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The association between fungi exposure and hypersensitivity pneumonitis: a systematic review

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Abstract

A systematic review of published studies focused on the association between hypersensitivity pneumonitis (HP) and fungi exposure was conducted on PubMed, following PRISMA guidelines for systematic reviews. A total of 14 studies met the inclusion criteria but only 6 of these studies were eligible, as the remaining 8 represented case reports that were separately included for further discussion. HP is an interstitial lung disease (ILD) characterized by a hypersensitization response to inhalable antigens and represents 1.5% to 12% of all ILD in the European population. Several fungi species that populate the indoor environment have been associated with the incidence of HP upon cumulative exposure, with *Penicillium* spp and *Aspergillus* spp being the fungi species most frequently associated with the onset of disease. Although some studies have shown that avoiding exposure to causative HP fungi tends to improve patients' symptoms, other studies were unable to identify the source of sensitization. More microbial exposure studies are needed to properly estimate the risk of HP development in the built environment.

Keywords: fungi, hypersensitivity pneumonitis, interstitial lung disease, occupational environment, residential environment

Introduction

Hypersensitivity pneumonitis (HP), also known as Extrinsic Allergic Alveolitis, is a common interstitial lung disease (ILD) characterized by a hypersensitization response to inhalable antigenic particles, commonly present in the environment. These antigens cause an immunological reaction in these individuals, resulting in parenchymal and small airways inflammation.[1,2] European population registries report that HP incidence represents 1.5% to 12% of all ILDs.[3]

HP has traditionally been classified into acute, sub-acute and chronic forms based on the time course and the presentation. But a more recent classification, based on clinical, radiologic and pathologic characteristics, into Acute or Inflammatory HP (symptoms last than 6 months) and Chronic or fibrotic HP, has been proposed.[1,4]

Acute HP typically presents with fever, malaise, cough with or without phlegm, chest pain and dyspnea within a few hours of heavy exposure to a specific antigen. However, long exposure to the sensitized antigen can result in subacute and chronic forms of the disease.[3] The subacute form presents symptoms such as asthenia, low-grade fever, weight loss, dry and/or productive cough, or exercise-induced dyspnea developed over a period of weeks or months.[5] The inflammation occurs especially in the airway because the injury is caused by inhaling a specific antigen.[6] The chronic form is characterized by grade III/IV dyspnea according to the New York Heart Association with or without current or previous antigen exposure,[7] and the occurrence of fibrosis which is detected by computed tomography or lung biopsy.[5] Around the bronchioles, sparse poorly formed and non-caseating granulomas and chronic inflammation with variable amounts of fibrosis can be observed.[3]

The diagnosis of HP requires a high index of suspicion on the part of the clinician and should be considered in any patient who presents clinical evidence of ILD. The diagnostic steps should include a complete and targeted evaluation of the patient's history, seeking to identify exposures and, requires a consistent radiological and bronchoalveolar lavage (BAL) features, sometimes with a lung biopsy in dubious cases within a likely exposure context. In addition, the determination of specific IgG antibodies and a specific inhalation challenge (SIC) can be useful to identify the responsible antigen.[1,4,8–10]

More than 300 antigens have been described to cause HP and can be classified into bacteria, fungi, animal and plant proteins, low molecular weight chemicals, and metals.[11] These exposures often occur in specific occupations or hobbies such as agriculture, but could also occur in the home environment. It's important to consider the complex interplay between host genetic factors and environmental agents because only a small proportion of the people who are exposed to these antigens develop HP.[8]

As previously mentioned, HP is most frequently caused by bird proteins (pigeon breeders' disease or bird fancier's HP) and microbiological agents (farmer's lung disease, FLD).[12] Regarding the first, regular exposure to avian proteins from droppings, feathers and blooms (white powder that coats the feathers) may cause the disease in sensitized individuals.[13]

