Pitfalls in diagnosis and management of hypersensitivity pneumonitis

Wim Wuyts[a], *Marina Sterclova*[b], *and Martina Vasakova*[b]

Purpose of review
Hypersensitivity pneumonitis is a complex syndrome characterized by a combination of inflammation and fibrosis located in both the airways and the lung parenchyma. Both diagnosis and treatment are a real challenge for physicians. This review will focus on recent developments in this emerging field; furthermore, we will emphasize major gaps in the current knowledge, to stimulate further research in this field.

Recent findings
The main diagnostic issue is not to miss the entity as the clinical presentation is extremely variable even as the nature of the causal antigen. This article provides an overview of current ways to uncover possible causes of hypersensitivity pneumonitis. A problem of another kind is treatment of this disorder. Crucial in treatment is antigen avoidance, often in combination with immunosuppressive agents. The treatment of acute forms is rather straightforward, but the biggest endeavour, however, is treatment of chronic forms of hypersensitivity pneumonitis, which not always respond to immunosuppressive agents. Therefore, new initiatives should be taken in order to help clinicians in making a proper diagnosis and develop more efficacious treatment especially for patients suffering from chronic hypersensitivity pneumonitis.

Summary
Diagnosis and treatment of hypersensitivity pneumonitis remain a real challenge; this article provides an overview of our current understanding and points out new opportunities for further research.

Keywords
challenges, diagnosis, hypersensitivity pneumonitis, treatment

INTRODUCTION

Hypersensitivity pneumonitis, also called extrinsic allergic alveolitis is characterized by a combination of inflammation and fibrosis located in both the airways and the lung parenchyma [1]. This field has majorly evolved in the past few years, but a better understanding of diagnosis and treatment is necessary. Epidemiological data are unreliable at present as many patients with hypersensitivity pneumonitis might be erroneously diagnosed with other (idiopathic) fibrotic diseases [2]. The clinical presentation might be extremely variable even as the nature of the causal antigen; therefore, the cause is often concealed. Furthermore, the diagnostic process is hampered by a lot of uncertainties such as the role of specific antibodies and lymphocyte stimulation test, the role of antigen challenge test and the role of bronchoalveolar lavage (BAL) in the diagnosis of hypersensitivity pneumonitis. Other fields that need further research are prognostic factors to guide clinical decision-making and large registries including both acute and chronic hypersensitivity pneumonitis.

A challenge of another kind is treatment of subacute and chronic forms. Next to antigen avoidance, pharmacological treatment still consists of immunosuppressive agents. This is a challenge as some chronic hypersensitivity pneumonitis patients suffer from a relentless progressive fibrosis [3,4▪]. Therefore, new initiatives should be taken in order to help clinicians in making a proper diagnosis and

[a]Department of Respiratory Medicine, Unit for Interstitial Lung Diseases, University Hospitals Leuven, Leuven, Belgium and [b]Department of Respiratory Medicine of the 1st Medical School, Thomayer Hospital, Videnska, Prague, Czech Republic

Correspondence to Wim Wuyts, Department of Respiratory Medicine, Unit for Interstitial Lung Diseases, University Hospitals Leuven, Belgium Herestraat 49, 3000 Leuven, Belgium. Tel: +32 16 34 68 02; e-mail: wim.wuyts@uzleuven.be

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KEY POINTS

- Hypersensitivity pneumonitis is a disorder caused by repeated exposure of a sensitised individual.
- Several forms are discribed: acute, subacute and chronic.
- Hypersensitivity pneumonitis is much more frequent than originally thought.
- The diagnosis is a complex interpley of clinical suspicion, laboratory, imaging and if necessary histopathology.
- Chronich hypersensitivity pneumonitis is often a relentless fibrotic disorder.

develop more efficacious treatment especially for patients suffering from chronic.

