical history in terms of exposure-related symptoms, positive antigen-specific IgG antibodies, and inspiratory crepitations on auscultation is 97%. If antigen exposure is not obvious, the probability drops to 62%, and in the absence of further criteria to below 50% [18]. This underlines the crucial importance of a detailed patient history to identify antigen exposure if HP is suspected based on clinical symptoms. Standardized questionnaires can be used for this purpose [135].

Taking into account the aforementioned findings, a European recommendation for diagnosis of both acute and chronic HP was published based on the German diagnosis criteria [1 , 2]. Although these criteria had originally been developed for occupational HP, they can be generally applied.

In addition to a combination of diagnostic criteria, diagnostic algorithms for HP were also described [256]. In a recently published international guideline, a diagnostic algorithm based on diagnostic criteria was published expert consensus [3]. In particular, the diagnostic algorithm emphasizes the importance of a multidisciplinary discussion of findings, in line with the approach used in other ILDs. The different combinations of findings result in different probabilities of the HP diagnosis: definite HP, high, moderate, or low confidence of HP, or HP cannot be excluded. The criteria and their significance for an acute or chronic, or for a non-fibrotic or fibrotic form were not evaluated separately. These different levels of diagnostic probabilities would cause problems, especially in the expert assessment of HP (occupational disease according to No. 4201). For example, invasive diagnostic procedures (BAL and/or lung biopsy) would always have to be performed in any case even if there is "high probability," even in acute HP.

It is, therefore, recommended to apply separate criteria for the diagnosis of acute or non-fibrotic HP and for chronic fibrotic HP (Table 9). This is based on the above-mentioned European diagnosis recommendations [2]. Contrasting with these European recommendations, it was specified, however, that a BAL lymphocytosis $\geq 30\%$ is required, as it provides the best differentiation between HP and IPF, especially in chronic fibrotic HP. In addition, the criterion of reduced DLCO and/or resting or exercise-induced hypoxemia was omitted for chronic fibrotic HP as it is not specific for chronic fibrotic HP, but is found in all fibrotic ILDs. The criterion of positive inhalation provocation test and/or antigen avoidance test was also omitted for chronic fibrotic HP as the guideline group does not recommend inhalation provocation testing in chronic fibrotic HP (see Inhalation Provocation Testing section) and considers antigen avoidance testing to be of limited relevance in chronic fibrotic HP (see Antigen Avoidance Testing section). Ideally, the diagnosis should always be determined in the context of the multidisciplinary ILD conference.

Diagnostic criteria for acute or non-fibrotic and chronic fibrotic HP

Recurrent symptomatic episodes, starting four to 8 h after exposure

Elevated specific IgG antibody titer against a potential antigen

Inspiratory crackles at clinical examination

HRCT findings consistent with inflammatory HP

If these 5 criteria are met, diagnosis of acute HP is confirmed. If not all of these criteria are met, the following invasive criteria can be used as a substitute

Evidence of lymphocytosis (>30%) in BAL fluid

Histopathological findings typical of or probable for acute or non-fibrotic HP on lung biopsy

Positive inhalation provocation test/re-exposure test or positive antigen avoidance test

Elevated specific IgG antibody titer against a potential antigen and/or lymphocytosis (>30%) in BAL fluid

HRCT findings consistent with fibrotic HP

Histopathologic findings of typical of or probable for chronic fibrotic HP on lung biopsy

The diagnosis of chronic fibrotic HP is confirmed if at least three of the above criteria are met

Patients with acute HP are often treated for suspected or recurrent respiratory tract infections or influenza. This is true especially for the rare cases of acute HP in children.

It is important to differentiate acute HP from toxic alveolitis (ODTS = organic dust toxic syndrome). ODTS is caused by endotoxins from the cell walls of gram-negative bacteria or by mycotoxins, and similar to acute HP, is characterized by a fever reaction approximately 3–12 h after inhalation of organic dusts, while there is usually no evidence of elevated specific IgG antibodies, no pulmonary dysfunction and no pathological chest X-ray [257 , 258]. ODTS is a non-infectious, febrile illness associated with cough, bronchial hyperresponsiveness, mild dyspnea, headache and general malaise [259]. The syndrome is also called “threshing fever” in farmers and “humidifier fever” in people exposed to humidifiers [260].