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On the other hand, FLD is often caused by thermophilic actinomycetes, such as *Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris, Thermoactinomyces viridis,* and *Thermoactinomyces sacchari*. Patients are frequently exposed to these microorganisms when in contact with hay, straw or grain dust stored in conditions of high humidity in the agricultural workplace, thus the term "farmer's lung disease".[14] However, a variety of fungal antigens have also been implicated in various forms of occupational HP, including *Alternaria alternata, Aspergillus* spp, and *Penicillium* spp, along with other molds and mushrooms.[12,15] It's believed that airborne spores and mycelial elements produced by fungi, contribute significantly to HP.[16–18]

Molds are present in various places in the indoor environment such as ventilation systems, humidifiers, heaters, but also in fruits and vegetables, and may vary in etiology according to the region of exposure. For instance, Japans's summer-type HP is caused by *Trichosporon cutaneum*, which are present in wood houses with high humidity and temperature leading to optimal fungal reproduction.[19,20] Another example is suberosis, a particularly concerning subtype of HP first identified in Portuguese cork workers that is caused by continuous exposure to fungi present in cork dust.[15,21] Despite having similar pathophysiological mechanisms, Morais et al showed that suberosis differs from other subtypes of HP not only in terms of etiology, but also in inflammatory response dynamics in the lung, suggesting that special attention should be given to fungi-triggered HP phenotypes, especially in regions, environments or occupations where fungi exposure is significant.[22]

Therefore, it is important to compile the available information regarding HP caused by fungi exposure to either residential and occupational environments. Hence, we aimed to systematically review published studies focused on fungi as causative agents of HP onset and/or exacerbation.

Methods

A systematic search was performed until the 25th of March 2020 in PubMed, according to PRISMA guidelines.[23] The search was conducted through the combination of the keywords HP, in combination with any term originated from fungus or indoor air quality (search term for PubMed database: "hypersensitivity pneumonitis"[Title/Abstract] AND ("fungi"[Title/Abstract] OR "fungus"[Title/Abstract] OR "mold"[Title/Abstract] OR "dampness"[Title/Abstract] OR "indoor air quality"[Title/Abstract])). Published peer-reviewed full-text articles in English concerning the risk assessment of fungi on HP development and/or exacerbation were assessed for eligibility. The inclusion criteria for qualitative synthesis were as follows: (a) original study in English; (b) the study was focused on HP; and (c) the study assesses the impact of fungi exposure on the disease.

Clinical cases were not considered eligible since they usually included limited sample sizes and thus the resultant observations may not be extrapolated. Nevertheless, and since there are still very few studies concerning the subject, these clinical cases were discussed in a separated section to provide further insight on the relation between fungi and the disease. The studies selection processed is depicted in Figure 1, according to the PRISMA guideline.[23] Information regarding study objectives, fungi species, type of study, as well as the main outcomes, were collected and are now summarized in the following section.

Results and discussion

As a result of this research method, 73 articles were retrieved from PubMed. In order to keep only 1 copy of each article, the eventual presence of duplicates was scrutinized and it was verified that there were none. Afterwards, it was verified if the 73 articles met all the following inclusion criteria: to be an original article, being focused on HP, the article mentions fungi or humidity problems (dampness or mold) and, finally, the article studies fungi as a risk factor for HP. After applying the inclusion criteria, only 14 articles were assessed for eligibility. Lastly, after applying the exclusion criteria (being a clinical case) just 6 studies were eligible for the qualitative synthesis. Nevertheless, since all the information on the topic could be essential to further scrutinate the association between fungi and hipersensitivity pneumonitis, the 8 clinical cases were included for further insights, as shown in Figure 1.

The following tables summarize the inferences drawn from each analyzed article. Table 1 shows the 6 eligible studies and Table 2 shows the 8 case reports.