DEFINITION AND CLINICAL PRESENTATION

Unfortunately, there is no uniform definition for hypersensitivity pneumonitis; however, a few items are commonly applied in former definitions: presence of pulmonary disease and systemic manifestations (weight loss, fever). The cause is an antigen to which the patient is sensitized, but this is not enough to develop lung disease [5,6]. A clear definition is needed both for daily clinical practice and to boost clinical trials, warranted to improve care and treatment of patients.

The clinical behaviour is conventionally classified into acute, subacute and chronic forms; however, there are no widely accepted criteria and it is not sure whether these represent clinical stages of the disease [7,8].

Acute hypersensitivity pneumonitis

Acute hypersensitivity pneumonitis is a syndrome characterized by fever, chills and diffuse myopathy, which often occur a few hours after exposure. Simultaneously dyspnoea, cough and chest tightness occur, but might be less prominent. Clinical examination reveals bibasilar crackles. The symptoms usually decrease over the course of a few hours or at maximum days. Acute hypersensitivity pneumonitis is thought to result from a significant exposure that makes antigen detection and subsequent avoidance crucial [8].

Subacute hypersensitivity pneumonitis

Usually, subacute hypersensitivity pneumonitis is characterized by an insidious onset of cough and dyspnoea over a few months, which can be difficult to distinguish from another (idiopathic) interstitial lung disease or even an infection. Patients seem to have more pronounced systemic symptoms [8]. It is thought to result from a repeated (low-level) exposure to inhaled antigens.

Chronic (progressive) hypersensitivity pneumonitis)

Chronic (progressive) hypersensitivity pneumonitis is assumed to be the result of continuous, low-level exposure to inhaled antigens [9]. Patients present with progressive dyspnoea, dry cough, fatigue and weight loss. This disease is often associated with progressive fibrosis, with a presentation and evolution that is difficult to distinguish from fibrotic nonspecific interstitial pneumonia (NSIP) or idiopathic pulmonary fibrosis (IPF) [10].

Acute exacerbations of chronic hypersensitivity pneumonitis

Acute exacerbations are well recognized in IPF [11], but have also been described in hypersensitivity pneumonitis [12]. They are characterized by fast progressive dyspnoea and the occurrence of new bilateral ground-glass opacities on high-resolution computed tomography (HRCT); exclusion of heart failure, infection or pulmonary embolism is mandatory [13]. Risk factors are low total lung capacity of diffusing capacity for carbon monoxide, a usual interstitial pneumonia (UIP)-like pattern on histology and increased neutrophils and decreased lymphocytes in BAL fluid [14].

Categorization of hypersensitivity pneumonitis remains artificial; however, studies should be conducted aiming to determine disease behaviour and response to immunosuppressive agents in the individual patient.

EPIDEMIOLOGY

Epidemiologic data vary according to local practices, geography, season, population studied and host risk factors. A very recent trial reported the annual incidence in Denmark to be lower than one per 100 000 inhabitants [15▪▪]. Similar numbers come from Great Britain with incidence rate 0.9 cases per 100 000 person-years [16]. Annual incidence of hypersensitivity pneumonitis in New Mexico was reported to be 30 per 100 000 inhabitants [17]. However, these numbers might not reflect all hypersensitivity pneumonitis cases and more probably hypersensitivity pneumonitis epidemiology data represent only the tip of the iceberg, due to substantial underdiagnosis. Despite diagnostic pitfalls, hypersensitivity pneumonitis was found third most frequent intestitial lung disease (ILD) after IPF and NSIP [15▪▪,17,18].

Also the data on prevalence of hypersensitivity pneumonitis cover a wide range: in the USA, it was estimated to be 420–3000 per 100 000 inhabitants, France 4370 per 100 000 inhabitants and Finland 1400–1700 per 100 000 inhabitants [19–21].

Another way of looking at epidemiology is through specific data sorted per individual antigen. The incidence of hypersensitivity pneumonitis among pigeon breeders reaches 6–21% per year and among farmers 0.4–7% per year. But the burden of hypersensitivity pneumonitis might be even much more important as in one report hypersensitivity pneumonitis has been reported to develop in up to 52% exposed office workers (humidifier lung) and 37% lifeguards exposed to public swimming pools [19,22].