Infectious (mycobacteriosis, histoplasmosis) and non-infectious (sarcoidosis) granulomatous lung diseases also need to be taken into consideration.

Other important differential diagnoses are drug-induced parenchymal lung diseases (www.pneumotox.com) and lung damage induced by inhaled noxious agents, e.g., silo-filler's disease [261 , 262], popcorn lung [263], Ardystil syndrome [264], or nylon-flock-associated ILD [265].

A variety of ILDs must be considered in the differential diagnosis of chronic EAA, e.g., lymphoid interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), cryptogenic OP, idiopathic NSIP, asbestosis, and others. Particularly in chronic fibrotic courses of HP, differentiation from other chronic fibrotic ILDs, especially IPF, can be difficult [24 , 266]. Pulmonary manifestations from autoimmune diseases must also be distinguished [267].

The difficulty of diagnosing HP correctly is shown in an article on the multidisciplinary team meeting agreement on diagnosis of ILDs including IPF and HP. Good agreement was reached for the diagnosis of IPF ($\kappa = 0.79$), while the agreement for HP was significantly lower ($\kappa = 0.29$) [266].

Acute episodes are usually self-limiting after antigen avoidance, which is why the timely, definite diagnosis of HP and, above all, identification of the triggering antigen, or at least the most likely

inciting antigen source, is of utmost importance. In some cases, antigen avoidance can be quite simple (e.g., removing indoor fountains, birds, down feathers), but may be almost impossible to implement in other cases (e.g., patients living in an agricultural environment).

Temporary drug therapy with oral corticosteroids can accelerate convalescence, as shown in a randomized study [268 – 270]. Although the same functional improvement was seen after 12 months of antigen avoidance, it was achieved significantly faster with corticosteroids. Ultimately, the decision for or against corticosteroids depends on the initial severity of clinical symptoms and functional impairment [271]. Evidence-based studies are lacking, and the therapy is often initiated with 0.5 mg/kg of body weight or 40 mg prednisolone-equivalent per day, similar as recommended for sarcoidosis, and then slowly tapered over e.g., 2–3 months and finally discontinued.

The use of other immunomodulators in acute HP has not yet been sufficiently investigated. If corticosteroid therapy is contraindicated (e.g., severe osteoporosis, type I diabetes mellitus), immunomodulator monotherapy might be considered based on expert assessment of the individual case. However, corticosteroid therapy generally is not a replacement for antigen avoidance.

Antigen identification and, above all, antigen avoidance are also of prognostic importance for patients with chronic HP [72 , 272]. Based on the consideration that chronic HP may respond to anti-inflammatory therapy if there is evidence of a relevant inflammatory component, the following diagnostic indicators provide the basis for further decisions regarding drug therapy: HRCT with centrilobular nodules or ground-glass opacities, BAL with lymphocytosis, histopathology with lymphocytic infiltration (NSIP-like) or epithelioid cell granulomas [14]. Another study showed that rapid clinical progression, subfebrile temperatures, typical signs of inflammation (laboratory parameters), inflammatory activity on HRCT, BAL lymphocytosis, and patterns of high inflammatory activity in the biopsy support the initiation of an anti-inflammatory therapy [273]. Based on the evidence available to date, purely fibrotic HP is unlikely to respond to anti-inflammatory therapy, which eventually could even negatively affect the prognosis [274].

