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POSITION STATEMENT

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Diagnosis and management of hypersensitivity pneumonitis in adults: A position statement from the Thoracic Society of Australia and New Zealand

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Abstract

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) relating to specific occupational, environmental or medication exposures. Disease behaviour is influenced by the nature of exposure and the host response, with varying degrees of lung inflammation and fibrosis seen within individuals. The differentiation of HP from other ILDs is important due to distinct causes, pathophysiology, prognosis and management implications. This Thoracic Society of Australia and New Zealand (TSANZ) position statement aims to provide an up-to-date summary of the evidence for clinicians relating to the diagnosis and management of HP in adults, in the Australian and New Zealand context. This document highlights recent relevant findings and gaps in the literature for which further research is required.

KEYWORDS

clinical respiratory medicine, environmental and occupational health and epidemiology, hypersensitivity pneumonitis, inflammation, interstitial lung disease, pulmonary fibrosis

FOREWORD: HYPERSENSITIVITY PNEUMONITIS—THE LIVED EXPERIENCE

The experience of living with hypersensitivity pneumonitis is impacted enormously by your medical team. My experience was extreme; my life changed with a specialist who provided the prognosis with empathy, allowed me to accept the results, while providing a positive focus on understanding impacts, managing actions and living my best life.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) caused by aberrant immune response to mostly inhaled environmental antigens in susceptible individuals. A non-inhalational variant of HP can be caused by some medications. The diagnosis of HP includes assessment of relevant clinical, radiological and in some cases histopathological information, ideally presented at an ILD-specific multidisciplinary meeting (MDM). The differentiation of HP from other ILDs is important as the causes, pathophysiology, prognosis and management implications are distinct from other ILDs, with particular focus on the home or workplace of the individual.

This Thoracic Society of Australia and New Zealand (TSANZ)-endorsed position statement aims to provide an up-to-date and comprehensive summary of the evidence for clinicians relating to the aetiology, diagnosis and management of HP in adults in the Australian and New Zealand context. It highlights recent findings and gaps in the literature for which further research is required. Notably, this is not a clinical practice guideline, rather, an expert consensus document synthesising relevant and contemporary evidence for this condition to enrich clinician knowledge for patient care.

METHODS

This position statement was convened by a diverse group of health-care providers from Australia and New Zealand. The expert panel included ten respiratory physicians, an immunologist, two specialist nurses, an exercise physiologist, radiologist, pathologist and consumer representative. Relevant articles were identified by searching Pubmed and MEDLINE, using the terms 'hypersensitivity pneumonitis', 'extrinsic allergic alveolitis', 'nonfibrotic HP', 'fibrotic HP', 'progressive fibrosing interstitial lung disease' and 'progressive pulmonary fibrosis'. Searches were performed up to 24 January 2024, limited to English language articles, and included systematic reviews, randomised controlled trials, prospective and retrospective cohort studies and case-controlled studies. Each author contributed sections most relevant to their field of expertise, and then had the opportunity to revise the manuscript. The manuscript was reviewed and endorsed by the TSANZ Clinical Care and Resources Subcommittee. This position statement will be available to TSANZ members via the society website, and will be considered for update in 2027.

OVERVIEW OF HYPERSENSITIVITY PNEUMONITIS

Disease definitions

HP is a heterogeneous disease characterized by varying degrees of pulmonary interstitial and peri-bronchiolar inflammation, with or without associated fibrosis. HP results from immune-mediated pulmonary inflammation triggered by exposure to one or more environmental antigens in susceptible and sensitised individuals. Historically, HP (previously known as extrinsic allergic alveolitis) was classified into acute, subacute and chronic subtypes,[1] however this classification system has now been largely abandoned due to

TABLE 1 Features of nonfibrotic and fibrotic HP.

Clinical features	Nonfibrotic HP	Fibrotic HP
Exposure duration	Short, high intensity exposure; or chronic exposure	Chronic, low-level exposure; no identifiable exposure; or past exposure
Clinical symptoms	Sudden onset dyspnoea, cough, fever, malaise, acute respiratory failure	Insidious onset dyspnoea, cough, subacute or chronic respiratory failure
HRCT features	Typical: Bilateral, diffuse mosaic attenuation (including the three-density sign), ground glass opacities, features of small airways disease (small centrilobular ill-defined nodules; gas trapping on expiration)	Typical: Bilateral, peribronchovascular interstitial thickening, traction bronchiectasis, honeycombing with ground glass opacities, mosaic attenuation (three-density sign), diffuse or mid-to-upper zone distribution
	Other: isolated gas trapping, airspace consolidation, cysts	Other: basal distribution, UIP, fibrotic NSIP, fibrotic OP patterns

BAL fluid features	Lymphocytosis	Less frequently lymphocytosis
Histopathological features	Chronic bronchiolitis, peribronchiolar interstitial lymphocyte-predominant inflammation and poorly formed granulomas/giant cells	Chronic fibrosing interstitial pneumonia, poorly formed granulomas (or giant cells), ± features of nonfibrotic HP. Absence of features to suggest an alternate diagnosis
Disease behaviour	Potentially reversible with antigen removal or immunosuppression	Chronic, irreversible, a subgroup demonstrates the PPF subtype

Abbreviations: BAL, bronchoalveolar lavage; HP, hypersensitivity pneumonitis; HRCT, high resolution computed tomography scan; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; PPF, progressive pulmonary fibrosis; UIP, usual interstitial pneumonia.

challenges in application, lack of objectivity and discordance with disease behaviour.[2–4] Recently published international diagnostic guidelines recommend HP classification into fibrotic or nonfibrotic phenotypes based on the presence or absence of radiological and/or histopathological fibrosis, supported by the observation that pulmonary fibrosis conveys important prognostic and treatment implications.[5–9] In addition to fibrotic and nonfibrotic features, HP may display overlapping clinical and radiological characteristics with other forms of ILD, highlighting the difficulty in confirming the diagnosis and tailoring management in many cases. Table 1 summarizes key differences between fibrotic and nonfibrotic HP phenotypes. It is important to recognise that these phenotypes occur on a disease continuum, noting that many patients exhibit overlapping features at diagnosis, with further evolution over the disease course.

Disease behaviour including the progressive pulmonary fibrosis phenotype

Disease behaviour in HP is highly variable. Individuals with nonfibrotic HP may exhibit more rapid onset of symptoms, inflammatory features on imaging, sometimes constitutional symptoms and generally a favourable response to treatment (including antigen avoidance).[3,10] In such cases, the causative antigen may be identifiable due to the short latency of symptom onset following exposure. In contrast, fibrotic HP is usually associated with chronic low-level or no clearly identifiable exposure, with affected individuals more likely to experience disease progression, decline in lung function and poorer survival.[7,8,11] Many with fibrotic HP demonstrate disease behaviour that resembles idiopathic pulmonary fibrosis (IPF), with similar rates of forced vital capacity (FVC) decline, risk of acute life-threatening exacerbations and death.[11–14]

Progressive pulmonary fibrosis (PPF) is a recently defined entity encompassing a subset of non-IPF ILD patients.[15] Several definitions of PPF (with varying names) have been published. The ATS/ERS/JRS/ALAT consensus guideline criteria for PPF include the presence of at least two out of three indices of disease progression over 12 months, including worsening respiratory symptoms, deterioration in lung function and radiologic progression of fibrosis.[15] Increasing recognition of PPF has occurred alongside a paradigm shift in the management of non-IPF fibrotic ILD, with randomised clinical trials demonstrating efficacy of anti-fibrotic therapy in patients with PPF, regardless of the underlying cause.[16–18] Between 30% and 60% of fibrotic HP cases are reported to display PPF behaviour in prospective registry data.[11,19]

Incidence and prevalence across different environmental settings

The reported incidence of HP is 0.3–0.9 per 100,000 people, with population data derived from countries other than Australia or New Zealand.[3] In international ILD registries, HP accounts for between 2% and 47% of cases, with highest rates in India, and lowest rates in European countries.[20–22] Region-specific environmental conditions, genetic differences between populations, reporting biases and under- or over-diagnosis may account for these discrepancies. Diagnostic rates for HP (and indeed all ILD) are impacted by imprecise, often non-standardised investigations with varying sensitivity and specificity (discussed in further depth under *Diagnosis*). In a census of early data from the Australia and New Zealand ILD Registry, 9.4% of 705 ILD participants had a HP diagnosis.[23] In other Australian ILD cohorts, HP accounts for 16%–30% diagnoses.[24,25] Data for HP prevalence in specific regions and communities within Australia and New Zealand, including First Nations people, are limited. Further research on the interplay between genetic susceptibility

and the environment is needed, particularly in agricultural and industrial settings.

HP is more prevalent in older populations of either sex, although can occur across the age spectrum. Clustering of HP cases is seen in specific occupational and recreational settings, discussed in further detail below; commonplace antigens encountered in the home environment (e.g., moulds, down bedding etc) are likely to be responsible for the majority of occult cases.[26–28] Incidence spikes have been reported with microbial contamination of building air conditioning units and other water reservoir systems.[29–31] Increased environmental mould concentrations associated with heavy precipitation events and rising global ambient temperatures have been linked with higher rates of respiratory disease, including HP.[32,33]

SUMMARY

- The spectrum of HP encompasses nonfibrotic and fibrotic forms, developing in response to acute or more chronic and insidious environmental exposures.
- Fibrotic HP patients commonly display PPF disease behaviour, impacting management and prognosis.
- Geographic conditions, cultural and social practices, genetic characteristics and methods for disease detection may influence regional differences in HP prevalence.

IMMUNOPATHOGENESIS

Both innate and adaptive immune responses contribute to acute lung inflammation in HP, with an eventual fibroproliferative response associated with disease chronicity in some susceptible individuals. Inhalational exposures are typically dusts containing multiple inducing or potentiating antigens such as bacterial and fungal pathogens, microbial toxins, volatile organic compounds and other proteins.[34] Organic antigens are recognised by conserved pattern recognition receptors on innate immune cells, which stimulate transcription and secretion of pro-inflammatory cytokines.[35] Inorganic antigens, including metals and specific drugs, bind to human proteins as haptens to become antigenic.[34,36] The initial stages of HP are characterised by neutrophil activation and infiltration, up-regulation of adhesion molecules and increased production of Interleukin (IL)-8.[37,38] B cell differentiation into antibody-producing plasma cells generates specific immunoglobulin G (IgG) antibodies, which can be detected in serum as 'precipitins'.[39] These antibodies can be present in exposed patients even in the absence of disease, thus their role in disease pathogenesis is uncertain.[39,40] Ongoing exposure in a sensitised host generates high-affinity antibodies and immune complexes; subsequent activation of the classical complement pathway stimulates macrophage activation and tissue injury.[34,41,42] Figure 1 depicts factors contributing to HP immunopathogenesis.