Research studies

Several studies have shown that people who are exposed to fungi have a higher risk of developing HP.[5,24–27] Moreover, the most frequently identified fungi species reported to cause HP were *Penicillium* spp and *Aspergillus* spp.[5,24,28]

Eligible studies either identified fungal species through specific biomarkers in human matrices, such as BAL,[5,25,27] or tested HP patients for fungal sensitivity (eg, by using SICs).[5,26,28]

A case-control study performed in Japan demonstrated that BAL collected from patients with home-related HP contained fungal DNA.[27] In addition, they showed that home-related HP may be caused by *Trichosporon asahii* or *Trichosporon mucoides*, and even if some patients with home-related HP test negative for antibodies against *Trichosporon*, other fungal species might be causative for the disease, including *T japonicum, C uzbekistanesis, and F napiforme.*[27]

In another example, a comparative study published in 2014 used antigen-SIC for the identification of fungal sensitivity in HP patients.[5] This study showed an increase in sputum neutrophils and eosinophils following exposure to the offending antigen during SIC in patients with HP, which indicates a presence of bronchial inflammation caused by the exposure to birds or fungi allergens, such as those from *Penicillium frequentans, Aspergillus fumigatus* or *Mucor mucedo*.[5]

Additional evidence regarding SIC as a method to diagnose HP were identified during the systematic review. As another example, a cohort study, also published in 2014, evaluated the health symptoms and lung function of 10 workers exposed to mold in a Norwegian sawmill, to assess the relationship between HP and mold spore exposure.[26] This study showed that, in the long term, the decreased *Rhizopus microsporus* exposure was associated with symptoms cessation and restored lung function.[26] In the same year, Muñoz et al performed another study where they used *P frequentans, A fumigatus* and *M mucedo* to determinate the sensitivity and specificity of SIC in HP diagnosis, corresponding to 72.7% and 84.0%, respectively.[28] Although a promising result for HP diagnosis has been obtained, efforts should be made to standardize the way in which SIC is performed, particularly when the suspected causal agent does not consist in avian or fungal proteins.[28]

