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HYPERSENSITIVITY PNEUMONITIS: PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT

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RESEARCH BASED BOOK CHAPTER

HYPERSENSITIVITY PNEUMONITIS: PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT

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Abstract

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an interstitial lung disease triggered by repeated inhalation of environmental antigens in genetically predisposed individuals. These antigens—ranging from microbial agents, animal proteins, and agricultural dust to chemical compounds—elicit a complex immune response that may progress from reversible inflammation to irreversible fibrosis. HP presents a broad clinical spectrum, from acute, self-limiting episodes to chronic, progressive fibrosing disease that can mimic other interstitial lung disorders, such as idiopathic pulmonary fibrosis.

The pathogenesis involves both type III (immune complex–mediated) and type IV (T-cell–mediated) hypersensitivity reactions, leading to alveolar and small airway inflammation, granuloma formation, and, in some cases, architectural remodeling and fibrosis. Genetic susceptibility, such as certain HLA haplotypes and telomere-related mutations, has been associated with disease development and progression. Accurate diagnosis remains challenging due to the nonspecific nature of symptoms—dyspnea, cough, fatigue—and the variability in radiologic and histopathologic findings. Diagnosis relies on a multidisciplinary approach integrating clinical context, high-resolution computed tomography (HRCT), pulmonary function tests, bronchoalveolar lavage, and sometimes lung biopsy. Identification and avoidance of the inciting antigen are critical and often determine long-term prognosis.

Therapeutic strategies vary depending on disease stage. Antigen avoidance is the cornerstone of treatment and can reverse early inflammation. In more advanced or fibrotic forms, systemic corticosteroids and immunosuppressive agents such as azathioprine or mycophenolate mofetil are commonly used. Recently, antifibrotic therapy with nintedanib has shown efficacy in slowing disease progression in chronic fibrosing HP. Lung transplantation remains an option for patients with advanced, treatment-refractory disease.

This chapter provides a comprehensive overview of hypersensitivity pneumonitis, emphasizing current understanding of its immunopathogenesis, the diagnostic

challenges it poses, and evolving approaches to management, including the role of antifibrotic therapy and transplantation.

Keywords
Hypersensitivity Pneumonitis, Interstitial Lung Disease, Antigen Avoidance, Fibrosis, Immunosuppressive Therapy

1. Background

Hypersensitivity pneumonitis (HP) is an inflammatory interstitial lung disease (ILD) caused by an abnormal immune response to inhaled organic antigens, often originating from environmental or occupational exposures. It is characterized by acute, subacute, or chronic inflammation and can lead to pulmonary fibrosis if left untreated. The disease primarily affects the alveoli, where the inhaled antigens trigger both innate and adaptive immune responses, leading to varying degrees of alveolar damage. Though the pathophysiology of HP is well-documented, the condition remains underdiagnosed and often misclassified, particularly in its chronic form, when the clinical presentation overlaps with other ILDs such as idiopathic pulmonary fibrosis (IPF) [1].

Over recent decades, there has been an observable shift in the epidemiology of HP, with a decline in cases related to agricultural exposures and an increase in those associated with indoor and occupational environments that were not traditionally linked to the disease. This change reflects evolving environmental factors, including urbanization, changes in work environments, and increased exposure to indoor allergens like mold and pet dander. Despite these trends, the awareness and understanding of HP remain limited in many healthcare settings, particularly in developing countries where limited access to occupational health infrastructure and diagnostic tools may contribute to underreporting. This underscores the need for a more nuanced and accessible approach to diagnosing and managing HP, particularly as awareness of non-classic disease phenotypes continues to improve [1, 2].

2. Materials and Methods

A thorough review of existing literature on hypersensitivity pneumonitis (HP) was conducted using widely recognized academic databases, including Clarivate Analytics, PubMed, and Google Scholar. The search aimed to gather relevant articles,

studies, and reviews that provide insights into the pathophysiology, epidemiology, diagnostic criteria, treatment options, and prognostic factors related to HP.

In order to ensure a comprehensive understanding of the subject, the review process focused on articles published in reputable peer-reviewed journals, prioritizing recent studies that contribute to current knowledge and clinical practice. The search terms included "hypersensitivity pneumonitis," "diagnosis," "treatment," "epidemiology," and other related keywords to identify relevant articles. Inclusion criteria involved articles written in English and studies that addressed both classic and emerging aspects of HP, including both acute and chronic forms of the disease.