Pathogenesis

Pathogenesis of hypersensitivity pneumonitis is currently not fully understood, although the understanding of the different processes has massively increased in the past few years. Some aspects of the disease point to a certain systemic compound. For instance, only a small proportion of individuals exposed to hypersensitivity pneumonitis-associated antigens develop the disease, which raises the possibility that intrinsic factors of the host including genetic susceptibility may play a role [23,24,25▪]. Other factors might be exposure to various environmental factors and subsequent changes in immune response in vitro and in early postnatal period. Examples are exposure to low doses of formaldehyde during pregnancy and perinatal antibiotics that may lead to alterations in susceptibility to Th2 or Th1/Th17-driven immune response [26▪]. Furthermore, it has been shown that higher age may predispose to more pronounced fibrotic response [27]. An alternative explanation for the effect of aging might be the associated prolonged exposure to potentially harmful environmental agents or changes in the immune system associated with aging; this is currently not recognized.

The pathogenesis of hypersensitivity pneumonitis with marked inflammatory involvement (more acute forms) and hypersensitivity pneumonitis with dominant fibrotic response (more chronic forms) may also vary. Exposure to inhalation antigen may lead to a proinflammatory response by respiratory epithelial cells with further attraction of neutrophils (producing interferon γ that is needed for Th1 immune response) and alveolar macrophages. Apoptosis of neutrophils leads to maturation of dendritic cells, which together with alveolar macrophages act as antigen-presenting cells. Release of interleukin-1, interleukin-12 and interleukin-18 enhances lymphocyte expansion and promotes Th1 differentiation. Profibrotic mechanisms have been less studied. Several mechanisms have been suggested: shift to Th2 cytokine milieu and role of interleukin-4 in fibroproliferation; exhausted antigen-specific T-cell lineage with functional impairment of antigen T-cell response may play an important role. Also bone marrow-derived circulating fibrocytes may participate in the pathogenesis of hypersensitivity pneumonitis by amplifying the inflammatory and fibrotic response [28▪].

It is clear that the fibrotic response in hypersensitivity pneumonitis patients is different from IPF, as gene profile studies distinguished specific gene signatures in chronic hypersensitivity pneumonitis [29] and multiplex protein profiling in BAL suggested major differences between IPF and chronic hypersensitivity pneumonitis [30].

DIAGNOSIS

The diagnosis of hypersensitivity pneumonitis is based on a combination of antigen exposure and compatible clinical, laboratory radiologic and pathologic findings, but validated diagnostic criteria are lacking.

Crucial is a meticulous history-taking, which should be performed by a clinician highly experienced in identifying relevant antigens. The right diagnosis can only be made by integrating data from history (i.e. exposure), clinical examination, laboratory findings, imaging pulmonary function tests (PFTs), BAL and histopathology. A confident diagnosis can only be achieved in a multidisciplinary discussion [2].

Antigen detection

Identification of causative antigen is crucial for diagnosis, preventive measures and prognosis of hypersensitivity pneumonitis; however, this represents a major challenge. Moreover, some cases primarily diagnosed as IPF or idiopathic NSIP might be revealed as undiagnosed hypersensitivity pneumonitis after multidisciplinary discussion [2].

All available tools should be used to detect the source of exposure. The first step is a highly detailed patient's history of exposure both at home and other situations. The investigating physician should have the necessary expertise in identifying all possible sources of sensitizing antigens, which is a challenge, as exposure is extremely specific and the amount of possible causes exponentially grows [31]. The second step is laboratory tests for confirmation of suspect antigen or as screening tool using precipitation reaction against causative antigens [32] and

