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REVIEW

Hypersensitivity Pneumonitis: A Silent Epidemic?

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Abstract

Purpose of Review Hypersensitivity pneumonitis (HP), along with interstitial lung disease as a whole, is a disorder with rising incidence, morbidity, and potentially mortality. Herein we review latest updates on epidemiology, environmental exposures, diagnosis, and treatment of this devastating disorder.

Recent Findings Both the American Thoracic Society as well as the American College of Chest Physicians have recently released diagnostic guidelines for HP, offering an opportunity to standardize patient care and research in the coming years. Novel exposures associated with HP highlight its ever-changing epidemiology amidst a world threatened by climate change.

Summary As diagnosis and treatment become more standardized for hypersensitivity pneumonitis, the varied presentations, exposures, and outcomes of the disorder lend itself to future research regarding both novel threats as well as precision approaches to care for patients with this heterogenous and incompletely understood disease.

Keywords Hypersensitivity pneumonitis · Interstitial lung disease · Environmental exposures

Introduction

Hypersensitivity pneumonitis (HP) is an increasingly recognized subtype of interstitial lung disease (ILD), characterized by an immunogenic reaction to specific inhaled substances. The clinical spectrum of disease varies widely, from inflammation of the lung parenchyma and small airways to severe and progressive fibrotic disease. Despite its position as one of the more common subtypes of ILD, reports on the epidemiology of HP are varied, and overall incidence, prevalence, and demographic patterns remain incompletely understood [1]. Age appears to have a strong correlation with disease prevalence, with the highest rates reported in those 65 years and older [2]. Additionally, females are disproportionately affected, particularly by fibrotic HP (fHP) [2–4]. Importantly, several studies have found that disease prevalence varies by geography and season, complicating our understanding of the global burden of disease [2, 5, 6].

A recent study of United States claims-based data reported a 1-year prevalence of 1.67–2.71 cases per 100,000 persons among an insured population [2]. This rate exceeds that of other developed European countries but is dwarfed by India, where rates have been reported as almost five times higher [7–9]. Furthermore, HP has eclipsed idiopathic pulmonary fibrosis (IPF) as one of the most common subtypes of ILD in Asia, representing almost half of all ILD diagnoses in the ILD India registry [10, 11•]. These shocking statistics raise a compelling question: *Is HP silently emerging as an epidemic in our midst?*

Pathophysiology and the Role of Autoimmunity

The pathogenesis of HP is mediated by underlying host genetic susceptibility, attributed to gene polymorphisms in the major histocompatibility complex (MHC) class II regions involved in antigen processing and presentation [12, 13]. In susceptible individuals, exposure to an environmental antigen triggers an innate immune response in which antigen recognition, processing, and expression occurs by antigen-presenting cells (APCs), in conjunction with host MHC I and II molecules [14]. Once expressed by the APCs, host T-lymphocytes become sensitized to the antigen and

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contribute to the development of immune memory [15]. Upon antigen re-exposure, sensitized T-lymphocytes instigate an inflammatory response leading to lymphocytic inflammation, granuloma formation, and if chronic, fibroblast proliferation similar to that seen in IPF [12].

The role of autoimmunity in the pathogenesis of HP is complex and remains incompletely understood. A subset of patients with HP appear to have features of autoimmunity, including underlying connective tissue disease (CTD) or the presence of symptoms and serologies seen in these disorders but without meeting formal criteria. HP with autoimmune features (HPAF) has conflicting associations with patient outcomes, with some studies reporting increased mortality compared to HP without autoimmune features and others finding no difference in clinical outcomes [16–18]. Further studies are needed to elucidate the complex interplay between autoimmunity and patient outcomes in this population.