Articles were reviewed for quality, relevance, and methodological rigor. Data from clinical trials, observational studies, case reports, and meta-analyses were analyzed to provide a well-rounded perspective on the disease. All retrieved publications were assessed critically, and key findings were synthesized to provide a comprehensive understanding of the current state of HP research [1-3].

The review does not involve any primary data collection or experiments, and all conclusions are drawn from secondary research based on the literature available in the aforementioned databases.

2.1. Introduction

- **Definition and Classification (acute, subacute, and chronic/fibrotic forms)**

Hypersensitivity pneumonitis is part of the category of diffuse interstitial pneumopathies, being marked by an inflammatory syndrome whose cause is the constant exposure to a habitual antigen (organic particles with a size below 5 microns) which most often can reach the pulmonary alveoli. Regarding the proportion of adults - children, this pathology affects both categories equally, as well as women - men.

There is an extremely wide range in terms of the incriminated factors and here we must point out - chemical compounds, fungi, bacteria, animal proteins, etc.

In the past, there were three forms – acute, subacute and chronic, but the 2020 ATS/JRS/ALAT guidelines preferred to reformulate these forms based on the respective symptomatology, imaging and functional tests of the response to treatment in non-fibrosing hypersensitivity pneumonitis and fibrosing hypersensitivity pneumonitis. The

former manifests itself in cough, dyspnea, fever, nausea, myalgia and begins relatively quickly after immediate exposure to a causative antigen. Most often, this form occurs in those exposed to *Saccharopolyspora rectivirgula* which is found in moldy cereals. Fibrosing hypersensitivity pneumonitis has an extremely noisy picture marked by respiratory failure given repeated exposure to a causative agent or in some cases due to the lack of identification of the antigen. It is an active and progressive form with significant changes on imaging, where even the appearance of honeycomb patterns can be found, which is why a clear differential diagnosis with idiopathic pulmonary fibrosis must be made [4, 5].

According to the ATS/JRS/ALAT 2020 guidelines, hypersensitivity pneumonitis (HP) is classified into two distinct forms: non-fibrotic and fibrotic. These forms are differentiated based on the degree of inflammation versus fibrosis in the lungs, as well as the clinical progression of the disease.

Non-fibrotic HP

In the non-fibrotic form of HP, the disease is primarily characterized by inflammation and granuloma formation without significant scarring or fibrosis in the lung tissue. This form is often seen in the acute or subacute stages of HP, where the immune response to the offending antigen is still reversible. Symptoms such as cough, fever, and shortness of breath are prominent, and the lung damage is typically reversible with prompt identification and avoidance of the antigen. Radiologically, non-fibrotic HP may present with patchy infiltrates, ground-glass opacities, and mild mosaic attenuation on high-resolution computed tomography (HRCT). If the antigen is avoided early, the prognosis is generally good, and lung function can improve [4, 5].

Fibrotic HP

In contrast, fibrotic HP represents a chronic and progressive form of the disease, where persistent inflammation leads to lung scarring (fibrosis), particularly in the interstitial spaces. This stage is often associated with irreversible damage and lung function decline. Fibrotic HP typically occurs when there has been repeated or prolonged exposure to the causative antigen, leading to the development of fibrosis even after

antigen removal. The hallmark of fibrotic HP on HRCT is the presence of honeycombing and traction bronchiectasis, signs of severe fibrosis. This form of HP has a much poorer prognosis and can progress to respiratory failure. In these cases, management options like immunosuppressive therapy or, in the most severe cases, lung transplantation, may be required.

This distinction is crucial for clinicians as it guides both diagnosis and treatment strategies, including the potential for reversibility or progression to more severe lung damage. The goal is early detection of the non-fibrotic form to prevent transition to the fibrotic stage [4-6].