Progression to fibrosis is associated with a switch to T_H2-mediated inflammation and production of type 2 cytokines IL-4 and IL-13.[43,44] Fibroproliferation within lung interstitium is further enhanced by neutrophils and fibrocytes. Increasing tissue hypoxia and stiffness acts to perpetuate a feed-forward loop amplifying pro-fibrotic molecular pathways, including those mediated by transforming growth factor (TGF)-beta.[34,45,46] Notably, the immunological mechanisms detailed above have largely been studied in non-fibrotic 'inflammatory' HP models, with uncertainty about whether the principles can be extrapolated to the fibrotic HP disease entity.

Some recent insights in fibrotic HP pathogenesis have been gained through spatial transcriptomic techniques, single cell molecular sequencing and microbiome analysis. De Sadeleer et al. compared the gene expression profiles in explant lungs of fibrotic HP of varying severity and IPF.[47] Transcriptome signatures favouring extracellular matrix deposition and T cell-driven antigen presentation/sensitisation were found in milder disease. Gene expression in more severe disease favoured increased B cell activation and honeycombing-associated signatures, with decreased intracellular homeostasis and endothelial functions.

Through integration of single cell RNA, single cell T cell receptor and bulk RNA sequencing techniques applied to cells obtained from fibrotic HP lung tissue, Wang et al. demonstrated an enhanced inflammatory signature within macrophages and monocytes, increased epithelial mesenchymal transition in fibroblasts and expanded disease-specific cell subpopulations.[48] The role of microbial influence on disease pathogenesis and fibrotic progression is uncertain. Whilst Invernizzi et al. found distinct microbiome profiles in fibrotic HP compared with IPF and normal controls, there was no association found in this cohort between the lung bacterial burden and survival.[49] Further characterisation of the fibrotic HP lung microenvironment with the use of emerging technologies may in the future enable precision-medicine approaches to HP classification and management.

RISK FACTORS FOR DEVELOPING HYPERSENSITIVITY PNEUMONITIS

Antigen exposure

Antigen exposure and sensitisation are central to disease pathogenesis. Inducing compounds elicit an inflammatory response in susceptible individuals, as detailed above. The list of such compounds known to be associated with HP is extensive, as summarized in Table 2. The causative exposure cannot be identified in up to two-thirds of individuals with HP, despite a detailed history and multidisciplinary diagnostic evaluation.[50] For cases where the antigen is unidentified or 'occult', inferior survival has been reported in some

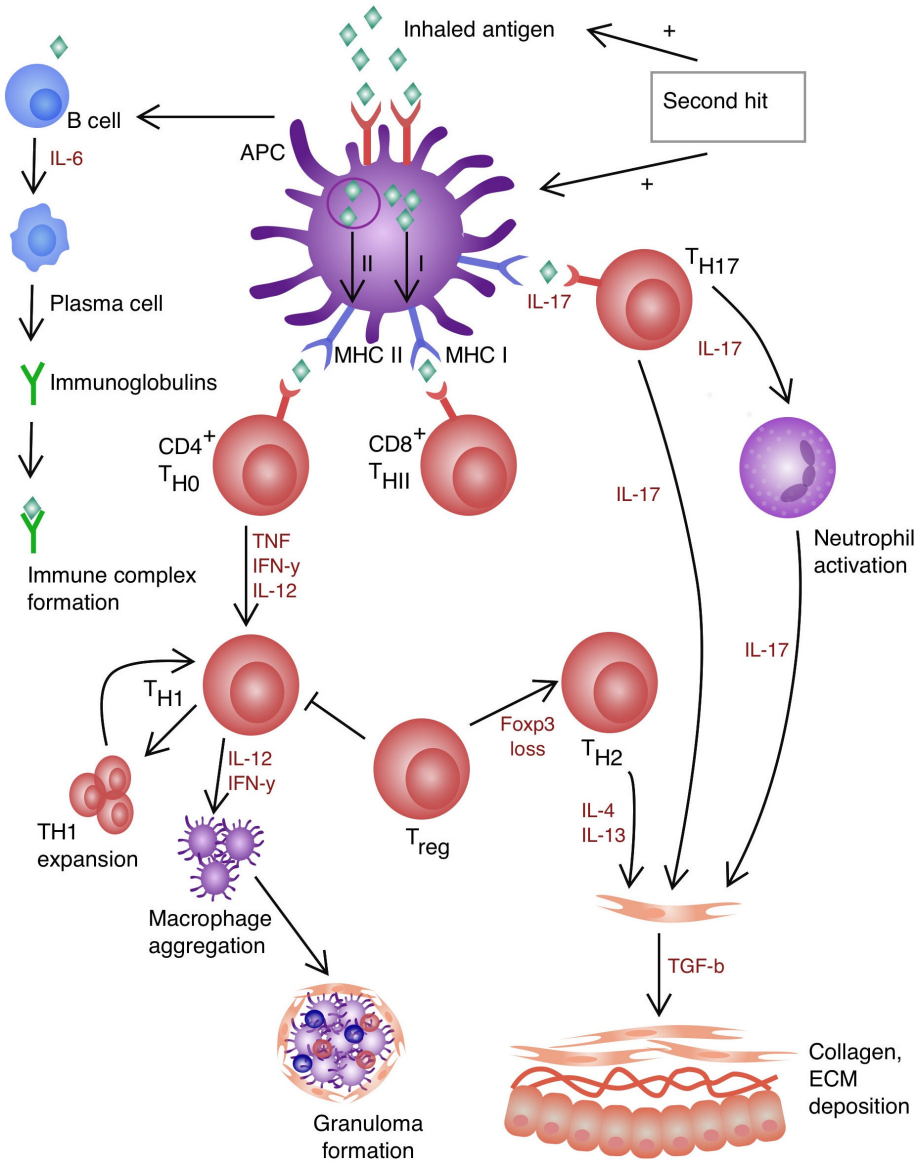

FIGURE 1 The role of T cell subsets in the immunopathogenesis of HP. Antigen presenting cells (APCs) phagocytose antigen, and present processed peptides on Class II major histocompatibility complex (MHC) molecules to $CD4^+$ T cells. T helper 1 (T_H1) differentiation and expansion is promoted by tumour necrosis factor (TNF), IL-12 and interferon gamma (IFNγ). The pro-inflammatory environment leads to macrophage activation, aggregation, and granuloma formation. Differentiation of $CD4^+$ T cells into a T_H17 phenotype stimulates IL-17 secretion leading to further inflammation and lung fibrosis. Reduced functional activity of $FOXP3^+$ regulatory T cells (Treg) favours a T_H2 CD4+ T cell phenotype and production of cytokines IL-4 and IL-13. This cytokine milieu promotes fibroblast proliferation and production of pro-fibrotic TGFβ, leading to collagen production and extracellular matrix (ECM) deposition.

cohorts,[10,14,51] but not in others.[5,52] These conflicting findings may be due to difficulties in confirming true antigen avoidance,[53] uncontrolled and retrospective study design, heterogeneity of study populations and insufficient statistical power. Some reports have suggested intensity, duration and nature of antigen exposure are determinants of disease progression,[54] however it is unclear if strict antigen avoidance can prevent progressive disease once a fibroproliferative response is initiated. Inability to identify or confidently link a causative antigen to the disease during initial evaluation can lead to misdiagnosis of the ILD, and a potential missed opportunity for early and impactful intervention.[55]

Bird-associated HP

Precipitins to proteins from avian feathers, faeces, serum and bloom (the waxy dust coating feathers for waterproofing), can be detected in people with repeated exposures to birds and have been associated with the development of HP. This condition, known as 'bird fancier's disease', 'pigeon breeder's lung' and 'feather duvet lung' may be caused by pigeons, birds of the *Psittaciformes* order (cockatiels, parrots, parrakeets, budgerigars, cockatoos), *Passeriforme* order (canaries, finches), fowl (chickens, ducks, geese, turkeys) and from down feathers within bedding and furniture.[56] Bird-associated HP is the most common of the HP subtypes, with pigeons being the most frequently reported exposure in this subgroup.[57,58] Up to 90% of pigeon breeders have detectable IgG antibodies to avian antigen, however only a proportion (6%–20%) are reported to develop HP.[59]

Water damage, rising damp and contaminated water sources associated with HP

HP may be caused by aerosolisation and inhalation of pathogens contaminating water reservoirs or growing on

TABLE 2 Key exposures associated with hypersensitivity pneumonitis.