The recommendation to attempt treatment with corticosteroids for a limited period of time and, if necessary, to use additional corticosteroid-sparing immunosuppressants (e.g., azathioprine, mycophenolate mofetil), if the patient responds to the therapy, is based on retrospective study data only [14 , 275 , 276]. The recommended maximum initial prednisolone dose is 0.5 mg/kg of body weight. The treatment goal of this approach is to improve the clinical and pulmonary function and/or chest X-ray findings, which should be verified ideally after 4–6 weeks. If the goal of improving or at least stabilizing the condition is not reached, the treatment approach must be reconsidered to avoid the side effects of an ineffective immunosuppressive therapy. If the patient responds to the therapy, a gradual dose reduction over 2–3 months to a maintenance dose of <10 mg/d should be aimed for, and this dose should be continued for at least 6 months.

Rituximab therapy, especially for refractory cases, was reported in small case series, and no recommendation can be derived from these studies [277 , 278]. If the above-mentioned signs of inflammation are lacking in chronic fibrotic HP, anti-inflammatory therapy is not a promising approach and it needs to be verified, if the indications for antifibrotic therapy as applied in progressive pulmonary fibrosis (PPF) are met [6]. If this is the case, this therapy should be initiated eventually without additional immunosuppression. It was shown that in patients with (critically) shortened leukocyte telomere lengths, immunosuppression is associated with an unfavorable course and increased mortality [279]. However, it is not (yet) possible to determine telomere length in clinical routine context.

The INBUILD study included various entities of chronic progressive fibrosing ILDs and demonstrated the efficacy of nintedanib in delaying disease progression as measured by FVC. Patients with HP were the largest subgroup (26%) in this study [280 , 281]. Nintedanib is approved for use in progressive fibrosing ILDs, including chronic progressive fibrosing HP. The efficacy of nintedanib was not affected by concomitant therapy with immunomodulators [282].

There is also evidence that antifibrotic therapy with pirfenidone delays the progression of the disease in this indication. In the relevant study, HP comprised nearly half (45%) of a study population of various chronic progressive fibrotic ILDs [283]. Other studies also found evidence supporting the efficacy of pirfenidone in chronic fibrotic HP [284 – 286]. However, pirfenidone is not approved for this indication.

If the characteristic features of fibrosis are not clearly dominant (see above), anti-inflammatory therapy should be chosen as the primary therapy with the aim of improving the symptoms. If marked but not dominant signs of fibrosis are present, combined anti-inflammatory and antifibrotic therapy can be initiated either simultaneously or in short sequence to stabilize the disease. This should be verified by monitoring the patient's clinical condition and lung function. As a general rule, the S2k Guideline of the German Respiratory Society for the Pharmacological Treatment of Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis can be consulted in this regard [6].

If the disease continues to progress despite the chosen therapeutic approaches, lung transplantation should be evaluated as a treatment option. Post-procedural survival was significantly superior to that of patients with IPF (HR 0.25). In rare cases, HP may re-occur in a donor lung after transplantation. This underlines the importance of a correct diagnosis of a fibrosing lung disease and the consecutive potential and necessary allergen avoidance [287]. Ideally, all treatment decisions should be made in a multidisciplinary ILD team meeting. Question 10: Shall HP patients be treated with anti-inflammatory drugs? Recommendation R10 1. In patients with acute or non-fibrotic HP, antigen avoidance shall be implemented as a first-line measure, if the inciting antigen is known

Patients with acute or non-fibrotic HP and moderate to severe clinical symptoms and functional impairment should be treated with corticosteroids in addition to antigen avoidance

Patients with chronic fibrotic HP shall be treated with anti-inflammatory drugs if there is evidence of a relevant inflammatory component

Antigen avoidance shall be implemented in patients with chronic fibrotic EAA if the inciting antigen is known

Patients with chronic fibrotic HP of a progressive phenotype shall be treated with nintedanib

Patients with chronic fibrotic HP of a progressive phenotype should be treated with pirfenidone (note: off-label), if treatment with nintedanib has proven to be insufficiently effective or has been discontinued due to side effects

Patients with chronic fibrotic HP of a progressive phenotype shall be evaluated for lung transplantation at an early stage, as necessary

Preventive measures have a high priority in the management of HP [288]. For specific risk populations (e.g., farmers), adjusting working conditions can have a primary preventive effect. This includes the targeted education of farmers, in particular regarding the prevention or reduction of antigen formation or exposure, the conversion from hay to silage feeding and from straw bedding to liquid manure management [289]. Secondary preventive measures such as the use of protective respiratory devices including FFP2 masks can be implemented, but are definitely not a substitute for antigen avoidance [290 – 293].