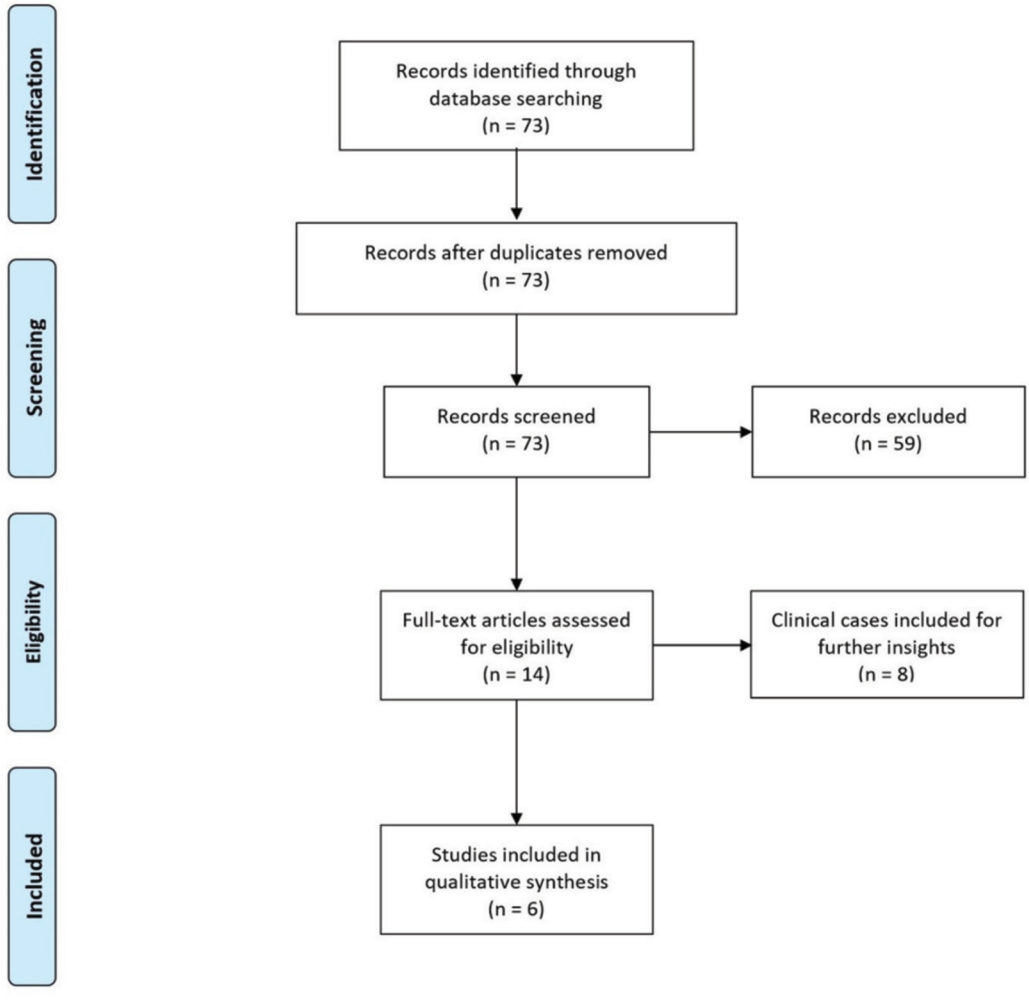

Figure 1. PRISMA flow chart.

Although there are no standardized consensus regarding the prevention of HP, a study published in 2016 by Bellanger et al showed promising results in this regard.[25] The study demonstrated that the protein dihydrolipoyl dehydrogenase (DLDH) from microorganisms involved in HP, such as *Lichtheimia corymbifera*, could be useful to develop an effective prevention strategy. For instance, the overlapping peptide pools covering the DLDH protein from *Mycobacterium immunogenum* and *L corymbifera* can induce specific recall responses and IFN-γ immune response after stimulation of peripheral blood mononuclear cells from healthy blood donors.[25]

The fungi that cause HP can be present in several places and objects, such as musical instruments. A recent study, published in 2019, showed that respiratory disorders in musicians were potentially caused by fungi contamination present in wind instruments.[24] In this study, conducted by Soumagne et al, the authors identified many fungal species associated with HP, but the most frequent were *Rhodotorula mucilaginosa, Penicillium* spp, *Phoma* spp, *Eurotium amstelodami, Fusarium* spp and *Candida* spp.[24] The authors also concluded that it is difficult to evaluate the risk of HP caused by fungi, but revealing that musicians may be more susceptible to fungi exposure and the consequent HP development than the control population, due to wind instrument use.[24]

In conclusion, all the eligible studies showed that the prolonged exposure to fungi may sensitize the patient to these antigens and, consequently, increase the risk of HP development. Moreover, the most common fungal species to cause HP in these studies were *Penicillium* spp and *Aspergillus* spp. Finally, although a study showed promising results for preventing HP using peptides, the current consensus to prevent disease is to avoid exposure to risk antigens.

Case reports

Several case studies were identified through the systematic review. Since these case reports represent very limited observations, thus not allowing scientific assumptions to be studied, they were not considered as eligible for the present review. Nevertheless, due to the novelty and scarcity of studies concerning HP, these case reports will be briefly discussed to provide additional insight regarding the associations between HP and fungi exposure.

In 2011, a study was carried out on 5 patients who had HP due to exposure to dry sausage dust.[29] This study aimed to analyze the relationship between the clinical condition of patients and the exposure to inhalable antigen particles at work. Of the 5 patients, 3 of them developed an acute form of HP since they worked on fungi cleaning, representing a massive exposure to the allergens of

Table 1

Research studies about hypersensitivity pneumonitis and associated fungi triggers.