Source and associated diseases	Domestic and occupational exposures	Antigens
Organic exposures		
Bird-associated		
Pigeons, doves, parrots, canaries, budgerigars, cockatiels, chickens, geese, ducks, down pillows, quilting	Pigeon breeding and racing Bird rearing/veterinary care Domestic pet ownership Agriculture Feather plucking, domestic use	Proteins from bloom, feathers, serum, droppings, organisms associated with birds (fungi, bacteria, viruses, parasites)
Water-associated		
Water damage, under-ventilation, contaminated water reservoirs	Domestic: rising damp, vaporisers, humidifiers, air conditioning, CPAP Occupational: heating, ventilation, and air conditioning maintenance	Moulds, bacteria (especially gram negatives and thermophilic *Actinomycetes*), non-tuberculous mycobacteria, bacterial endotoxins, protozoa (*Amoebae*)
Organic matter-associated		
Agriculture, gardening, food manufacture, lumber work	Farming, organic waste handling, grain processing, animal husbandry, lumber milling, wood stripping and manufacture	Moulds, yeasts, bacteria (thermophilic *Actinomycetes*), grain dust mixtures, mushroom spores, animal fur proteins, insects, mites
Selected diseases arising from contaminated water and organic matter sources		
Hot tub lung	Domestic or occupational hot tub and sauna exposure	*M. avium complex, M. abscessus, M. fortuitum, M. mucogenicum*
Humidifier lung	Polymicrobial contamination of ultrasonic and steam humidifiers	Thermophilic *Actinomycetes, Aspergillus fumigatus, Cladosporium spp, Fusarium* spp., *Klebsiella oxytoca,* bacterial endotoxins, *M. gordonae, Amoebae*
Lifeguard lung	Aerosolisation of contaminated water spray features (indoor pool cleaning and lifeguarding)	Gram negative bacteria, for example, *Pseudomonas* spp., *Stenotrophomonas maltophilia;* endotoxins
Machine operator's lung	Aerosolisation of contaminated water-based metalworking fluid	*M. avium complex, M. immunogenum, Bacillus* spp., *Trichophyton* spp., *Penicillium* spp., *Pseudomonas* spp., *bacterial endotoxin*
Musical instrument HP	Microbes from pooled saliva in wind instruments: bag pipes, saxophone, trombone, bassoon	*M. chelonae, M. abscessus*, *Fusarium* spp., *Penicillium* spp., *Ulocladium botrytis, Phoma* spp., *Stenotrophomonas maltophilia*
Summer-type HP	Mould contamination of Japanese wooden houses	*Trichosporon* spp.
Farmer's lung (and variants)	Mouldy hay, silage	*Saccharomycetes* spp., *Aspergillus* spp., *Absidia corymbifera, Wallemia sebi, Penicllium* spp.
	Soil, compost (gardening, handling of organic waste)	*Aspergillus fumigatus, thermophilic Actinomycetes*, for example, *Saccharopolyspora rectivirgula*
	Contaminated crops: corn, potatoes, onion, nuts, barley, tea, coffee, cane sugar, wine, etc.	*Penicillium chrysogenum, Mesophilic streptomyces, Aspergillus* spp., *Botrytis* spp. *Thermoactinomyces sacchari, Mucor spp*
	Animal husbandry	Animal fur proteins, micro-organisms in feed
Woodworker's lung, Suberosis (from cork)	Contaminated cedar, mahogany, pine, redwood, spruce, maple bark, cork	*Alternaria* spp., *Bacillus subtilis*, *Mucor* spp., *Rhizopus* spp., *Pantoea agglomerans, Penicillium* spp., *Cryptostroma corticale*
Miller's lung, Baker's lung	Contaminated grain and flour dust	*Aspergillus* spp., *Sporobolomyces, grain dust mixture (silica, fungi, insects, mites), wheat weevil*
Mushroom worker's lung	Mouldy compost and mushrooms	Shitake, bunashimeji, himeji, thermophilic *Actinomycetes*

TABLE 2 (Continued)

Selected diseases arising from contaminated water and organic matter sources		
Salami worker's lung, Cheese washer's lung	Inhalation of mould dust during food manufacture	*Aspergillus* spp., *Cladosporium* spp., *Penicillium* spp., *Mucor* spp., *Rhizopus* spp.
Heiner's syndrome	Rare food-induced HP in infants	Cow's milk protein
Inorganic exposures and diseases (selected)		
Chemical alveolitis	Dental products (dental technicians), lacquer, glue	Methyl acrylates
	Manufacture or occupational use of glue, polyurethane foam, spray paint, plastic, car parts, shoes, rubber, elastic fibres	Acid anhydrides and isocyanates
	Powder coating (painters)	Triglycidyl isocyanurate
	Degreaser for metal parts, cleaning agents (e.g., rug-cleaning, spot-cleaning, paint remover)	Trichloroethylene
Berylliosis	Batteries, metals extraction, dental alloy preparation, electronics	Beryllium
Hard metal lung disease	Tool sharpening, manufacture, cutting machine operation, diamond polishing	Tungsten carbide, cobalt
Drug-induced HP	DMARDs, antibiotics, anti-neoplastic agents	Methotrexate, azathioprine, rituximab, penicillins, nitrofurantoin, gemcitabine, bleomycin, immune checkpoint inhibitors

Abbreviations: CPAP, continuous positive airway pressure; DMARDs, disease modifying anti-rheumatic drugs.

surfaces in poorly ventilated or water-damaged living quarters. Polymicrobial fungal and bacterial contaminants are commonly found in water sources associated with HP outbreaks, such as with water-based metalworking fluid in factories, air conditioning and cooling services and fountain features in indoor pools.[29–31] In domestic settings, contamination of stagnant water that is subject to repeated heating, such as misting vaporisers, humidifiers, wind instruments and CPAP machines, may also lead to HP in susceptible individuals.[60–63] Implicated pathogens include mould species (e.g., *Aspergillus, Penicillium, Cladosporium, Trichosporon* and *Mucor* spp.), protozoa (e.g., Amoebae) and some bacteria [e.g., thermophilic actinomycetes (e.g., *Saccharopolyspora rectivirgula*); gram negative rods (e.g., *Pseudomonas* spp., *Stenotrophomonas maltophilia*); and non-tuberculous mycobacteria (NTM)].[42,57,64] Bacterial endotoxin may induce or potentiate HP in some cases.[31,60,63] 'Hot tub lung' is a form of HP associated with frequent use of spas contaminated with *Mycobacterium avium complex* and other NTM species. 'Summer-type' HP is caused by inhalation of the fungus *Trichosporon cutaneum* known to colonize decaying wood in humid climates, and is typically seen in Japan.[65]

Organic matter associated with HP

'Farmer's lung' refers to HP arising from repeated exposure to organic matter such as mouldy hay, contaminated grain silage, compost and damp soil. Indeed, many agriculture-based occupations can lead to HP development due to acute or chronic inhalation of bacteria, moulds, yeasts and/or animal fur proteins. Crop picking, grain refining, fermented food production, bark stripping, animal husbandry and lumber work are notable examples where risk of HP may be increased. Gardening may be an important exposure source in some individuals. Thermophilic actinomycetes, *Aspergillus* spp. and *Penicillium* spp. are the most frequently reported causes for HP in agricultural settings, with hot and humid conditions ideal for their growth.[56] Incidence of HP is reportedly 0.5%–4.4% in farming cohorts.[66]

Inorganic compounds associated with HP

Inorganic compounds are rare but important causes for HP, with specific implications for workplace safety and health. Chemicals such as acid anhydrides, isocyanates, methyl acrylates and chloroethylenes are used broadly in the manufacture of synthetic materials and may induce HP when workers are insufficiently protected from inhalation. Exposures to these compounds may also occur with use of paint, sealant, epoxy resins and glues in occupational and domestic settings. Rare cases of HP have been reported in tilers, dental workers, hairdressers, nail technicians, currency workers, laboratory workers and other professions with regular chemical inhalation.[57] Heavy metals used for industrial purposes such as cobalt, beryllium and zinc can also cause HP.

Drug-induced HP

Specific drugs (e.g., nitrofurantoin, rituximab, penicillins, immune checkpoint inhibitors, cytotoxic agents, etc.) are an important non-inhalational cause of HP, with evidence of increasing incidence of drug-induced ILD due to widespread use of immunogenic agents particularly in oncology.[67,68] Notably, not all drug associated lung pathology manifests as HP, with other well-described patterns including organising

pneumonia (OP), non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), eosinophilic ILD and diffuse alveolar damage. Granulomatous (or sarcoidal) pneumonitis, with or without the interstitial inflammation and bronchiolitis seen in HP, is temporally associated with many agents (e.g., methotrexate, fluoxetine, cocaine, procarbazine, etc.), and may represent a spectrum of hypersensitivity responses to inorganic antigens.[69] A comprehensive list of drugs associated with HP and other lung toxicities is included in the online resource 'Pneumotox'.[70]

Mechanisms for drug-induced HP are poorly understood, however risk is increased with older age, pre-existing lung disease, concomitant lung-toxic therapies such as ionizing radiation and some genetic factors.[68] Due to the frequency of drug induced-ILD (including DI-HP) in oncology, the National Cancer Institute of the National Institutes of Health have developed a severity grading system, (grade 1—mild to grade 5—fatal).[71] These principles may be useful for broader application to non-oncological drugs.

Genetic risk factors

It is now understood that genetic predisposition plays an important role in the development of HP. Various risk alleles have been associated with the development and severity of HP. While genome wide association study (GWAS) data is limited in HP, GWAS in IPF have identified susceptibility polymorphisms in genes involved in innate immunity, antigen presentation, mucin homeostasis and telomere biology.[72] This knowledge has led to identification of specific genetic loci implicated in chronic (fibrotic) HP development and disease outcomes. In a study of two large fibrotic HP cohorts, the MUC5B rs35705950 single nucleotide polymorphism was found with increased frequency and was associated with moderate-to-severe radiographic fibrosis.[73] This minor allele was associated with reduced survival of borderline significance, with adjusted hazard ratio (HR) 2.01, 95% confidence interval (CI) 0.97–4.20, $p = 0.061$. The same polymorphism has also been implicated in IPF pathogenesis but with improved survival.[74] A study comparing tissue transcriptomes in 82 fibrotic HP and 103 IPF subjects identified both shared and distinct patterns of gene expression, with similar MUC5B minor allele frequency.[75] Variants in telomere maintenance genes,[76] and shortened peripheral blood leukocyte telomere length[73,76] have been associated with more extensive fibrosis and inferior survival in both HP and IPF. Other studies have shown associations between HP risk and variants of major histocompatibility complex (MHC) Class II region (HLA-DR and HLA-DQ loci),[77,78] tumour necrosis factor (TNF)-alpha promotor region (associated with reduced TNF-alpha expression) and immunoproteasome/transporter alleles.[79,80] Novel genetic loci (and associated molecular pathways) that are unique to the HP spectrum may be identified through future disease-specific GWAS analyses.

SUMMARY

- Birds, contaminated water reservoirs, and agricultural exposures are common inducers of HP, however a causative antigen is unidentifiable in a proportion of patients.
- Many professions and pastimes are associated with increased HP risk due to antigen sensitisation and repeated exposures.
- An increasing list of therapeutic agents, particularly for oncologic indications, have been associated with development of HP as one of several ILD patterns caused by drugs.
- Several genetic variants have been linked with development and severity of HP.

DIAGNOSIS

Clinical evaluation and multidisciplinary meeting diagnosis

A high index of clinical suspicion for the diagnosis of HP should be maintained in every patient with newly identified ILD. A detailed clinical evaluation for suspected HP should include presenting symptoms and signs, assessment of risk factors relating to HP and ruling out other ILD causes. An exhaustive history of exposures is critical; however, antigen encounters may be overlooked due to varying recollection by the patient or under-emphasis by the clinician. Revisiting the history at subsequent encounters may yield key information, by further prompting or corroborative information from family members.