HP tends to have a very good prognosis, if it is diagnosed timely and if the inciting antigen is identified. Data on the prognostic relevance of antigen avoidance are inconsistent. In a retrospective analysis of 116 (acute and chronic) HP patients, no survival benefit was found in 116 patients with antigen avoidance, taking into account the patients' age, gender and initial FVC (in %)

(HR 1.29; 95% CI: 0.57–2.93) [274]. In another study, however, significantly reduced mortality was seen after antigen avoidance (HR 0.18; 95% CI: 0.04–0.77) [253]. Also, the type and number of antigen(s) in patients with identified causative antigen(s) does not seem to affect transplant-free survival [131]. The intensity of persistent antigen exposure is relevant for the progression of the disease [64 , 131]. In chronic fibrotic HP, failure to identify the inciting antigen has been shown to be an independent predictor of poorer survival [72 , 294].

Lung function is also a relevant prognostic factor. A decreased FVC at baseline and an FVC decline of $\geq 10\%$ within 6–12 months were predictors of increased mortality [253]. In chronic HP, DLCO ($< 50\%$ predicted) and SaO₂ during exercise were independent predictors of survival [295 , 296].

In HP, radiologic evidence of pulmonary fibrosis per se, the extent of pulmonary fibrosis, and especially the presence of traction bronchiectasis and honeycombing is associated with a poor prognosis, whereas a mosaic pattern or air trapping points to superior survival [266 , 297 – 301]. If honeycombing affects only one or two lobes, the fibrotic phenotype has a significantly better prognosis than IPF (median survival for fibrotic HP: 8 years vs. IPF: 5.2 years). When honeycombing is found in all five lobes, the median survival in fibrotic HP is similar to that of IPF at only 2.8 years [302]. In a retrospective analysis of 101 patients, reticulations and ground-glass opacities were found to be independent predictors of mortality, in addition to a fibrosis score [303].

Lymphocytosis in BAL in fibrotic and non-fibrotic HP is associated with a better prognosis and response to immunosuppressive therapy [274 , 304 , 305]. Histopathological evidence of pulmonary fibrosis is also associated with a poorer survival [300 , 301 , 306]. In particular, patients with a histopathologic pattern of UIP or a fibrotic NSIP pattern have the worst survival [206 , 300 , 301 , 307].

Evidence of pulmonary hypertension is associated with significantly reduced survival, as shown in a retrospective analysis [197]. In a prospective study [199], pulmonary hypertension was identified by right heart catheterization in an even larger percentage of patients with chronic HP than in the aforementioned retrospective analysis (43% versus 19%).

In chronic HP, as in IPF and other fibrotic ILDs, acute exacerbations may occur, which are associated with a high mortality rate [194 – 196 , 308]. Recent data suggest that antigen exposure, younger age and reduced lung function results are associated with an increased risk of acute exacerbation [308]. Antinuclear antibodies can be detected in 10–20% of HP patients and are associated with a poorer prognosis [309 , 310].

Variants in the telomere-encoding genes associated with short telomere length in peripheral blood have recently been identified and linked to a significantly reduced transplant-free survival [57]. The minor T allele in the MUC5B gene polymorphism was also found to be associated with the extent of pulmonary fibrosis in HRCT and shorter survival [56]. Similar to IPF, genetic molecular diagnostic tests have been shown to be increasingly important to assess mortality and disease progression in HP, but validation studies are needed.

Finally, various biomarkers such as KL-6 or YKL-40 in serum are associated with disease progression and increased mortality; CCL17 in serum is only associated with disease progression [164 , 311 – 313]. However, no biomarker has yet been validated for clinical-routine use.