Reference	Year	Type of study	Purpose	Fungal species	Results
24	2019	Case control-study	To assess the current prevalence and type of fungal contamination of wind instruments; To identify potential risk factors associated with instrument contamination; To evaluate the prevalence of sensitization to these fungi among musicians.	*Phoma* spp, *Penicillium* spp, *Rhodotorula mucilaginosa, Eurotium amstelodami, Fusarium* spp, *Cladospotium* spp, *Aspergillius* spp, *Alternaria* spp, *Candida* spp, *Cryptococcus* spp, *Trichosporon* spp, Unidenitified white yeast, *Ulocladium* spp.	The current study demonstrated that fungal contamination of wind instruments containing a reed is frequent and specific. The risk of HP caused by fungi is difficult to evaluate. This study revealed greater sensitization of musicians against the fungi in instruments than control population. In view of this findings, it seems reasonable to recommend regular cleaning and systematic drying of the instrument after playing to reduce fungal exposure.
25	2016	Cohort study	To investigate the potential of overlapping peptide pools covering the MiDLDH and LcDLDH to induce specific recall responses and IFNγ immune response after stimulation of PBMC from healthy blood donors.	*Lichtheimia corymbifera*	This study demonstrated that peptides from microorganisms involved in HP were able to induce a high IFNγ specific immune response after stimulation of PBMCs from healthy blood donors which could be useful to develop an effective prevention strategy.
28	2014	Cross sectional	To establish the diagnostic yield of SIC in patients with hypersensitivity pneumonitis.	*Penicillium frequentans, Aspergillus fumigatus, Mucor mucedo*	The results of the present study showed that SIC could be useful in the diagnosis process of HP. It was also showen to be a safe test, with few adverse effects. Nonetheless, efforts should be made to standardise the way in which SIC is performed, particularly when the suspected causal agent is not avian or fungal proteins.
26	2014	Cohort study	To evaluate the health symptoms, work-related sick-leave, and lung function of 10 workers exposed to mold in a Norwegian sawmill.	*Rhizopus microsporus*	In spite of an initially high occurrence of symptoms, long-term clinical and physiological outcomes were satisfactory. With reduced exposure to mold spores, symptoms declined and lung function was restored
5	2014	Comparative Study	To compare the inflammatory profile before and after SIC in induced sputum from patients with HP and to investigate whether different causal antigens define the resulting profile.	*P frequentans, A fumigatus, M mucedo*	Bronchial inflammation was present in patients with HP, evidenced by increases in sputum neutrophils and eosinophils following exposure to the offending antigen during SIC.
27	2011	Case control-study	To detect fungal DNA in BALF cell pellets from patients with home-related HP.	*Trichosporon* spp, *Acremonium chrysogenum, A fumigatus, Aspergillus niger, Fusarium napiforme, Humicola fuscoatra, Penicillium corylophilum, Pezizia domiciliana*	Fungal DNA was detected in the BALF from patients with home-related HP. This method might be especially useful for patients with home-related HP with a negative antibody test to help identify a causative antigen.

BALF = bronchoalveolar lavage fluid, DLDH = dihydrolipoyl dehydrogenase, HP = hypersensitivity pneumonitis, IFNγ = interferon gamma, LcDLDH = DLDH protein from *Lichtheimia corymbifera*, MiDLDH = DLDH protein from *Mycobacterium immunogenum*, PBMC = peripheral blood mononuclear cells, SIC = specific inhalation challenge.

interest. The other 2 patients worked as a secretary and supervisor, developing a subacute form of disease. Hence, this report suggested that HP was caused by fungi, although it was not possible to identify which species were the main responsible agents for HP development and worsening. However, SIC suggested that the main fungi involved was *P frequentans*, thus supporting the aforementioned observations concerning the influence of *Penicillium* spp on HP.[29] The authors also verified that the clinical symptoms disappeared for the 3 patients who discontinued exposure, but for the 2 patients who did not avoid exposure and only used a protective mask, the clinical condition actually worsened. In conclusion, patients who had avoided the exposure to antigen had good prognosis but it was difficult to identify the causative agent.[29]

In another study, a clinical case of a 37-year-old man with HP identified the causative agent to be medium density fiberboard (MDF) material.[30] Initially, the authors hypothesized the disease to be caused by fungi present in the wood fiber, including *Candida* spp, *P frequentans* and *A fumigatus*. To identify the determinant of disease, several tests were performed such as wood cultivation and

Table 2

Case reports of patients with hypersensitivity pneumonitis caused by fungal species