Confirmation of HP diagnosis involves the integration of clinical assessment, high-resolution computed tomography (HRCT) imaging, and in some cases, bronchoalveolar lavage (BAL) and/or lung biopsy, preferably within an ILD-specific MDM. The MDM should consider what is required for high diagnostic confidence, and identify features of non-fibrotic HP and fibrotic HP. Ideally the MDM should comprise of respiratory clinicians, a thoracic radiologist, pathologist, and where available, rheumatologists, immunologists and occupational physicians.[9,81,82] The opportunity for cross-disciplinary experts to examine key clinical material for consensus diagnosis is of particular importance in HP, where the label may carry major occupational and lifestyle implications. If drug-induced HP is the suspected diagnosis, it is essential to involve the prescribing specialist in disease-specific management decisions. Drug cessation may impact overall prognosis and/or quality of life, necessitating highly specialised knowledge to inform the discussions. Low diagnostic agreement has been reported among experts for HP diagnosis,[83] highlighting the challenges of identifying this condition.

Several ancillary tests have been integrated into the diagnostic workup of HP, some of which are described in further detail below. An American Thoracic Society expert working group evaluated the performance characteristics of tools such as antigen-specific serology, specific inhalational challenges, detailed environmental assessment, lymphocyte proliferation testing and HP questionnaires, finding limitations with each due to lack of standardization and variable diagnostic sensitivity.[84] The need for both clarification of the role of these tests and development of more precise diagnostic biomarkers were highlighted by the working group.

Presenting features

Dyspnoea and cough are often presenting features of HP.[85–87] Additional reported symptoms include chest discomfort or tightness, often with an exertional component. Constitutional or 'flu-like' symptoms (malaise, fevers and chills) and weight loss are uncommon but more likely in the nonfibrotic (inflammatory) form of HP. Depending on the form of HP, symptoms may develop acutely, over days or weeks or insidiously, over months or years. Episodic worsening of symptoms may follow periods of increased allergen exposure.

The most common auscultatory finding is inspiratory crackles. Wheeze and inspiratory squawks are detected less frequently, and are thought to reflect small airways involvement.[88] Digital clubbing is seen in a minority.[87] Exertional and nocturnal oxygen desaturation may be seen, with resting daytime hypoxaemia developing as fibrosis progresses. Pulmonary hypertension and right heart failure may become apparent with advanced disease. Lung function tests commonly demonstrate a restrictive pattern, with reduced spirometric and lung volume measurements and impaired gas transfer, evidenced by reduced diffusing capacity for carbon monoxide (DLCO). Obstruction and evidence of bronchodilator reversibility may also be seen.[87] Specific inhalation challenges to a select panel of antigens have been shown to elicit a hypersensitivity response (e.g., decline in spirometry, leukocytosis on peripheral blood testing, increase in temperature, development of radiologic changes, oxygen desaturation and/or development of symptoms) in sensitised individuals, however reported sensitivity and specificity for the diagnosis of HP are variable.[84,89] Due to lack of standardisation, safety considerations and very limited availability for testing, this is not included in the diagnostic evaluation of HP. Notably, there are no laboratories in Australia or New Zealand currently performing these tests for this indication.

Assessing exposures in the clinical history

A thorough and iterative exposure assessment (including domestic, occupational, medication and hobby exposures), is essential. A systematic approach is important, incorporating the nature, duration, frequency and intensity of exposure contact, as well as the temporal relationship with symptom onset, and whether avoidance led to improved symptoms. HP and ILD-specific exposure questionnaires have been developed for this purpose and may aid in identifying causative antigens by providing a more structured framework than clinical history alone.[58,90,91] Such questionnaires have not been broadly validated, however locally adapted versions including relevant culture- and region-specific exposures may be clinically useful, noting the importance of developing non-English language translated materials.[84,90]

Smoking is associated with reduced risk of HP compared to IPF, however in those who develop HP, smoking increases risk of progression.[92] Viral infections may also sensitize the susceptible individual to environmental antigens.[93] As with all ILD under evaluation, clinical assessment for autoimmune disease as an alternative or overlapping diagnosis is important. Autoantibodies including antinuclear antibody (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), anti-topoisomerase 1/Scl-70, anti-Ro/SSA and anti-La/SSB may be detected in patients with HP, with or without overt clinical features of connective tissue disease (CTD). Coinciding HP and autoimmune features have been reported in up to 15% of patients in fibrotic HP cohorts and may portend poorer prognosis.[94] Where there is difficulty in interpreting the clinical relevance of positive autoantibodies in patients with suspected HP, specialist rheumatology or immunology evaluation may be considered.

Consultation with an occupational or environmental physician or hygienist may be appropriate when an antigen is not clearly identifiable, however, access to such services may be limited. In addition to more detailed history taking and expert knowledge of implicated exposures, these specialists may facilitate home or occupational visits. Causative antigens may be discovered through inspection of ventilation and water stores; identification of water damage, visible mould or other sources of contamination; and sampling of surfaces or air.[84] Given constrained resources and limited evidence of benefit in this area, specialist involvement may be most useful for workplace evaluation (e.g., contaminated metal-workers fluid) or where distinction between several exposures at different sites is important.

Imaging

Volumetric HRCT imaging is an essential component of HP diagnosis and fibrotic versus non-fibrotic phenotyping to inform prognosis and management. The HRCT protocol consists of supine images captured both at deep inspiration and full expiration. Expiratory films are used to confirm variable lung attenuation due to air trapping. Notably, HRCT findings for the different causes of HP, including organic, inorganic and drug exposures, are indistinguishable from each other.

HRCT findings in non-fibrotic HP

The typical non-fibrotic HP pattern demonstrates diffuse lung abnormalities indicative of parenchymal infiltration, including ground glass opacities (GGO) and mosaic attenuation, and evidence of small airway disease with ill-defined, centrilobular nodules and air trapping on expiratory images (Figure 2A).[3] Features of airspace consolidation and cysts may be suggestive but not definitive for HP, within the appropriate clinical context. A mosaic pattern results from areas of increased attenuation secondary to pneumonitis adjacent to areas of normal or low attenuation secondary to bronchiolar obstruction.

HRCT findings in fibrotic HP

Patients with HP may also display features of fibrosis, including reticulation, traction bronchiectasis and honeycombing (Figure 2B). These morphologic features of fibrotic HP portend a poorer prognosis.[5,7,52,95] Mosaic attenuation adjacent to normal lung and ground glass is known as the 'three-density' pattern (previously called the 'headcheese sign'), and when present in ≥5 lobules and in ≥3 lobes is highly specific for fibrotic HP.[96]

Additional HRCT findings

Concomitant emphysema is reported in 7%–23% fibrotic HP patients (including a proportion without any smoking history).[97,98] Demographics, age and synergistic effects of tobacco and occupation-related inhalational exposures are among suggested risk factors.[97,98] Progressive fibrotic HP and concomitant emphysema are associated with the development of pulmonary hypertension (PH), with suggestive features on imaging including right ventricular and atrial enlargement, and dilated pulmonary artery trunk.[99] Correlating findings may be evident on clinical examination and can be confirmed with echocardiography and/or right heart catheter, as clinically indicated.

Distinguishing HP from other disease patterns on HRCT

Differentiating HP from other ILDs, especially IPF, may be difficult when atypical imaging features are present. Aside from the typical features detailed above, other radiologic patterns including UIP, NSIP, OP or a combination of these entities may be seen with HP. Several clues may assist with the distinction of atypical fibrotic HP from UIP due to IPF, including distribution of fibrosis, ground glass change and air trapping. Basal-predominant fibrosis is more suggestive of UIP-IPF, whereas diffuse abnormalities, in a craniocaudal or slight upper zone distribution may favour HP. Mosaic attenuation can be present to some degree in association with areas of fibrosis in IPF but is more suggestive of HP when well-demarcated and occurring away from fibrotic areas. The three-density pattern of hypoattenuation, hyperattenuation and normal areas of lung parenchyma enables a high-confidence fibrotic HP diagnosis due to its specificity.[96,100] A pragmatic approach for distinguishing UIP-IPF from fibrotic HP has been described by Marinescu and colleagues, integrating features from each of the recent respective international guidelines (reproduced in Figure 3).[100]

The role of bronchoalveolar lavage analysis and lung biopsy

Where diagnostic confidence remains low despite clinical history and HRCT, further investigations including BAL and/or lung biopsy may be undertaken.

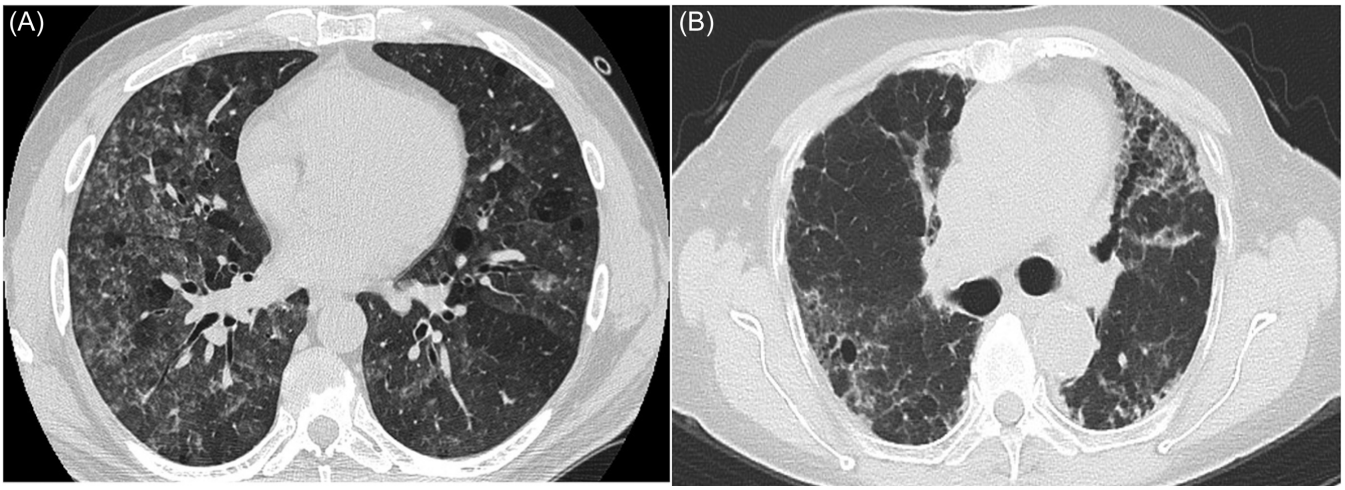

FIGURE 2 Radiologic features of HP. (A) Nonfibrotic HP demonstrating centrilobular nodules, regions of mosaic attenuation and occasional lung cysts. (B) Fibrotic HP demonstrating reticular fibrosis and architectural distortion associated with background mosaic attenuation.