HP is included in the German list of occupational diseases (Berufskrankheiten, BK) (BK number 4201) with the legal definition of “HP” (Exception: Isocyanate alveolitis (which is very rare) is covered by BK number 1315). Doctors are obligated to report any illness reasonably suspected to be of occupational origin to the German Statutory Accident Insurance or to the state-certified occupational physicians (responsible governmental officers). The duty to report overrides the medical confidentiality obligation. Full proof of the disease is required for recognition as an occupational disease.

In Austria, HP is included in the occupational disease list as number 1.8, formerly number 43, with the following legal definition: "Hypersensitivity Pneumonitis presenting with objectively measured loss of lung function, provided the antigen identified as causal is objectively identifiable and has had a decisive influence during insured employment." In Switzerland, HP is recognized by the SUVA (Swiss National Accident Insurance Fund) pursuant to Article 9, Section 1 of the Accident Insurance Act.

The following applies under the German Social Accident insurance Act: If there is concrete evidence that an insured person is at risk of developing an occupational disease, if there is a risk of recurrence or deterioration of an occupational disease, accident insurance institutions have a duty to mitigate this risk through all suitable means (Paragraph 3 of the Occupational Diseases Regulation (Berufskrankheitenverordnung), the so-called "prevention paragraph"). If the specific risk cannot be eliminated, efforts must be made to discontinue the harmful activity. Paragraph 3 applies in particular if the development of an occupational disease is imminent, and there is not yet a claim for benefits. The hierarchy of preventive measures follows the STOP principle: substitution measures (e.g., replacing feeding with (potentially moldy) hay by silage feeding), technical measures (e.g., installation of extraction devices), and organizational measures (e.g., redesigning the workplace or work processes) have priority over personal protective measures. The latter include primarily fan-assisted breathing devices. The costs of these measures as well as the costs of filters are covered by accident insurance in the case of an impending occupational disease.

Between 1999 and 2022, an average of 112 suspected HP cases per year were reported to the German Statutory Accident Insurance for the industrial sector and to public sector occupational accident insurance funds, of which an average of 17 cases per year were recognized as occupational disease (recognition rate 6–25%) (data from the BK-Dokumentation 2023 of the DGUV). A total of 1,158 suspected cases of BK 4201 were reported to the Social Insurance Fund for Agriculture, Forestry and Horticulture (SVLFG) between 2011 and 2022 (mean = 97 cases/year). During this period, 304 cases were recognized as BK 4201 (mean = 25 cases/year, corresponding to a recognition rate of 26%) (information from the basic data SG, BK-Dokumentation, SVLFG). Microbial antigens are listed as the most common triggers in both the commercial and agricultural sectors (more than 50% of cases).

The symptoms of occupational HP do not differ from those of other causes, but the timing of the symptoms may vary depending on the occupational circumstances. When acute symptoms are triggered by a workplace-related antigen, the onset of symptoms is usually at/after the end of a work shift and symptoms will have improved by the end of a time off. In contrast, chronic HP induced by a workplace-related antigen often has no definite pattern associated with short periods off work. A precise medical history based on occupation and exposure is of the utmost importance for identifying a suspected occupational factor in the first place. Pathophysiology and basic diagnostic procedures (serology, lung function, radiology) as well as exposure testing and possibly histopathology are the same for occupational and non-occupational types of HP.

Independent consensus-based recommendations for the expert assessment of HP as an occupational disease are not available. However, the Falkenstein Recommendation (recommendation for the expert assessment of asbestos-related occupational diseases) is available as a reference base to assess a reduction in earning capacity (Minderung der Erwerbsfähigkeit, MdE) for predominantly restrictive phenotypes of the disease, and the Reichenhall Recommendation (recommendation for the expert assessment of professional illnesses numbers BK 1315 (without alveolitis), BK 4301, and BK 4302) can be applied for obstructive or emphysematous phenotypes.

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