Reference	Year	Fungal species	Results
36	2017	*A niger*	A case of HP caused by *A niger*. Although HP caused by *A niger* is not common, physicians should aware the possibility of pathogenic antigens of *A niger* because this pathogen is universally present in vegetables and fruits.
35	2017	*Phoma* sp, *Rhodotorula* sp, *Paecilomyces ilacinus, Fusarium* sp	HP is more common among wind musicians than previously thought. This study suggests that any type of wind instrument can be contaminated with microbes associated with HP.
34	2016	*Trichosporon asahii, Trichosporon mucoides*	A case of summer-type hypersensitivity pneumonitis developed in a patient with RA treated with immunosuppressive agents. The patient had serum antibodies against *T asahii*, a fungal pathogen. The mildew in her bathroom and washing machine which were the source of the fungus were removed, which resulted in no further relapse of the condition.
33	2015	*Fusarium vasinfectum*	The first reported case of fatal HP related to an acute exacerbation of a chronic form of HP following continuous and intense exposure to *F vasinfectum.* Although uncommon, a high index of suspicion for HP is necessary in patients with progressive respiratory symptoms and known environmental antigen exposure.
32	2014	*A fumigatus*	The study described a case of HP due to the inhalation of a variety of flours and their contaminant molds. HP in addition to asthma and allergic rhinitis should be suspected in bakers with respiratory symptoms.
31	2013	*Phanerochaete chrysosporium*	*P chrysosporium* was demonstrated to cause hypersensitivity pneumonitis in animal models. This case was the first documented report of *P chrysosporium* associated with granulomatous lung disease in humans. If, in the future, this organism is applied in a widespread fashion to degrade plastics, it would be important to recognize its potential as a human pathogen.
30	2011	*Candida* spp, *P frequentans, A fumigatus*	The cultivation of the wood was only positive for *Candida* spp. Excluding the fungal etiology of this HP, the cause of this disease it is the MDF material itself.
29	2011	*P frequentans, A fumigatus, M mucedo, Rhizopus nigricans*	A short patient series affected by a little-known cause of occupational HP is described. Altough *P frequentans* seems to be one of the main fungi involved in this cause of HP, a multifactorial origin cannot be ruled out, with other fungi such as *A fumigatus*, *M mucedo*, or *R nigricans* being implicated.

HP = hypersensitivity pneumonitis, MDF = medium-density fibreboard, RA = rheumatoid arthritis.

immunological tests. Although wood cultivation was positive for *Candida* spp, the immunological tests were negative for *Candida* spp, *P frequentans* and *A fumigatus*. Authors also performed a challenge test which was positive to sawdust from MDF and negative for *Candida* spp. In this particular case, results suggest that wood itself was the cause of HP in this patient and not the fungal species present in the material.[30]

In another example, Lanspa and Hatton reported a clinical case of a 50-year-old woman that had exertional dyspnea, diffusion impairment, and radiographic abnormalities.[31] Surgical biopsy of her lung tested positive for *Phanerochaete chrysosporium*, a fungus known to cause white rot in tree bark. This fungal species has been demonstrated to cause HP in animal models, but this case was the first documented report associated with granulomatous lung disease in a human. The authors believed that this patient's lung disease resulted of recurrent exposure to *P chrysosporium*, while gardening with rotting wood mulch, which may represent either fungal infection or subacute HP. In conclusion, a fungus that is normally seen as a harmless microorganism that is able to biodegrade phenolic resin plastic, showed to be a human pathogen.[31]

In 2014, a case report of non-smoker 30-year-old female emerged with progressive dyspnea on exertion and dry cough for 3 months.[32] She had been working as a baker for 8 months and was exposed daily to wheat and oat flours while making bread. When she was away from work symptoms improved. A diagnosis of HP related to molds and mites contaminating cereal storages and baker's flours was made, being confirmed by strongly positive precipitins against *Aspergillus* spp and a flour mite (*Acarus siro)*. Hence, the immunological tests confirmed that this case of HP resulted from the inhalation of a variety of flours and their contaminant molds and mites.[32]