Table 1. Diagnostic criteria for extrinsic allergic alveolitis

	Subacute	Chronic
History of exposure to inhaled antigen	+	+/−
Respiratory symptoms	+	+
Crackles	+/−	+
Positive IgG antibodies or precipitins[a]	+/−	+/−
Confirmation of causal antigen in environment	+	+
Abnormal pulmonary function test	↓	↓
BAL fluid lymphocytosis	+	+/−
BAL fluid CD4/CD8	↓	↓/normal/↑
HRCT pattern	Centrilobular nodules, GGO	Centrilobular nodules, GGO
	Mosaic perfusion	Mosaic perfusion
	Condensations	Condensations
		Interstitial septa thickening
		Honeycombing
Histology pattern	Mononuclear cell infiltrate	Mononuclear cell infiltrate
	Granuloma (often poorly formed), OP, DIP	Granuloma (often poorly formed), OP, DIP, NSIP, UIP

This table depicts elements that should be taken into consideration before making a diagnosis of HP. Moreover, this table highlights the differences between subacute and more chronic forms of HP. BAL, bronchoalveolar lavage; DIP, desquamative interstitial pneumonia; GGOs, ground-glass opacities; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia. Possible chronic EAA: negative history of exposure to inhaled antigens + BALF lymphocytosis + typical HRCT pattern/histology pattern (see the table). Probable chronic EAA: positive history of exposure to inhaled antigen + typical HRCT/histology pattern (see the table). Definite chronic EAA: positive history of exposure to inhaled antigen + BAL fluid lymphocytosis + typical HRCT/histology pattern (see the table).
[a]The basic list of antigens usually used for specific antibodies detection comprises: moulds (*Aspergillus spp.*, *Penicilium spp.*), thermophilic actinomycetes (*Saccharomyces rectivirgula*, *Thermoactinomyces viridans*), bacteria and mycobacteria (*Pseudomonas spp.*, nontuberculous mycobacteria) and pigeon and parakeet droppings and feathers.

detection of specific immunoglobulin G (IgG) antibodies [33]. A third method is an exposure test that can be performed by exposure to the environment with potential source of antigen or by direct inhalation of the antigens or their mixtures (for instance, purified and diluted derivatives from the dusts or liquids from the workplace) [34▪].

There is a long list of potential antigens and there is only a limited number of antigens available for detection (Table 1). It would be helpful to have panels of antigens for screening, but the value of these panels should be investigated [35▪,36]. Moreover, we also miss reliable normal values of the specific IgGs [37]. It is also not known whether longitudinal monitoring of the specific IgGs has a meaning for evaluation of the disease activity or prognosis of the patient.

Imaging

Chest imaging is a crucial part of diagnostic process in hypersensitivity pneumonitis, as this should raise the suspicion of a possible hypersensitivity pneumonitis.

Chest radiograph has almost always in sufficient resolution to recognize the typical changes of hypersensitivity pneumonitis [38]. Acute hypersensitivity pneumonitis can present with ill-defined nodules and areas of ground-glass opacification in both the lungs. In chronic hypersensitivity pneumonitis, reticulation and a honeycomb pattern can be detected.

HRCT has substantially better resolution to distinguish and define the typical changes. Hypersensitivity pneumonitis presents as ground-glass opacification, centrilobular nodules, air trapping (mosaic pattern), fibrosis, emphysema and often a combination of patterns [39,40] (Fig. 1). For prognostic reasons, hypersensitivity pneumonitis can be subdivided into two radiological subtypes: fibrotic and nonfibrotic hypersensitivity pneumonitis. The presence and the extent of fibrosis on computed tomography are associated with increased mortality [41]. Moreover, the severity of traction bronchiectasis and extent of honeycombing are powerful predictors of mortality in chronic hypersensitivity pneumonitis. In the study of Walsh *et al.* [42], scoring system for estimating prognosis of hypersensitivity pneumonitis was used. It comprised whole disease extent, ground-glass opacification, fine and coarse reticulation, honeycombing, emphysema and consolidation. The authors concluded