Classification Scheme

Historically, HP was classified by disease duration as either acute, subacute, or chronic. This scheme was notoriously difficult to delineate and somewhat arbitrarily determined, leading to biased and inconsistent associations with patient outcomes in the reported literature. Recent guidelines sought to improve the clinical utility of disease classification and recommended an updated scheme based on the presence or absence of radiographic or histopathologic fibrosis [19••, 20••]. Patients with purely inflammatory disease are now classified as "non-fibrotic HP", while patients with either partially or entirely fibrotic disease are classified as "fibrotic HP". This updated, objective approach more consistently correlates with disease course and patient outcomes and may provide important prognostic information to inform management decisions [19••, 21, 22].

Exposures and their Evaluation

While there has been increasing recognition of the contributory role of inhalational exposures toward a variety of ILDs, the causative relationship between exposures and HP has remained predominant [23–25]. The most common exposures associated with HP have historically been related to farming and birds, but a large proportion of patients presenting with disease that would otherwise be considered pathognomonic HP have an unknown inciting environmental agent [26, 27]. Novel environmental exposures with proposed associations with HP continue to emerge every year; select exposures are highlighted in Table 1 [28–34].

Table 1 Select Recent Novel Antigens Associated with HP

Exposure	Clinical Scenario	Reference
Moldy foam pillows	Biopsy-proven HP improved with cessation and worsened with reintroduction of moldy foam pillows	Moran-Mendoza et al. CHEST 160 (3):e259–263
Moldy hazelnut husks	Biopsy proven HP in 2 hazelnut farmers; patients reported visible moldy husks, symptoms worsened in summertime, when working	Kurt et al. Med Lav. 2023 Oct 24;114(5):e2023041
Fluorocarbon waterproofing spray	Biopsy-proven fibrotic HP in warehouseman who regularly sprayed furniture with aerosolized waterproofing spray	Walters et al. Occup Med (Lond). 2017 Jun 1;67(4):308–310
Citrus farming	Biopsy-proven fibrotic HP in citrus farmer whose symptoms increased whenever at workplace	Kutsuzawa et al., Intern Med. 2021 Nov 15;60(22):3581–3584. Walters et al. Curr Opin Allergy Clin Immunol. 2023 Apr 1;23(2):85–91
Koji brewing	Koji brewer with new-onset ILD and same mold from BAL culture and factory	Ishiguro et al., Clin Case Rep. 2018 Jan 19;6(3):461–464, Walters et al. Curr Opin Allergy Clin Immunol. 2023 Apr 1;23(2):85–91
Tile manufacturing	Biopsy-proven HP in tile polisher with serologic response to clam and mollusk protein	Armentia et al., Clinica Chimica Acta 524:139–145. Walters et al. Curr Opin Allergy Clin Immunol. 2023 Apr 1;23(2):85–91

A universal assessment of inhalational exposures in patients suspected of having HP remains elusive, but recent studies have begun to validate exposure instruments for use in these patients. Most notably, Barnes and colleagues utilized the Delphi technique to elicit agreement among ILD experts regarding 18 antigens to ask every potential HP patient, as well as important characteristics that clinicians should consider regarding the circumstances surrounding these exposures [35]. Moua and colleagues have also proposed a questionnaire in these; both instruments require future clinical validation as well as evaluation for utility among differing geography [26].

Making the Diagnosis

The diagnosis of HP is made through gold-standard multidisciplinary committee review of exposure history, imaging, and bronchoscopic and histopathologic findings if available [36]. In addition to a careful assessment of patient history (see ***Exposures*** section above), inciting antigen exposures can sometimes be identified through the use of serum immunoglobulin G (IgG) test panels, available through a variety of commercial test kits [37]. While some guidelines do suggest performing serum IgG testing in patients with suspected fibrotic or non-fibrotic HP, available test kits are limited in the number of antigens tested, lack standardization in included antigens, and vary in performance by antigen and geography [38]. Additionally, serum IgG positivity lacks specificity in distinguishing HP from other subtypes of ILD [37]. In patients with an identifiable exposure by history, the addition of an HP IgG panel is likely of limited utility; however, it may guide the search for an exposure in patients in whom one has not yet been identified [39].