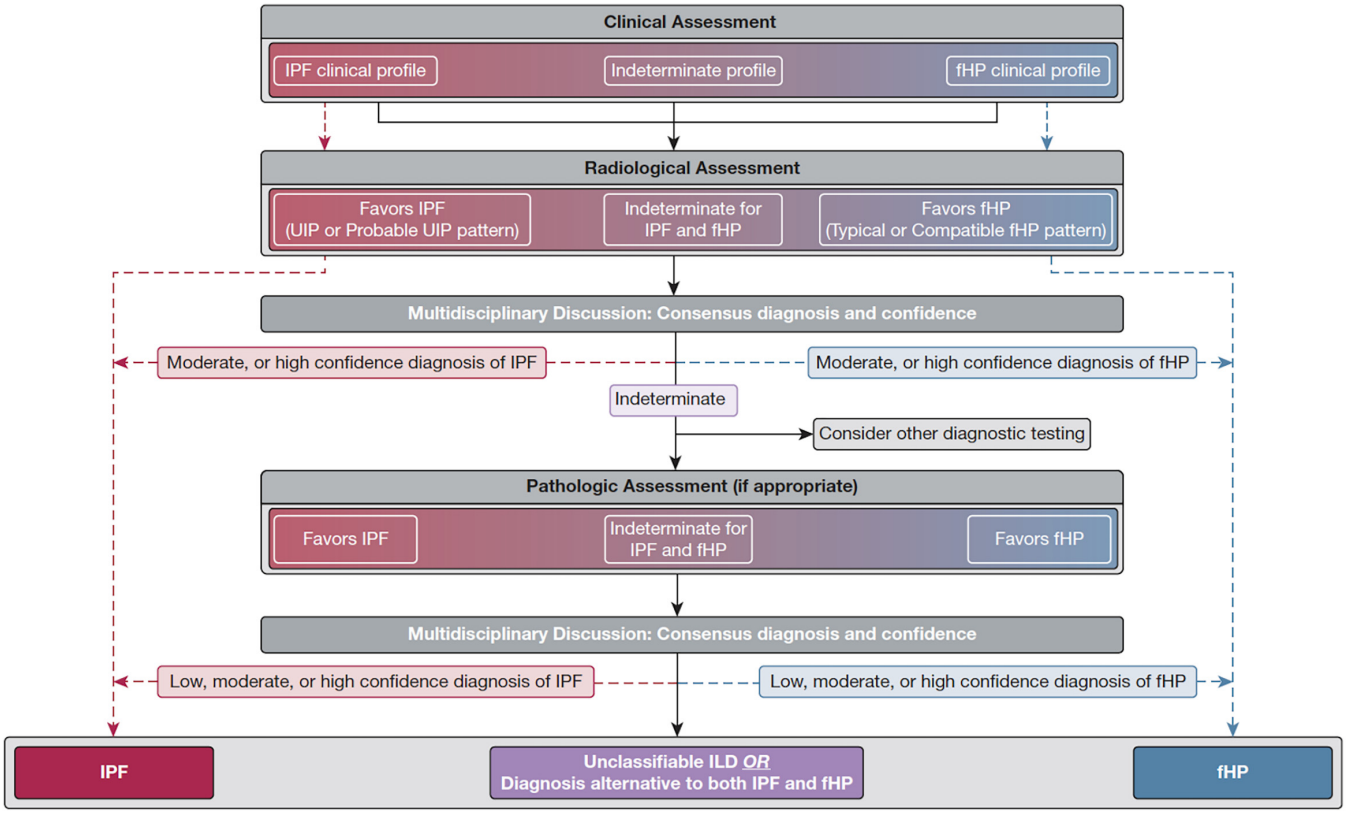

FIGURE 3 Stepwise algorithm for distinguishing fibrotic HP from IPF. From: Marinescu et al. Integration and Application of Clinical Practice Guidelines for the Diagnosis of Idiopathic Pulmonary Fibrosis and Fibrotic Hypersensitivity Pneumonitis. Chest 2022. Reproduced with permission from publisher.

BAL fluid analysis

Bronchoscopy is performed to obtain BAL fluid for evaluation, including differential cell counts. Lymphocytosis supports a diagnosis of HP, but absence of lymphocytosis does not exclude HP.[101,102] There is no clear diagnostic threshold for a confident diagnosis of HP; a >40% threshold is used in diagnostic guidelines, but this threshold has limited accuracy (sensitivity 43%, and specificity 86% in a meta-analysis of studies), and lower thresholds (including 30% and 20% lymphocytosis) may be supportive of a diagnosis of HP in the context of other features.[103,104] The degree of lymphocytosis is inversely correlated with degree of fibrosis, and may be lower in elderly patients and smokers.[59,104] A low CD4:CD8 BAL lymphocyte ratio may be seen, but this index is poorly sensitive and specific for HP, limiting its utility as a discriminatory index. Other BAL fluid analyses (e.g., cultures, staining and cytology) may be useful for revealing alternate diagnoses, for example, eosinophilic pneumonia, infection and malignancy.

Biopsy techniques

Histopathologic sampling may be required when the diagnosis remains uncertain despite baseline investigations. Surgical lung biopsy (SLB) is most likely to yield sufficient tissue for diagnosis but carries morbidity and mortality risk. Adverse outcomes with SLB are more likely with non-elective biopsy for rapidly progressive disease, male sex, advanced age and multi-morbidity.[105–107] The transbronchial lung cryobiopsy is performed in many centres as a less invasive alternative to SLB with 79%–85% diagnostic yield, and good diagnostic agreement with SLB at MDM.[108,109] In distinguishing HP from IPF, however, the cryobiopsy may be less reliable than SLB.[110] Transbronchial forceps biopsy is unlikely to yield sufficient diagnostic material and thus is not recommended. The decision to proceed to biopsy and choice of technique is influenced by patient factors and available resources. Expert guidelines in both IPF and HP recommend MDM discussion should inform this decision, aiming to minimise unnecessary invasive investigations if the diagnosis can be made through other means.[3,15]

Histopathological findings

Histologically, nonfibrotic HP classically shows a triad of chronic bronchiolitis, adjacent peribronchiolar interstitial lymphocyte-predominant chronic inflammation and poorly formed interstitial non-necrotising granulomas and/or giant cells (Figure 4A).[101,111–114] The complete triad of features is

present in 50%–73% of SLB specimens enabling a histologic diagnosis of 'typical for HP', when alternative diagnostic features are absent.[102,108,115,116] Focal organising pneumonia may be seen, typically in a peribronchiolar distribution.[111,117] Features suggesting an alternative diagnosis include lymphoid follicles with germinal centres and anything more than rare eosinophils or neutrophils.[3,101,117]

Fibrotic HP is characterized by a chronic fibrosing interstitial pneumonia together with poorly formed non-necrotising granulomas or giant cells (in some cases), with or without co-existent features of nonfibrotic HP and absence of features to suggest an alternative diagnosis (Figure 4B).[3] The three main patterns of interstitial fibrosis are UIP-like, fibrotic NSIP-like and peribronchiolar; a combination of UIP-like fibrosis along with peribronchiolar fibrosis is commonly seen.[102,111,115,118–120] Bridging fibrosis or peribronchiolar metaplasia may also be observed.[114,118,121] The presence of co-existent nonfibrotic HP features, interstitial giant cells or poorly formed granulomas, peribronchiolar or bridging fibrosis and less subpleural fibrosis all suggest a diagnosis of fibrotic HP over UIP-IPF.[118,119] As with imaging patterns, there are no specific distinguishing histopathological characteristics for the different causes of HP. An exception is hot tub lung, where airway-centred granulomata tend to be more well-formed than in classical HP.[113]

Serology

Detection of serum-specific IgG antibodies to the suspected offending antigen can sometimes prove useful in guiding avoidance strategies as well as diagnosis. Commonly available tests for identifying sensitisation towards inhaled antigens include serum specific IgG for *Saccharopolyspora rectivirgula* (formerly known as *Micropolyspora faeni*, a spore-forming thermophilic bacteria associated with farmer's lung), pigeon and budgerigar proteins (associated with bird fancier's lung) and *Aspergillus fumigatus*. Serum-specific IgG antibodies can be detected by several techniques. Semi-quantitative immunoprecipitation techniques (Ouchterlony double immunodiffusion method, electrosyneresis or immunoelectrophoresis) are highly specific but technically challenging to perform. Alternative immunoassays include enzyme-linked immunosorbent assay (ELISA) or ImmunoCap, with ELISA demonstrating higher sensitivity.[122] Correlations have been found between increasing antibody titres (using either assay) and likelihood of disease due to the specific corresponding antigen; conversely, decreased titres have been observed with successful antigen avoidance.[123]

The diversity of antibody detection methods and antigen preparations, each with distinct performance characteristics and suboptimal standardization, results in significant inter-laboratory variability.[39] Regardless of methodology, it is noteworthy that positive antibody detection is a marker of exposure and sensitisation, but does not necessarily indicate disease causality.[124] The concentration, frequency and latency of exposure before development of detectable antibodies is not known. Furthermore, false negative results can occur, and relevant antibodies may be missed in the presence of incorrect serum dilution or inappropriate antigen selection.[125] In a recent pooled analysis, serum-specific IgG had a sensitivity of 83%, and specificity of 68% for probable HP diagnoses in unspecified ILD populations.[84] In particular, sensitivity and specificity are reduced in fibrotic disease compared with acute and recurrent disease phenotypes.[123,126] In practice, serological testing serves as a complementary rather than primary