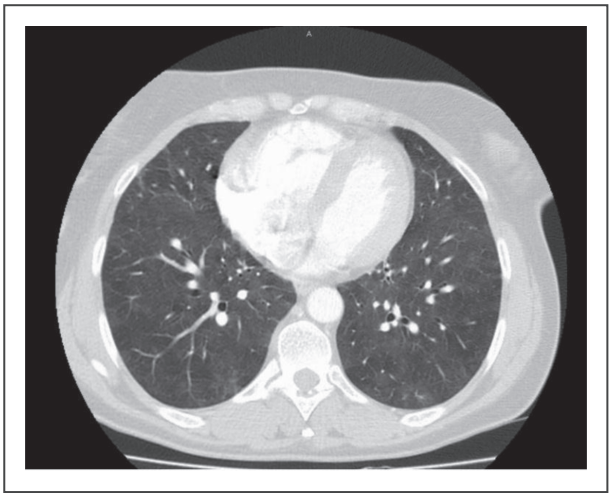

FIGURE 1. High-resolution computed tomography scan of a 38-year-old woman with acute hypersensitivity pneumonitis. The image shows extensive ground-glass opacities.

that HRCT patterns, in particular, severity of traction bronchiectasis and extent of honeycombing, are superior to PFTs for predicting mortality in patients with hypersensitivity pneumonitis. Differentiation of NSIP and IPF is difficult; if lobular areas with decreased attenuation and vascularity, centrilobular nodules and absence of lower zone predominance are present, chronic hypersensitivity pneumonitis is more likely (Fig. 2) [43].

Pulmonary function tests

In acute hypersensitivity pneumonitis, PFTs might be normal [44]; however, PFT are often characterized by a restrictive pattern and a decreased diffusing capacity for carbon monoxide. In some patients with farmer's lung, an obstructive pattern might be present, resulting from emphysema. The role of PFTs is mainly to determine the severity of the functional impairment both at diagnosis and at follow-up [7]; however, serial PFT data are sparse.

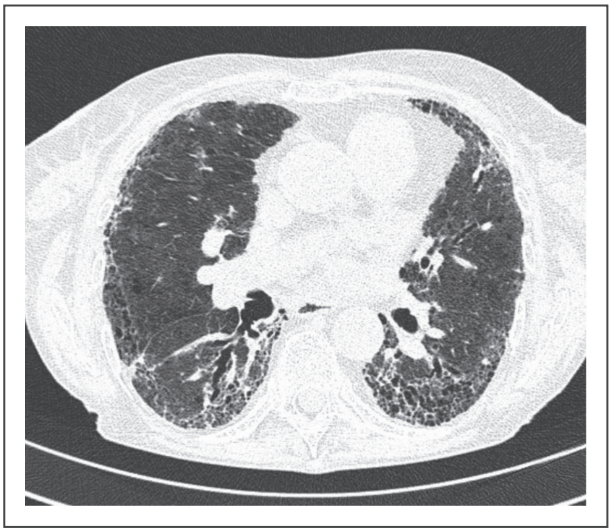

FIGURE 2. High-resolution computed tomography scan in a 72-year-old woman with chronic hypersensitivity pneumonitis with advanced fibrotic changes and traction bronchiectasis.

Bronchoalveolar lavage

However, BAL is not recommended routinely in the diagnosis of IPF, it is considered a highly sensitive method to evaluate lung inflammation in a patient suspected of having hypersensitivity pneumonitis [7]. In acute forms of hypersensitivity pneumonitis, an increase in both total cell count and percentage lymphocytes is usually found [7]. In chronic forms, BAL fluid lymphocyte count is lower or can even be normal. Lymphocyte count might also be influenced by age, smoking status and the use of corticosteroids [9,45,46]. A low T4/T8 ratio has been pathognomonic for hypersensitivity pneumonitis; however, this is not absolute [47,48].

The main discussion is raised by the inflammatory pattern (elevated lymphocyte count) in BAL fluid becoming less prominent the more fibrotic the disease becomes [49▪▪]. The cutoff for lymphocyte count also differs, but 30% is often used. However, in patients with hypersensitivity pneumonitis with a UIP pattern, lymphocyte count is lower than 30% [50,51]. More than 80% of chronic hypersensitivity pneumonitis patients have at least 20% lymphocytes in BAL fluid [52,53]. Also in the follow-up, BAL might be useful as persistent BAL fluid abnormalities may indicate that complete avoidance has not been achieved [1].