2.2. Occupational and Environmental Exposures

Source of Antigen	Causative Agent	Associated Syndrome
Moldy hay, straw	*Thermophilic actinomycetes* (*Saccharopolyspora rectivirgula*)	Farmer's lung
Bird droppings, feathers (e.g. pigeons)	Avian proteins	Bird fancier's lung
Humidifiers, air conditioning systems	*Thermophilic actinomycetes*, fungi, *Mycobacterium avium*	Humidifier lung / Hot tub lung
Wood dust (carpentry, woodworking)	Organic wood particles (oak, maple, pine)	Woodworker's lung
Fermented grain silos (e.g. corn)	Anaerobic bacteria and fungi	Grain handler's lung
Mushroom cultivation	Fungal spores (*Aspergillus spp.*, others)	Mushroom worker's lung
Textile industry (flax, cotton)	Textile dust	Textile worker's lung
Contaminated metalworking fluids	Microbial agents in emulsions	Metalworking fluid–induced HP
Household mold	*Penicillium, Cladosporium,*	Mold-induced hypersensitivity

Source of Antigen	Causative Agent	Associated Syndrome
(walls, HVAC, etc.)	*Aspergillus*	pneumonitis
Laboratory animals (rats, rabbits, etc.)	Animal proteins from urine, fur, saliva	Laboratory animal worker's lung

The number of potential causative agents is extremely large, and in some cases, identifying the responsible antigen may remain challenging even after a thorough exposure history. As previously mentioned, most antigens are of fungal, bacterial, or protein origin. Moreover, hypersensitivity pneumonitis may be classified as an occupational disease, in which case the patient may be eligible for financial compensation, job reassignment, or extended medical leave [7].

2.3. Epidemiology

Hypersensitivity pneumonitis (HP) is a relatively uncommon but potentially underrecognized interstitial lung disease (ILD) that arises following repeated inhalational exposure to a wide range of environmental antigens. The epidemiology of HP is complex and influenced by factors such as geographic location, climate, occupational and domestic exposures, socioeconomic status, and variability in diagnostic practices.

Incidence and Prevalence

Accurate estimates of the incidence and prevalence of HP are challenging due to heterogeneous diagnostic criteria, lack of standardized case definitions, and significant regional variability. Recent epidemiologic data suggest that HP represents approximately 4–15% of all ILD cases globally. However, in populations with known high exposure risk, such as agricultural workers or bird breeders, the prevalence may be considerably higher [1, 8].

In the United States, data from ILD registries estimate an incidence of around 1 to 3 cases per 100,000 persons per year, although these figures likely underrepresent the true burden due to underdiagnosis and misclassification, often as asthma, chronic

obstructive pulmonary disease (COPD), or idiopathic pulmonary fibrosis (IPF). In Europe, HP incidence varies widely—from less than 1 per 100,000 per year in urban settings to over 10 per 100,000 in rural regions. Japan has reported relatively higher rates of HP compared to many Western countries, possibly due to increased awareness and active surveillance.

The disease can affect individuals across all age groups, though it is most commonly diagnosed between the fourth and sixth decades of life. Males and females are affected equally, although occupational roles and gender-based exposure patterns may introduce variability [9, 10].

Geographic and Environmental Variation

The distribution of HP is strongly influenced by local environmental and occupational exposures. In agricultural regions, farmer's lung—associated with exposure to thermophilic actinomycetes from moldy hay or grain—is one of the most frequently reported phenotypes. In urban or peri-urban areas, domestic sources such as pet birds, humidifiers, and contaminated HVAC (Heating, Ventilation, and Air Conditioning) systems are increasingly recognized as antigen sources.

Climate plays a significant role in the environmental burden of HP. Warm and humid climates favor the proliferation of fungi and bacteria, leading to increased risk of HP related to mold and thermophilic organisms. In contrast, arid regions may have lower incidence but could harbor specific exposures related to dust or industrial processes [9].

Occupational Exposure Patterns

Occupational HP continues to be a major contributor to disease burden in many countries. The most commonly implicated professions include:

- **Farmers and agricultural workers:** Exposure to hay, straw, grain, silage, and animal feed.
- **Bird breeders and poultry workers:** Exposure to avian proteins from feathers and droppings.

- **Metalworking and manufacturing personnel:** Exposure to aerosolized metalworking fluids containing mycobacteria or bacterial endotoxins.
- **Woodworkers:** Exposure to moldy or processed wood dusts.
- **Mushroom growers, veterinarians, and textile workers:** are also at increased risk due to specific occupational environments.