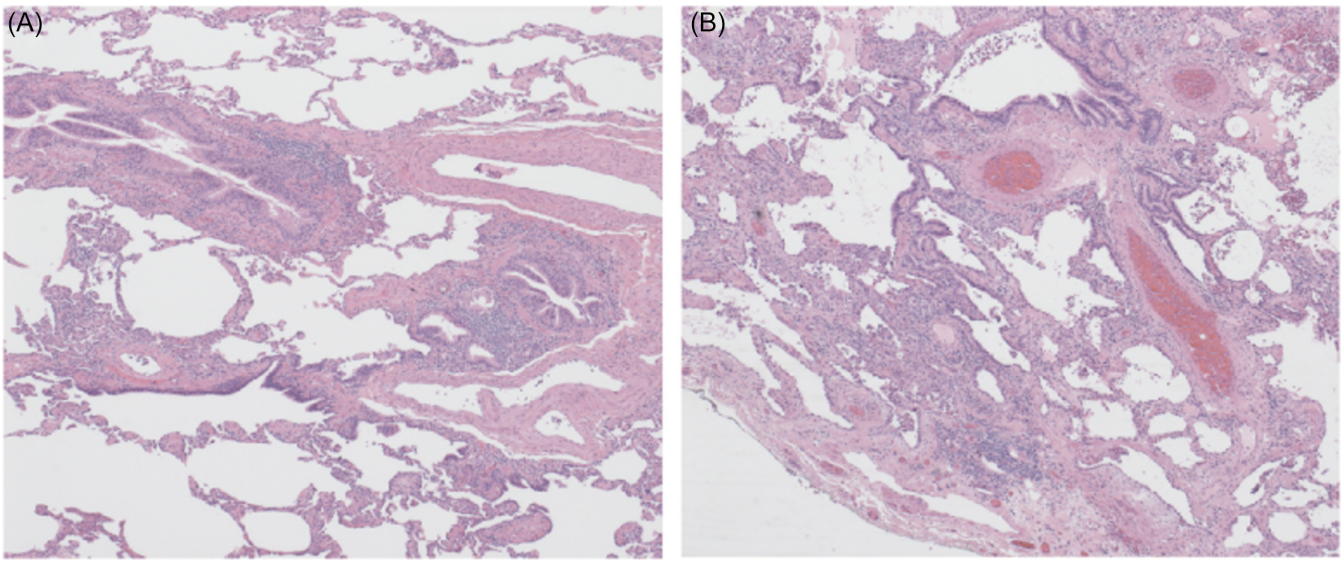

FIGURE 4 Histopathological features of HP. (A) Nonfibrotic HP showing chronic bronchiolitis, peribronchiolar interstitial chronic inflammation and interstitial giant cells. (B) Fibrotic HP showing interstitial fibrosis (with a non-specific interstitial pneumonia-like pattern in this case), peribronchiolar fibrosis and peribronchiolar chronic inflammation. Interstitial giant cells were also present elsewhere in the biopsy (not shown). (Haematoxylin and eosin stained sections). Original magnification × 100.

diagnostic tool, with limited ability to definitively confirm or exclude disease. Findings should be interpreted in combination with other clinical parameters.

SUMMARY

- Diagnosis of HP requires a detailed exposure history, HRCT with expiratory sequences and exclusion of other causes of ILD, particularly IPF and CTD-ILD.
- Elevated serum-specific IgG titres for common inhaled antigens associated with HP (e.g., avian proteins, bacteria and fungi) indicate sensitisation but do not confirm disease causality.
- Ancillary testing with serum-specific IgG, BAL fluid analysis and occasionally tissue histopathology, may help to increase diagnostic confidence when clinical and radiologic features are atypical and/or causative antigens are not clearly identified.
- Ideally, all cases of suspected HP should be discussed within an ILD MDM.

MONITORING

Patients with HP should be monitored closely to ensure treatment goals are met and to assess for disease progression. Review should be undertaken every three- to six-months, depending on disease status. Clinical history, lung function tests (particularly FVC and DLCO), six-minute walk tests and periodic HRCT are used to monitor disease. Ancillary testing including echocardiography, polysomnography and bone mineral densitometry, may be indicated over the disease course.

PROGNOSIS

Accurate prediction of HP disease behaviour is an important but elusive goal, and while there are several recognized prognostic variables (Table 3), no single variable can reliably predict prognosis. A study of plasma biomarkers in 589 ILD patients, including 242 (41%) with fibrotic HP, identified a 17-protein signature predictive of progressive disease at baseline blood sampling.[131] Further development and validation of such proteomic platforms for personalised disease prediction may lead to their future translation into clinical practice.

Pattern and extent of pulmonary fibrosis

The extent of fibrosis as well as the presence of traction bronchiectasis and honeycomb cysts signify 'IPF-like' disease behaviour and poorer prognosis in HP.[7,132] Histopathological analyses have also demonstrated that UIP pattern, fibroblastic foci and dense collagen fibrosis confer a universally poor prognosis in HP.[8] Contrastingly, radiological features of inflammatory alveolitis (ground glass attenuation) and/or bronchiolitis (air trapping and mosaic attenuation) predict survival benefit in HP.[95]

TABLE 3 Risk factors for poor prognosis in HP.

Intrinsic factors	Older age[26,127]
	Male sex[26,53,127]
	Presence of concomitant autoimmune features[94]
	Genetic (shortened telomere length, rare variants in telomere-related genes, MUC5B rs35705950 minor allele)[73,76]
Exposures	Unidentifiable inciting antigen[10,14,51]
	Duration of exposure to inciting antigen[128]
	History of smoking[10,129]
Physiology	Low baseline or decline in FVC[14,129]
	Low baseline DLCO[6]
	Desaturation <88% on 6MWT[127]
Radiology	Presence and extent of fibrosis on HRCT[5,7,52,127,129]
	UIP pattern or honeycomb cysts on HRCT[6,7,127]
	Absence of air trapping and mosaic attenuation[95,127]
BAL and Histopathology	Lower lymphocyte count on BAL[6,130]
	UIP or fibrotic NSIP pattern[6,8]

Note: Adapted from with permission from Hamblin, Prosch et al. Diagnosis, course, and management of hypersensitivity pneumonitis. *European Respiratory Journal*. 2022.[124]

Abbreviations: DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

BAL lymphocytosis

Preliminary data suggest the presence of BAL lymphocytosis may predict response to immunosuppressive treatment in patients with HP, although the optimal lymphocytosis threshold has not been determined.[133,134] Conversely, the absence of a BAL lymphocytosis is associated with a poorer long term survival.[130]

MANAGEMENT

Antigen avoidance

The initial step in the management of HP is identification and avoidance of active causative exposures. Ongoing exposure is associated with further lung function decline, and removal of exposure may result in improvement.[14] There is little evidence-based guidance on how to remediate exposures in HP, and recommendations are derived from other

occupational related respiratory conditions such as asthma.[135]

At a population level, preventative public health measures have been shown to positively impact respiratory health, and may be an important strategy for those at risk of HP. A landmark New Zealand study showed that the intervention of improved insulation in 1350 households from seven low-income communities led to a significant reduction in household mould, reduced incidence in self-reported respiratory symptoms and lower health-care utilization.[136] Elimination of the source is far more effective than personal protective equipment for all causes of HP (Table 4). Examples include a change in role or location for workplace exposures, and complete removal of birds, feathers and droppings, as well as a deep clean of soft furnishings for avian-associated HP. As detailed in Section 7.1.2, occupational medicine specialists and environmental hygienists can play an important role in evaluating the work and home environment, especially when there are clusters of cases, or the cause for confirmed HP remains occult despite detailed exposure assessment in the clinic.

For suspected drug-induced HP, severity-based recommendations for drug cessation with or without institution of corticosteroids, have been developed for oncological medicines but may be useful to consider for other agents.[68,71,142] Notably, the level of evidence for these recommendations is low. Given the potential impact on underlying disease control and prognosis, all management decisions should be made in consultation with the treating clinician.

TABLE 4 Exposure remediation and harm minimisation measures.

Hierarchy of controls based on effectiveness[a]	Examples
Elimination	Change in work role Removal of birds and deep cleaning[137] Removal of mould, replacement of plaster board, broken water pipes, ventilation systems
Substitution	Using fresh metal-working fluids[138] Replacement of fertilizers that cause high dust levels with liquid formulations
Engineering controls	Storing hay in bales rather than loose to reduce mould growth[139] Dry machining or minimum quantity lubricant for machine operation[140]
Administrative controls	Education and training programs Shift rotations to limit number of exposed workers
Personal protective equipment	Respirators for farmers[141] and other agricultural workers

[a]Elimination is the most important intervention for mitigating or reversing the impact of antigen exposure on human health. Personal protective equipment whilst important, should be considered the least effective of the strategies for harm minimisation.

Pharmacotherapy

Where there are ongoing clinical symptoms or lung function decline despite exposure avoidance (or where the exposure is unknown), pharmacotherapy is recommended. There is limited availability of high quality, prospective evidence to inform the optimal management of HP. In the absence of specific therapeutic guidelines, treatment approaches are derived from expert consensus opinion, clinical experience and extrapolation from other inflammatory and fibrotic lung diseases. Previously, the standard treatment regimen included systemic corticosteroids followed by a steroid-sparing agent. Although this strategy may be reasonable in many, an increasing understanding of the pathogenesis and disease trajectory of HP and other ILDs highlights the need for more individualized therapeutic pathways. Clinical features that may direct treatment decisions throughout the disease course include extent of radiologic inflammation and/or fibrosis, airways versus parenchymal involvement, physiologic severity, disease behaviour, relevant comorbidities, likelihood of complete remediation from the causative antigen and response or lack of response to prior therapy through serial evaluation (Figure 5).

Careful discussion of anticipated treatment side effects with the patient and their carer(s) is important, as is the establishment and communication of goals of therapy. For nonfibrotic HP, improvement in clinical parameters with therapy may be expected, whereas disease stabilization (or slowing of progression) may be more realistic goals in patients with predominantly fibrotic HP.