With the advent and increased utilization of high-resolution CT (HRCT), imaging review has become a key component of diagnosis, particularly in light of the substantive number of cases in which an inciting antigen exposure cannot be reliably identified [40]. Imaging features associated with a "typical" non-fibrotic HP diagnosis include a diffuse distribution of: a) at least one feature of parenchymal infiltration, including ground-glass opacities and/or mosaic attenuation, and b) at least one feature of small airways disease, including ill-defined centrilobular nodules and/or air trapping [19••]. A "typical" fibrotic HP diagnosis is characterized by: a) features of lung fibrosis in one distribution, including irregular linear opacities/course reticulation with lung distortion, traction bronchiectasis, and/or honeycombing, and b) at least one feature of small airways disease. In both fibrotic and non-fibrotic HP, imaging may also reveal features "compatible with" or "indeterminate" for HP [41].

The diagnostic confidence achieved through identification of an exposure and "typical" imaging alone differs greatly in the literature. Joint guidelines from the American Thoracic Society (ATS), Japanese Respiratory Society (JRS), and Asociacion Latinoamericana de Torax (ALAT) published in 2020 apply only "moderate confidence" to diagnoses made without bronchoalveolar lavage (BAL) and/or histopathologic review, and necessitate that both must be performed in order to achieve a definite diagnosis [19••]. In contrast, guidelines published the following year by the CHEST Foundation allow for a definite diagnosis in the absence of both BAL and histopathology, noting that these more invasive procedures should only be obtained if appropriate, particularly in cases in which an inciting antigen exposure could not be reliably identified or imaging was not "typical" [42]. Further comparison of these guidelines is outlined in Table 2.

In cases of diagnostic uncertainty, BAL lymphocytosis > 20% can increase diagnostic confidence to "high", but this feature may not be present in fibrotic HP [43]. In such cases, only histopathologic review allows for a definite diagnosis to be achieved [44]. Similar to HRCT review, histopathologic findings differ based on disease subtype. Pathologic features of "typical" non-fibrotic HP include: 1) a small airway distribution, 2) uniform distribution of cellular bronchiolitis, 3) lymphocytic inflammation, and 4) scattered, poorly-formed non-necrotizing granulomas and/or multinucleated giant cells [45]. These same poorly-formed granulomas are seen in "typical" fibrotic HP, which is also characterized by: 1) small airway-centered fibrosis, and 2) fibrosing interstitial pneumonia in various patterns [46]. Historically, surgical lung biopsy (SLB) has been the gold standard for pathologic diagnosis, but bronchoscopy with transbronchial biopsy (TBBx) has emerged as the preferred option due to its less invasive methodology and more favorable complication rate. In a study of patients with HP, TBBx revealed "typical" pathologic findings in approximately 40% of cases [47]. More recently, transbronchial lung cryobiopsy (TBLC), which allows for larger quantities of lung tissue compared to TBBx, has been shown to yield highly concordant results to SLB and increase the diagnostic confidence of patients with uncertain noninvasive ILD diagnoses [48, 49]. However, the risk of procedural complications is moderate, with 15% of patients experiencing pneumothorax and/or moderate to severe bleeding [48]. As with all procedures, careful patient selection and risk stratification should be considered before proceeding with TBLC.

After publication in 2020, the diagnostic performance of the ATS/JRS/ALAT practice guidelines has been compared to diagnosis achieved through multi-disciplinary discussion. The guidelines' "moderate confidence" diagnostic threshold performed well, with a sensitivity and specificity of 73% and 89%, respectively [50]. Importantly, guidelines performance was best in patients with non-fibrotic HP, compared to fibrotic HP (AUC 0.92 vs. 0.82), highlighting the ongoing