So it is clear that an elevated lymphocyte count in a patient with suspected UIP warrants thorough investigation to rule out chronic hypersensitivity pneumonitis. But a more comprehensive approach toward interpretation of BAL fluid is urgently necessary.

Histopathology

Histopathological evaluation is another crucial element in the multidisciplinary diagnosis. This is needed in case when antigen exposure is missing and/or when radiologic findings are not typical for hypersensitivity pneumonitis. Not all patients are able or willing to have a surgical biopsy, which leads to major diagnostic uncertainty. Recent developments show promising results for transbronchial cryobiopsy in the diagnosis of ILD [54], although further confirmation of sensitivity and specificity is necessary.

In the more acute form of the disease, the typical histopathologic changes comprise lymphocytic alveolitis with bronchiolocentric accentuation, non-necrotizing epitheloid cell granulomas, intra-alveolar fibrosis and cellular bronchiolitis [55]. On the contrary, in chronic hypersensitivity pneumonitis, the morphologic features are not always specific to be diagnostic for hypersensitivity pneumonitis: UIP-like patterns can be observed, even as NSIP-like patterns with peribronchial distribution, mild alveolitis/bronchiolitis and limited granuloma formation [51]. In most cases, the histopathologic findings might suggest the diagnosis of chronic hypersensitivity pneumonitis, but as the differential with fibrotic NSIP and IPF should be thoroughly made, the definite diagnosis should be resulting from a multidisciplinary team discussion. UIP-like pattern exhibits the worst survival in chronic hypersensitivity pneumonitis patients [51,56,57].

Current diagnostic criteria

The diagnosis of hypersensitivity pneumonitis and more particular chronic hypersensitivity pneumonitis is difficult and as a result often missed. The diagnosis should be kept in mind when there is evidence of exposure to a relevant antigen. A relation between (start of) exposure and onset of symptoms is useful. In this regard, serum IgG/precipitins can be of help and in some instances challenge tests could be considered. In addition, BAL can provide more evidence for hypersensitivity pneumonitis. However, if the diagnosis is more difficult, surgical lung biopsy might be mandatory [58]. The use of lymphocytic transformation test should be considered in specific situations, for example if beryllium exposure is expected [59]. Specific inhalation testing has been described in a recent article suggesting that a positive test could be helpful in the diagnosis, whereas a negative test could not rule out hypersensitivity pneumonitis [60▪▪]. In conclusion, an appropriate diagnosis of hypersensitivity pneumonitis is extremely complex, information of different levels should be integrated (clinical, radiologic, laboratory, histopathological data) and even then the diagnosis is often missed.

Treatment

Sustained antigen exposure is associated with adverse outcome in many cases, so antigen avoidance is the main action, highlighting the importance of identifying hypersensitivity pneumonitis and uncovering the causal antigen in a certain patient. Another important issue is that the disease might relentlessly progress despite discontinuation of exposure. Next to prevention, the mainstay of pharmacological treatment is anti-inflammatory treatment (corticosteroids alone or in combination with immunosuppressive drugs), which might affect the disease course in few patients, especially in those with acute and subacute forms of the disease. However, it has become clear that more chronic forms do not always respond as well as expected.

Prevention is important, not only for the patient but also for sensitized individuals exposed to the same antigens without signs of the disease yet, to avoid them developing hypersensitivity pneumonitis in future. Also changes in the industrial or agricultural process might be imposed (introduction of full face masks, regular measurements of air quality, . . .) or the patient is advised to avoid exposure by all means (change work post or even profession).

PHARMACOLOGICAL THERAPY

The mainstay of treatment in hypersensitivity pneumonitis is corticosteroids, based on a randomized, double-blind, placebo-controlled study in acute farmer's lung. The authors have shown that patients given prednisolone showed more rapid improvement in lung function and a significantly higher diffusing capacity at 1 month compared with the control group. However, there was no difference in the long-term outcome between the two groups [61].