Immunosuppression

Corticosteroids

Moderate-to-high dose systemic corticosteroids would usually be considered for HP patients with features of inflammation (e.g., GGO on HRCT, BAL lymphocytosis, well-documented exposure with acute or sub-acute symptom onset). For rapid onset pneumonitis with severe physiologic compromise, induction therapy may comprise of pulsed-dose intravenous methylprednisolone, followed by high-dose oral corticosteroids and often steroid-sparing agents (see below). The quality of supportive evidence for corticosteroids in HP is very low and thus, decision-making for dose and duration may best be informed by clinical judgement of disease-responsiveness and side effect profile. In a randomized controlled trial of 36 patients with acute farmer's lung, prednisolone compared with placebo resulted

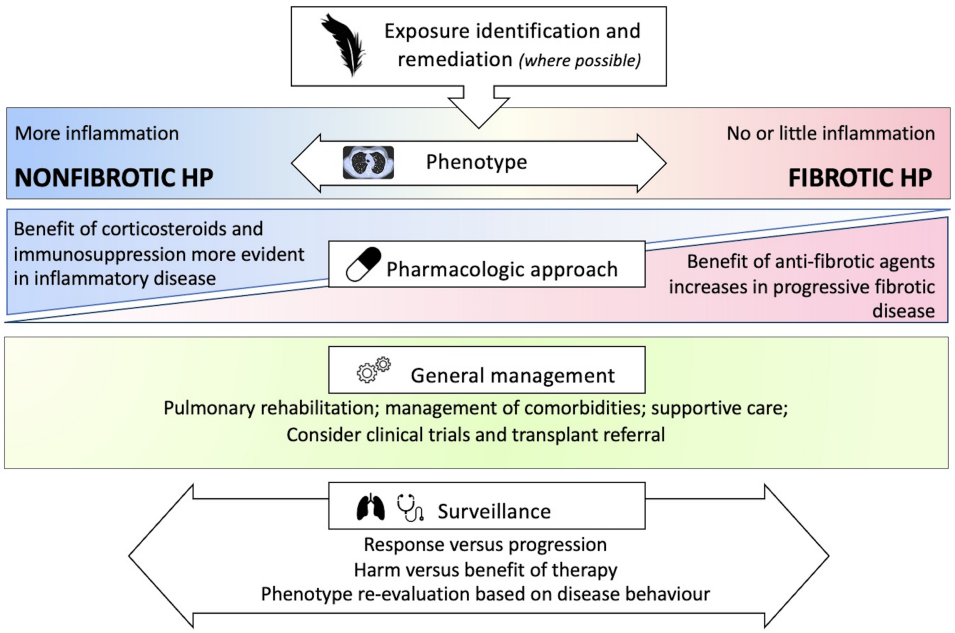

FIGURE 5 Management approach to HP. Priority must be given to the identification and complete removal of causative antigens in confirmed or suspected HP cases. Initial pharmacotherapy should be guided by the extent of inflammatory and fibrotic features using available clinical data. Non-pharmacologic management focusing on quality of life is crucial for all patients. Regular surveillance is recommended, with introduction of additional or alternative therapies informed by careful consideration of risk versus benefit.

in improved DLCO at 1 month, but not in FVC or DLCO at 5 years.[143] In a retrospective cohort study including both fibrotic and nonfibrotic HP patients, both corticosteroid initiation and antigen avoidance were associated with improved lung function in nonfibrotic HP.[51] Following commencement of corticosteroids, nonfibrotic HP patients experienced a reversal in monthly FVC trends from a decline of 0.35% to an increase of 0.84% ($p < 0.001$), and a non-significant increase in DLCO of 3.38% ($p = 0.081$).[51] Neither corticosteroids nor antigen avoidance resulted in statistically significant responses in the fibrotic group. The retrospective nature of the study limits any conclusions regarding immunosuppression in fibrotic HP, however the question of harm versus benefit of such treatment is important to consider in clinical practice. Following corticosteroid initiation, timely re-evaluation (e.g., between 6 and 12 weeks) is important to ensure improvement or stabilization in clinical symptoms and lung function, and to manage steroid-related side effects.

Immunosuppressive agents

A steroid-sparing agent (e.g., mycophenolate mofetil (MMF), azathioprine, cyclophosphamide, rituximab) may enable weaning of corticosteroids and maintenance of therapeutic benefit. In some patients, upfront combination low-to-moderate dose corticosteroids and steroid-sparing therapy may be reasonable, particularly if unacceptable risk of steroid side effects prohibits higher dosing. Several retrospective studies demonstrate a statistically significant improvement in DLCO or FVC following treatment with either MMF or azathioprine.[144–146] It is uncertain if the modest improvements in DLCO (at best 4.2%) and nearly equivocal FVC in these studies represent clinically important differences, with the greatest benefits appearing to be disease stabilization along with reduction in corticosteroid dosage. Other studies of fibrotic HP have shown progression despite MMF, azathioprine or corticosteroids.[51,146] All studies of this nature may be confounded by greater use of immunosuppression in patients with progressive disease behaviour and worse outcomes, compared with those with an inherently favourable prognosis. In a retrospective study of 131 HP patients, MMF or azathioprine use was associated with fewer treatment-emergent side effects than prednisone monotherapy, and similar rates of FVC decline were seen with each of these second agents.[146] Notably, FVC decline was attenuated in the group commenced on MMF or azathioprine after initial prednisone (−0.7% pre-treatment vs. −0.2% post-treatment, $p = 0.001$), supporting the benefit of timely introduction of these agents in selected patients. Second-line immunosuppressive agents (MMF, azathioprine, methotrexate) have not been compared head-to-head, and so the choice of agent is often guided by potential side effects and clinician experience. Limited evidence suggests type of antigen exposure may influence response to specific agents.[147] There is case series-level evidence only for third-line agents including rituximab in HP.[148,149] In a population with CTD-ILD or idiopathic NSIP, rituximab combined with MMF had a superior impact on lung function to MMF monotherapy.[150] A higher incidence of infections was observed with combination therapy. A similar study evaluating rituximab in patients with PPF and overlapping inflammatory features, including those with HP, is underway (ClinicalTrials.gov ID: NCT05596786). Accelerated disease following infective exacerbations is an important consideration when prescribing immunosuppression in HP patients with fibrotic features. Increased observed mortality was seen with azathioprine and prednisone in IPF subjects in the PANTHER trial, likely relating to increased vulnerability to infection.[151]

One retrospective multi-centre study evaluated the impact of MMF (vs. no treatment) on survival in 208 fibrotic

HP patients, stratified into quartiles by peripheral blood telomere length.[152] Patients in the quartile with shortest telomere length had poorest survival, with no benefit seen with MMF use. MMF did confer a mortality benefit in those with higher telomere lengths. Contrastingly, a subsequent multicentre retrospective study by the same authors, expanded to include 938 non-IPF fibrotic ILD patients, found no survival benefit with immunosuppression across the spectrum of telomere lengths, including in the subgroup (~25%) with fibrotic HP.[153] The poorest outcomes were found with immunosuppression use in patients with telomere length below the 10th centile. Further evidence evaluating the benefits and potential harms of immunosuppression in fibrotic HP is needed.

Despite this uncertainty, when both inflammatory and fibrotic clinical features are present, immunosuppressive therapy may still be reasonable, albeit with a lower expected magnitude of benefit than predominantly inflammatory lung disease.

The duration of treatment for predominantly inflammatory HP is not clear. If clinical remission is achieved, it may be reasonable to taper immunosuppression after 2 years of treatment, particularly when antigen avoidance can be assured. Long-term maintenance with a degree of immunosuppressive therapy (either combination or as monotherapy) is common in clinical practice, particularly in the setting of occult exposure, or if substantial irreversible lung disease has already developed before treatment initiation. Some experts, however, have proposed complete withdrawal of immunosuppression in progressive fibrotic HP where no benefit has been demonstrated.[102] Notably, the evidence for either approach is limited.

Modifiers such as patient preference, disease severity, comorbidities, side effects, telomere length (where available) and expected response to immunosuppression should guide dosage and treatment course for the individual. Where there is a temporal relationship between immunosuppression and disease worsening due to recurrent or severe respiratory tract infections or uncontrolled weight loss from treatment side effects, the decision to cease therapy will be more straightforward. Importantly, fibrotic HP may progress even in the absence of antigen, as considered in further detail below. Three-to-six-monthly clinical assessment, including serial lung function tests, is important. Clinical indices of disease worsening can be evaluated with progress imaging, with HRCT providing more objective quantification of inflammatory and fibrotic features to enable further treatment decisions.

Antifibrotic agents

Patients with fibrotic HP who progress despite antigen remediation, with or without immunosuppression, are considered to have PPF disease behaviour. In such cases, there is good evidence for the introduction of antifibrotic therapy, as supported by the ATS/ERS/JRS/ALAT clinical guidelines for PPF.[15] Both nintedanib and pirfenidone have had regulatory body approval and subsidization for the indication of IPF in Australia and New Zealand for several years. In addition to IPF, nintedanib can be prescribed for the indication of non-IPF 'PF-ILD' (PPF) in Australia, but not in New Zealand (as of April 2024). Pirfenidone is not authorized for diseases other than IPF in either country. Criteria for accessing nintedanib in Australia through the Pharmaceutical Benefits Scheme are based on the INBUILD trial, (>10% relative FVC% decline or 5% relative FVC% decline plus radiological or clinical progression over 24 months).[18] The INBUILD trial recruited patients with progressive fibrosing ILDs other than IPF (including fibrotic HP), demonstrating reduction in the rate of FVC decline in the nintedanib arm compared to placebo at 52 weeks, with a similar efficacy to IPF.[18] Although underpowered to detect any subgroup differences, subgroup analysis in HP revealed a nonsignificant reduction in FVC decline (73 mL/year, 95% CI −8.6 to 154.8).[154] The RELIEF trial studied 127 PPF patients (21% with fibrotic HP), randomly assigned to pirfenidone or placebo, in addition to background therapy.[16] The study was terminated early due to slow recruitment, but demonstrated a significantly lower decline in FVC in the treatment arm at 48 weeks ($p = 0.043$). Another study, terminated early due to COVID-19, demonstrated reduced FVC% decline, and improved progression-free survival.[155] A small randomised controlled trial ($n = 40$) compared pirfenidone plus usual therapy to usual therapy alone in fibrotic HP patients with an absolute FVC decline >5% in the preceding 6 months.[156] Significant between-group differences at 6 months were demonstrated in FVC, DLCO, and 6-minute walk distance (6MWD), favouring pirfenidone.

Evidence for upfront anti-fibrotic therapy (i.e., initiated prior to clinical progression) is limited. A randomised prospective open-label study in 22 fibrotic HP patients (all receiving background prednisone plus azathioprine) found no differences in FVC or DLCO at 12 months using pirfenidone compared to placebo.[157]

Ongoing clinical trials

A small number of HP-specific trials are currently in progress, evaluating the role of mycophenolate mofetil (NCT05626387), prednisolone (NCT04402177) and pulmonary rehabilitation (NCT04561479). Numerous clinical trials are recruiting PPF patients (inclusive of fibrotic HP), with recent promising results in phase II trials of agents inhibiting various pro-fibrotic mediators, (NCT05139719, NCT05321082 and NCT05321082).[158–160] Randomised clinical trials designed specifically for HP cohorts are critically needed. Robust evidence is necessary not only to clarify the role of commonly available treatments such as immunosuppressants and antifibrotic agents, but also for the development of new therapies to improve outcomes in HP.