Table 2 Comparison of Diagnostic Guidelines for Hypersensitivity Pneumonitis

	Diagnostic Classification	Exposure Questionnaire Or History	IgG testing	Bronchoalveolar Lavage	Transbronchial Biopsy	Cryobiopsy	Surgical Lung Biopsy
ATS/JRS/ALAT							
Fibrotic	Division of guidelines into fibrotic and non-fibrotic disease states	No recommendation for or against questionnaire	Suggestion to perform, very low confidence	Recommendation, very low confidence	Suggestion, very low confidence	No recommend-ation for or against	Suggestion when all other diagnostic testing has not yielded diagnosis, very low confidence
Non-fibrotic		No recommendation for or against questionnaire	Suggestion to perform, very low confidence	Suggestion, very low confidence	No recommend-ation for or against	Suggestion, very low confidence	Suggestion when all other diagnostic testing has not yielded diagnosis, very low confidence
CHEST	Weak recommendation to classify as fibrotic or non-fibrotic, very low quality evidence	Consensus statements to gather history, consider inclusion of occupational medicine specialist	Weak recommendation to not rely solely on IgG testing, very low quality evidence	Weak recommendation to not routinely use in typical HP; very low quality evidence	Weak recommendation when all available data not confident, very low quality evidence	Not mentioned	Not mentioned

challenge of differentiating fibrotic HP from other fibrotic ILDs [50].

Treatment

The most critical aspect of HP management is identification and remediation of the inciting exposure, which when achieved, is associated with significantly improved survival [51]. However, in more than half of cases, an exposure is unable to be identified even after thorough review of occupational and environmental history [51]. Furthermore, when identified, antigen avoidance cannot always be achieved secondary to financial limitations or lack of resources, patient beliefs and/or attachments to the antigen source, and gaps in clinical knowledge and testing capabilities [52].

In such cases, corticosteroids often are the first line of treatment, despite mixed evidence for their use [53]. Observational studies have shown reduced lung function decline and improved survival with corticosteroid treatment; however, this benefit was only seen in patients with non-fibrotic HP [54, 55]. Amongst patients with fibrotic HP, the presence of lymphocytosis on BAL has been associated with improved FVC following initiation of corticosteroids, though the yearly rate of lung function decline before and after treatment was no different [55]. Indeed, one recent study suggests that in fibrotic HP with an unknown inciting antigen, immunosuppression may be associated with worse survival, and another suggests that patients with fibrotic HP and short telomeres may have worse survival with these agents [56, 57]. When trialing steroids, experts recommend a course of 0.5-1mg/kg daily of a prednisone equivalent tapered to 20mg daily in the first three months, based on data from a randomized controlled trial of patients with acute farmer's lung [22].

The multi-organ morbidity associated with long-term corticosteroid therapy has led to a search for alternative, corticosteroid-sparing regimens. Two small retrospective studies evaluating the use of mycophenolate mofetil (MMF) and azathioprine in chronic HP showed reduced decline in diffusing capacity of carbon monoxide (DLCO) after 1 year of treatment [58, 59]. However, other studies have found no additional benefit in lung function decline or survival with the addition of MMF or azathioprine compared to corticosteroids alone [60]. In a French study of 20 patients with chronic HP, treatment with rituximab appeared to stabilize lung function decline in some patients [61].

As the evidence for immunosuppression in HP comes primarily from observational data, expert opinion continues to play an important role. We agree with other experts in the field, who recommend considering immunosuppression as first-line therapy in patients with evidence of inflammation on imaging, cellular analysis, or histopathology, in

conjunction with antigen avoidance [22]. In patients with ground-glass opacities on HRCT, significant lymphocytosis on BAL, or evidence of cellular interstitial pneumonia on pathology, we recommend initiating treatment with corticosteroids, followed by close monitoring of symptoms and pulmonary function tests every 3 months. In patients with symptomatic, physiologic, or radiographic improvement, the addition of corticosteroid-sparing immunosuppression should be considered.