Interestingly, recurrence of acute farmer's lung was more common among corticosteroid-treated patients who had continuing antigen exposure, raising the possibility that corticosteroid treatment was also suppressing the counterregulatory aspects of the immune response in these patients.

Determination of dose and duration of systemic immunosuppressive drugs is still not really established. The empiric scheme that is suggested is 0.5 mg/kg/day of prednisolone for 4–6 weeks followed by a gradual reduction until maintenance dose of approximately 10 mg/day [62]. Some authors suggest for a (sub)acute form of hypersensitivity pneumonitis between 3 and 6 months of treatment duration to achieve disease remission [7]. Usually, it is thought that for chronic forms, corticosteroids should be continued for a longer time.

A pragmatic approach is used in several experienced centres. In case the extent of the pulmonary involvement is mild, the patient has almost no symptoms and a causal antigen has been identified, prevention is crucial and steroids could be avoided. This approach should be further evaluated in specific clinical trials.

The more inflammation is prominent, the better the effect of anti-inflammatory drugs can be anticipated; however, in more chronic forms, fibrosis might be the main driving mechanism. Therefore, the effect of anti-inflammatory treatment in these cases cannot be overestimated, as suggested by Fink *et al.* [63] and has been recently confirmed in an Asian population [9,64]. This is supported by the findings of several articles that steroids seem not to alter the long-term course of the disease as shown in patients with farmer's lung [65,66]. In order to find a solution for patients with relentless fibrotic forms of hypersensitivity pneumonitis, not responding to classical immunosuppression, we should urgently develop new clinical trials with antifibrotic agents that have shown efficacy in IPF. One of the key questions of the design of such trials is whether they will be performed with anti-inflammatory or antifibrotic agents or their combination [67▪].

Prognosis

Data concerning mortality trends are scarce in the literature. In England and Wales from 1968 to 2008, 878 deaths due to hypersensitivity pneumonitis were reported and increased in time from a first period (1968–1972) to a later period (2005–2008). Mortality was higher in men and with increasing age [68]. In the recent Danish cohort, 5-year survival in the hypersensitivity pneumonitis group was 93% [15▪▪].

An interesting finding is that depending on the causative antigen, the prognosis seems to differ as there are some data suggesting that bird fancier's hypersensitivity pneumonitis might have a worse prognosis than farmer's lung. This might be because of the fact that patients with established fibrosis on HRCT and/or surgical lung biopsy have a poorer prognosis [50,69,70].

The prognoses of other varieties of hypersensitivity pneumonitis are less well described; this is another unexplored field with a high unmet need, even as the use of biomarkers that might be helpful in determining prognosis.

Another problem is that acute forms seem to be more easily diagnosed, which might lead to underreporting of more chronic cases that have a worse prognosis. This may lead to an overestimation of real life survival. A possible way to get more insight in this problem is the start of new registries to help us solve these questions.

CONCLUSION

In conclusion, we can state that hypersensitivity pneumonitis seems to be much more prevalent than initially thought as there is no clear definition and differential diagnosis is challenging in unexperienced hands. There is an urgent need for better definition, diagnostic criteria setting and validation (including panels of IgG) and closer collaboration with occupational physicists. Imaging is important and, if not specific, histopathology is of real help if possible. BAL cell analysis can be helpful when an integration is done in a multidisciplinary discussion. Further research is warranted to develop prognostic markers that can drive clinical decision-making even as worldwide registers to increase our knowledge on evolution of the different disease forms.

Perspective for the future

Although treatment is rather easy for acute forms, it is a real challenge for more fibrotic chronic forms. Here it is crucial to start new trials to find more efficacious ways of treating those patients.

However, the future for hypersensitivity pneumonitis patients might look brighter, as with the rapidly expanding programmes on genotyping, proteomics and biomarkers which are being put into position, the field will not be alike in 10 years from now.

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Conflicts of interest

There are no conflicts of interest

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