One year later, the first fatal case related to the chronic form of HP following continuous and intense exposure to *Fusarium vasinfectum* was reported.[33] Due to the self-renovation of a mold-infested mobile home, a 37-year-old male presented a 6-month history of progressively worsening dyspnea. From the culture of fungi collected at the patient's home, *F vasinfectum* was isolated and antibodies against this fungal species were founded in immunological tests. Even after removing the patient from the mobile home, thus halting exposure, and treating him with corticosteroids, his lung function declined, ultimately resulting in

the patient's death due to a complication in a lung biopsy. Concluding, if the patients have progressive respiratory symptoms and known antigen exposure, although uncommon, HP shall be suspected.[33]

Summer-type HP is caused by *Trichosporon* spp, which are present in wood houses with high humidity and temperature. An example of this type of HP was reported in a 59-year-old woman with rheumatoid arthritis treated with immunosuppressive agents (methotrexate and tacrolimus).[34] These agents may have masked and suppressed summer-type HP. The medical team advised mold removal from the bathroom and washing machine, which were the source of fungi in the dwelling, resulting in no further relapse of the condition. This report shows how some comorbidities and associated pharmacological treatments may complicate HP diagnosis, being important to pay attention to immunomodulatory effects, such as those from biological immunosuppressors.[34]

In the previous section, a study associating HP risk with musical instruments was reported. These observations are corroborated by a case study, published in 2017, where molds and mycobacteria isolated from wind instruments were associated with 2 cases of HP.[35] The first case, was a 56-year-old woman that played the bassoon. Her respiratory symptoms had disappeared during a summer holiday, where she had not been playing. In the samples taken from the bassoon, *Mycobacterium chelonae, Phoma* and *Rhodoturola* were found. The other case was 64-year-old woman previously diagnosed with systemic sclerosis that played trombone. *Paecilomyces ilacinus* and *Fusarium* were found in samples taken from the trombone. The patient was diagnosed with *Trombone Player's Lung*, caused by molds present in the wind instrument. Both cases were recommended to clean their instruments frequently to avoid recurrent exposure.[35]

Another case of HP was reported in a 62-year old onion farmer who had dry cough, general fatigue, and dyspnea on effort.[36] After ceasing exposure to the onions, his clinical symptoms gradually improved in a week without any treatment. The results of immunological tests for *Aspergillus* was positive. *A fumigatus* and *Aspergillus niger* were found at the workplace and only *A niger* was identified on the onion peels. Subsequently, the patient was submitted to a home-returning provocation test without cleaning the onion peels at his workplace and no resurgence of symptoms occurred. Concluding, the patient had HP caused by inhalation of *A niger* present at work, although there is a possibility that other fungal species could have induced HP as well. Nevertheless, the patient was advised to avoid exposure to onion peels.[36]

Altogether, these reports have shown that it is hard to diagnose HP because it sometimes can be masked by other comorbidities, therapies, or exposure agents. Also, it is not easy to determine the causative agent of the disease because HP may be induced by multiple fungal species. Lastly, all case reports showed that when the patients avoid exposure to the antigenic particle causative of HP, their symptoms tend to improve significantly. In these cases, antigen avoidance seems to be the most effective approach to treat the symptoms.

Conclusions

HP is a disease that can be caused by fungi, being *Penicillium* spp and *Aspergillus* spp the fungi species most frequently associated with the disease. Fungi are associated with humid environments, and are often present in places of significant exposure such as domestic environments, at workplace or in musical instruments.

Despite the inflammatory and acute cases, HP is often diagnosed in chronic form and requires a demanding monitoring and therapeutic approach. Patients often suffer from a progressive disease with respiratory insufficiency eventually leading to death, and lung transplantation is the only therapeutic solution with efficacy at this stage. The antigen avoidance is crucial to improve the outcome and those patients with disease progression are associated with undetermined or persistent exposure.

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Conflicts of interest

The authors declare no conflicts of interest.

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