Current best practice for HP management involves offering all appropriate patients the ability to enrol in suitable clinical trials. In Australia and New Zealand, a list of

the active ILD clinical trials, and their recruiting trial sites is available on the Pulmonary Fibrosis Australasian Clinical Trials Network (PACT) website (https://pact.lungfoundation.com.au/). While some patients may have difficulty accessing clinical trials, current efforts are being focused on improving and standardising trials access for all patients with HP across Australia and New Zealand, particularly those in rural and remote settings.

SUMMARY

- The current pharmacotherapeutic approach for nonfibrotic HP typically involves combinations of corticosteroids and other immunosuppressive agents.
- Antifibrotic agent nintedanib is approved for HP patients with progressive fibrotic disease in Australia, but is not yet funded for indications other than IPF in New Zealand. This agent may be used on its own or in addition to immunosuppressive therapies, depending on individual features.
- Clinical trial referral may be appropriate for some HP patients.

Non-pharmacological therapy

In addition to antigen avoidance and pharmacological agents, several non-pharmacological therapies have demonstrated efficacy in HP and apply to the general management of all ILD patients. Pulmonary rehabilitation, oxygen therapy, lung transplantation and palliative care are discussed here. Other measures such as vaccination, monitoring for and managing disease complications such as pulmonary hypertension, and self-management strategies are covered in the 2023 revised TSANZ position statement for treatment of IPF and PPF.[161]

Pulmonary rehabilitation

People living with HP frequently experience dyspnoea, fatigue, reduced exercise tolerance and diminished quality of life.[162] Although not studied in HP specifically, robust evidence indicates improved symptoms, functional capacity and overall health status with the intervention of pulmonary rehabilitation in ILD cohorts.[163–165] These improvements are apparent regardless of ILD subtype or disease severity. Participation in pulmonary rehabilitation, particularly those with exertional symptoms, should be encouraged, with data suggesting greater response in those with early disease.[166] Despite the expected benefit, standard guideline-based exercise training strategies may not be optimal for ILD patients. Pulmonary rehabilitation programs rely on progression of exercise training, and this may not be achieved in all ILD patients. High intensity interval training, as an alternative strategy is currently under investigation in an Australian multi-centre trial.[167] Telerehabilitation appears to confer similar benefits to centre-based pulmonary rehabilitation in patients with chronic respiratory disease including ILD, but outcomes specific to ILD or HP have not been fully elucidated.[168]

Oxygen therapy

Patients with HP (and ILD broadly) may develop clinically significant hypoxaemia in the setting of progressive lung fibrosis. Clinical practice guidelines recommend long-term oxygen therapy (≥15 h/day) in patients with severe chronic resting hypoxaemia, based on evidence for mortality benefit in chronic obstructive pulmonary disease populations.[169,170] The benefit of ambulatory oxygen in patients with isolated exertional hypoxaemia is less clear. Although improved exercise performance has been reported in ILD patients using supplemental oxygen in laboratory settings, the impact in daily life is less well defined.[171,172] A crossover trial of 2-week ambulatory oxygen in fibrotic ILD demonstrated improved quality of life, however the longer-term impact is unknown.[172] A current multi-centre Australian study may provide insight in this area.[173] Whilst oxygen therapy may improve exercise tolerance, confidence and symptom control, it can be associated with substantial patient and caregiver burden, including embarrassment, fear of running out of oxygen, difficulty managing complex equipment and unmet expectations for symptom relief.[171] Access programs and cost reimbursements also vary across jurisdictions. Ambulatory oxygen therapy for use in those with isolated exertional hypoxaemia should, therefore, be a shared decision between patients, caregivers and clinicians, considering the complexities of likely benefits, potential harms and personal circumstances and preferences.

Lung transplantation

ILD (including fibrotic HP) has been the most common worldwide indication for lung transplantation since 2007 and continues to increase.[174] Patients with HP that have a PPF phenotype may have a trajectory similar to IPF and should be referred early for transplant consideration.[12,175] When determining suitability for referral to a lung transplant centre, considerations should include comorbidities, prognosis, transplant risk and patient goals.[176] While there is no absolute upper age limit, increased recipient age is a risk factor for both 12-month and conditional 5-year survival post lung transplantation.[174]

Indications for transplant referral and listing are summarised in previously published guidelines.[174] Lung transplant should be considered for patients with >50% risk of

dying from their disease within 2 years, and >80% likelihood of 5-year post-transplant survival provided there is adequate graft function if transplanted.[176] Factors affecting transplant referral and evaluation in the ILD population include blood type, size matching, breadth of alloimmune sensitisation, advanced age, known telomere disorders, prior corticosteroid use, body mass index, deconditioning, frailty and single versus bilateral lung transplantation.[175] Retrospective cohort studies of transplanted HP patients demonstrate survival rates of 85%–89%, 75%–84% and 70%–84% at 1, 3 and 5 years post-transplant, respectively.[177,178] Median survival of 9.2 years for HP patients reported in one study was significantly better than survival in transplanted IPF patients.[178] In the same study, recurrence of HP was identified in 6% of grafts post transplantation following re-exposure to the culprit antigen.[178] The recurrent disease was manageable with subsequent antigen avoidance and increased immunosuppression.

Palliative care

Palliative care entails both supportive measures for symptom management and end-of-life care. While few studies specifically focus on the HP population, evidence-based strategies for ILD more broadly are applicable. Integration of palliative care in the management of patients with ILD and other diseases with refractory breathlessness can improve symptom control and health-related quality of life, as well as reduced healthcare use and in-hospital deaths.[179–184] Palliative care involvement may be prompted by deterioration in health status, such as hospitalisation, functional decline and initiation of oxygen therapy.[185] There are limited evidence-based supportive measures in alleviating dyspnoea and cough in ILD populations with symptoms often requiring individualised treatment trials. A placebo-controlled crossover study of controlled-release morphine in 44 IPF patients demonstrated a significant reduction in cough frequency with the morphine, supporting the common practice of opiate use in patients with advancing fibrotic lung disease.[186] Timely discussion of end-of-life care, including treatment goals and limitations, with shared decision-making between patients, caregivers and the treating team is desirable, and can improve the illness experience.[187]

ACUTE EXACERBATIONS

Acute exacerbations (AE) in HP may relate to continuous and intense antigen exposure, characterized by increased or new mosaic attenuation and air trapping on HRCT, and varying degrees of respiratory compromise. Patients generally respond well to antigen removal and high dose corticosteroids in such instances, however refractory, fatal cases have been reported.[56] AEs may also develop from other causes, similar to IPF and fibrosing-ILDs in general. Known non-antigen triggers for AE include infection, airway procedures, mechanical ventilation, aspiration, pneumothorax, drug toxicity and ionizing radiation.[188,189] In one series of patients with biopsy-proven HP, AE of any aetiology were associated with 44.4% in-hospital mortality risk and poorer long-term prognosis compared with those who had no AE.[188] A recent study comparing fibrotic HP and IPF cohorts, however, showed lower 1-year and 3-year incidence of AE in HP patients and more favourable outcomes in AE-HP versus AE-IPF.[190] Putative risk factors for AE in HP include male gender, smoking, decreased lung function and UIP features on HRCT.[188,191–193]

The optimal treatment for AE in HP and indeed for all fibrotic ILD is uncertain. In the absence of other proven therapies, many clinicians initiate high dose corticosteroids.[194] Antibiotics may be given where bacterial infection is suspected or confirmed. Whilst a lower risk of AE or death was seen in PPF patients on nintedanib over the course of the INBUILD study,[195] there is no evidence to support the initiation of this therapy for the management of AE.

SUMMARY

- Pulmonary rehabilitation should be offered to all patients with HP, with expected benefits in symptoms and functional capacity.
- Oxygen therapy, transplant referral and palliative care strategies are recommended for select groups of patients with progressive fibrotic disease.
- Acute exacerbations, triggered by known or unknown causes, can impact long-term survival. Inpatient management may be necessary, with consideration of high-dose corticosteroids.

FUTURE DIRECTIONS AND CURRENT UNMET NEEDS

Despite progress in the field, many questions remain unanswered regarding pathogenesis, diagnosis and management of HP. Clinical registries and biobanking repositories are critical for accrual of further knowledge, providing opportunities for linking environmental, demographic and genetic factors in context. More work is needed on the identification and characterisation of disease inducers, particularly important in the consideration of antigen-indeterminate disease.

High diagnostic confidence can be elusive in many cases of HP, highlighting the necessity for more precise diagnostic tools. Various biological, genomic and artificial intelligence-aided imaging biomarkers are under evaluation[196–198] and may one day contribute to a personalised approach to HP and other ILDs. For new technologies to be successfully integrated into practice, however, they must be reliable, highly reproducible and cost-effective.

Pharmacological approaches to HP also require further appraisal. Uncertainty around ideal induction treatments,

maintenance therapies, and exacerbation management arises from limited direct evidence for this population. Whilst current immunosuppressive and antifibrotic treatment options play a role in HP, more individualised approaches may better serve patients due to unique aspects of disease pathobiology. As more therapeutic options become available, the sequence of treatments and whether to withdraw, switch or add needs to be clarified. Furthermore, goals for pharmacological and non-pharmacological interventions should not only be to slow or reverse disease, but also to help patients feel better.

As with all ILD, the impact of disease needs to be recognised and factored into all treatment decisions and management advice. Livelihood, living circumstances and pastimes may be strongly discouraged by clinicians, with consequences beyond the sphere of an individual's health. Patients with HP are known to experience a poorer quality of life compared to other ILD subgroups, possibly due to these factors.[162] In the future, genetic susceptibility profiling for individuals engaging in high-risk occupations or hobbies, or those with affected family members, may allow for more conscientious antigen avoidance strategies and disease prevention. Finally, further investment in public health measures aimed at primary disease prevention must be part of a comprehensive approach to addressing the impact of a changing environment on human health and wellbeing.

CONCLUSION

Encompassing a broad spectrum of causes, manifestations and disease behaviour, the entity of HP in adults presents both diagnostic and management challenges. The profound impact of this diagnosis relates to both direct effects of the disease and the necessity of major lifestyle changes for many. Clinical suspicion of HP should be maintained for all undifferentiated ILD cases, with thorough exposure evaluation essential for antigen identification and remediation. Treatment options are currently guided by the balance of inflammatory and fibrotic features in individuals with the goals of mitigating disease progression and optimising quality of life.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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