In some developing countries, HP may be underreported due to lack of occupational health infrastructure, inadequate surveillance systems, and low clinician awareness, despite significant exposure risks [11].

Temporal Trends

There is some evidence suggesting a shift in the epidemiology of HP over recent decades, with a relative decrease in agricultural HP and an increase in cases linked to indoor and occupational environments not traditionally associated with the disease. This trend may reflect changes in work environments, urbanization, increased indoor antigen exposure (e.g., mold, birds, HVAC systems), and improved recognition of non-classic HP phenotypes.

HP is also increasingly recognized in association with indoor air quality problems in modern buildings with poor ventilation, water damage, or extensive air conditioning systems. As global awareness improves, more subacute and chronic cases are being diagnosed—often late in the disease course when fibrosis is already present [9-11].

2.4. Challenges in Epidemiological Assessment

Several factors complicate the epidemiological assessment of HP:

- **Diagnostic inconsistency:** There is no single gold-standard test for HP, and diagnostic criteria differ across guidelines (e.g., ATS/JRS/ALAT 2020, ERS 2022), leading to variability in reported rates.
- **Overlap with other ILDs:** HP can mimic other interstitial lung diseases, particularly IPF, sarcoidosis, or nonspecific interstitial pneumonia (NSIP), leading to misclassification.

- **Underreporting:** Mild or acute forms of HP may be transient or attributed to viral infections, asthma, or bronchitis, especially in primary care settings.
- **Delayed recognition of antigen exposure:** In many chronic cases, the antigen source is unidentified or only discovered after a detailed environmental history.

2.5. Pathophysiology and Immunological Mechanisms

HP arises in genetically predisposed individuals after repeated or prolonged inhalation of small particles (typically <5 μm in diameter) that deposit in the terminal bronchioles and alveoli. The immune system misidentifies these antigens as threats, initiating a hypersensitivity reaction dominated by both Type III (immune complex–mediated) and Type IV (delayed-type, cell-mediated) mechanisms [12].

The disease spectrum varies depending on the timing and intensity of exposure, host immune response, and progression to chronic fibrosis.

2.5.1. Antigen Recognition and Innate Immune Activation

The pathophysiologic process begins when inhaled antigens are recognized by the lung's innate immune cells, particularly alveolar macrophages, dendritic cells, and epithelial cells. These cells express pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) that detect pathogen-associated molecular patterns (PAMPs) or danger signals.

This leads to:

- Activation of nuclear factor-kappa B (NF-κB) and other transcription factors,
- Secretion of proinflammatory cytokines (e.g., IL-1β, IL-6, TNF-α),
- Recruitment of neutrophils, monocytes, and lymphocytes to the alveolar space.

In the early or acute phase of HP, this results in a predominantly neutrophilic alveolitis, which may resolve if antigen exposure ceases.

2.5.2. Adaptive Immune Response and Hypersensitivity Reaction

The adaptive immune system plays a central role in the development and chronicity of HP.

a. Type III Hypersensitivity (Immune Complex–Mediated)

- Circulating IgG antibodies are produced against the inhaled antigen.
- Repeated exposure leads to the formation of antigen–antibody immune complexes, which deposit in the alveolar walls.
- These complexes activate complement pathways, particularly C3a and C5a, enhancing neutrophil recruitment and inflammation.

This mechanism is most prominent in the acute and subacute phases.

b. Type IV Hypersensitivity (Cell-Mediated)

- Dendritic cells present processed antigens to naïve CD4+ T lymphocytes, promoting Th1 polarization.
- Th1 cells secrete IFN-γ, IL-2, and TNF-α, supporting macrophage activation and granuloma formation.
- Chronic inflammation leads to the recruitment and activation of CD8+ cytotoxic T cells, contributing to epithelial injury.

In chronic HP, the immune response shifts from being Th1-dominant to a mixed Th1/Th17 profile, with increasing involvement of fibroblasts, TGF-β, and fibrogenic cytokines that promote lung remodeling and fibrosis [4, 7].

2.5.3. Granuloma Formation

A hallmark of HP is the presence of non-caseating granulomas, typically located in the peribronchiolar regions. These granulomas are composed of activated macrophages (epithelioid cells), multinucleated giant cells, and T lymphocytes, reflecting a chronic antigenic stimulus and a delayed-type hypersensitivity reaction.