Alternatively, in patients without significant inflammation, or in those without a clear response to immunosuppressive therapy, the mainstay of treatment is anti-fibrotic agents. In 2019, a landmark randomized controlled trial evaluating the use of nintedanib in patients with progressive fibrosing ILD (PF-ILD), 25% of which had HP, showed a reduction in annual FVC decline with treatment compared to placebo [62]. Following this trial, the US Food and Drug Administration (FDA) expanded approval for nintedanib to all patients meeting criteria for PF-ILD. Additionally, though underpowered for its primary endpoint, a randomized controlled trial of pirfenidone in HP found an association with improved clinical outcomes [63]. In addition to antifibrotics, transplant referral and evaluation should also be considered in select patients.

In 2022, the ATS/ERS/JRS/ALAT released a clinical practice guideline revising the definition of progressive non-IPF ILD, now termed progressive pulmonary fibrosis (PPF) [64]. Patients meeting criteria for PPF must have non-IPF ILD and a one-year decline in two of three designated domains: symptoms, pulmonary function, and appearance on HRCT [64] . While specific thresholds defining worsening in each domain are easily clinically applicable, some experts suggest more research linking these thresholds to clinical outcomes be completed before these definitions become associated with treatment guidance [65]. Indeed, multicenter data have demonstrated that compared to other functional and radiologic thresholds, PPF criteria capture a smaller amount of patients ultimately experiencing lung transplant or death, and these associations are associated with disease subtype [66, 67].

Prognosis

Despite advances in understanding of disease pathophysiology, the clinical course of HP remains highly variable. Predicting which patients will experience self-limited inflammatory disease, compared to progressive and debilitating fibrotic disease, remains challenging. Recent data from the multicenter Canadian Registry for Pulmonary Fibrosis (CARE-PF) registry revealed that up to 58% of patients with fibrotic HP met criteria for PPF, which matched rates of PPF in those with IPF [68]. HP has also been associated with an increased number of hospital readmissions compared to other ILDs [69].

Other studies have found prognostic factors in HP outside of the PPF paradigm. Phenotypic cluster analyses in fibrotic HP have revealed worse survival amongst elderly male patients with comorbid cardiovascular disease and improved survival in younger patients with baseline obstructive physiology and identifiable antigens [70, 71]. The ongoing, multicenter PREDICT study seeks to pair such important clinical factors with transcriptomic data from peripheral blood mononuclear cells to provide more accurate prognostication in fibrotic HP [72]. Insights gained from this undertaking may improve our ability to predict disease progression amongst patients with less predictable, but clearly fibrotic, HP.

New Challenges on the Horizon?

Looking ahead, the management and prognostication of patients with HP faces many challenges, chief among them being antigen identification. While significant strides have been made in characterizing and identifying certain triggers, there remains a vast reservoir of antigens yet to be characterized. Moreover, the specter of climate change looms in the background, introducing a new layer of complexity to the equation. A recent study from Germany found that increased fungal infections in maple trees, driven by changes in the climate, led to cases of HP in exposed workers [73]. As climate patterns continue to evolve, so too may the landscape of potential antigens, further challenging our efforts to predict and prevent disease. As we look to the future of HP, a comprehensive approach integrating advanced antigen identification techniques and proactive mitigation strategies will be crucial in navigating potential uncertainties posed by our changing environment.

Conclusion

Hypersensitivity pneumonitis continues to be a disease of considerable, and increasing, morbidity and mortality [74]. With the advent of relatively recent diagnostic criteria, the scientific community is well-poised to better define individual and global disease burden, investigate therapeutic targets, and identify novel and ongoing inhalational exposure risks. Through these efforts, emerging research should discover and implement therapies and techniques to treat and ultimately prevent the worst ramifications of this as-yet incurable disorder, making the effects of this disorder silent no more.

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Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest Dr. Selvan reports grant funding from the NIH (T32 HL007605). Dr. Lee reports grant funding from the Pulmonary Fibrosis Foundation (Scholar Award).

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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•• Of major importance

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