Granuloma formation serves both as a marker of antigen-driven immunity and a potential driver of parenchymal damage and fibrosis.

2.5.4. Chronic Inflammation and Fibrosis

When antigen exposure is sustained or unrecognized, inflammation becomes chronic and leads to structural lung damage:

- Epithelial injury and loss of alveolar integrity
- Fibroblast recruitment and activation
- Extracellular matrix deposition, particularly collagen types I and III
- Development of fibrotic remodeling, often in a centrilobular distribution

In advanced cases, the radiologic and histopathologic features may overlap with usual interstitial pneumonia (UIP), complicating differentiation from idiopathic pulmonary fibrosis (IPF).

Persistent inflammation may also promote bronchiolitis obliterans and honeycombing, with progressive respiratory insufficiency.

2.5.5. Genetic and Epigenetic Influences

Recent studies suggest that genetic susceptibility plays a role in HP development and progression. Variants in HLA class II alleles (e.g., HLA-DRB1, HLA-DQB1) have been associated with disease risk and antigen sensitivity.

Additionally, polymorphisms in MUC5B (also associated with IPF) and epigenetic changes affecting immune regulation may influence individual outcomes and response to therapy.

2.5.6. Immunologic Biomarkers

Several immunologic markers have been investigated for their diagnostic and prognostic utility in HP:

- BAL fluid lymphocytosis (>20–30% lymphocytes)

- CD4+/CD8+ ratio (often decreased, though variable)
- Serum precipitins (IgG antibodies) against known antigens
- Elevated serum KL-6 and surfactant proteins (SP-D, SP-A) in fibrotic forms

These markers, though not pathognomonic, support the clinical suspicion when integrated with history, imaging, and lung biopsy findings.

The pathophysiology of hypersensitivity pneumonitis is driven by a coordinated immune response to inhaled antigens, involving both innate and adaptive mechanisms. Early disease is dominated by immune complex deposition and Th1-mediated inflammation, while chronic forms are characterized by persistent antigenic stimulation, granulomatous inflammation, and progressive fibrosis. Understanding these mechanisms is crucial for improving diagnostic accuracy and identifying novel therapeutic targets to halt disease progression [9, 13].

2.5.7. Radiological Features

Radiologic imaging plays a central role in the diagnosis and classification of hypersensitivity pneumonitis (HP), particularly high-resolution computed tomography (HRCT), which has become the cornerstone in evaluating interstitial lung disease. The radiological manifestations of HP vary depending on the stage of the disease—acute, subacute, or chronic—and the degree of fibrosis. Recognizing the typical imaging patterns is crucial in differentiating HP from other ILDs such as nonspecific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis (IPF).

2.5.7.1. Imaging Modalities

a. Chest Radiography

- Acute/Subacute HP: May show diffuse, bilateral, ill-defined reticulonodular or ground-glass opacities.
- Chronic HP: May reveal reticular changes, volume loss, or signs of fibrosis, though findings are often nonspecific.

- Chest X-rays lack sensitivity and specificity and are inadequate for detecting early or subtle changes.

b. High-Resolution Computed Tomography (HRCT)

HRCT is the gold standard imaging modality for HP due to its superior spatial resolution and ability to characterize interstitial abnormalities.

2.5.7.2. Radiologic Patterns by Disease Stage

a. Non-Fibrotic (Acute and Subacute) HP

Typical HRCT features include:

- **Centrilobular ground-glass nodules:** Small, ill-defined nodules in a centrilobular distribution, reflecting bronchiolocentric inflammation.
- **Ground-glass opacities (GGO):** Patchy or diffuse; often with a mid or upper lobe predominance.
- **Mosaic attenuation:** Due to air trapping and perfusion abnormalities from small airway involvement.
- **Air trapping:** Best seen on expiratory scans; reflects bronchiolar inflammation and is highly suggestive of HP.
- **Absence of fibrosis:** In early stages, there is minimal to no architectural distortion.

These findings are usually reversible if antigen exposure is eliminated promptly.

b. Fibrotic (Chronic) HP

Chronic HP shows a combination of inflammatory and fibrotic changes. Key HRCT features include:

- Reticulation and traction bronchiectasis, predominantly in a mid to upper lobe distribution (contrast with IPF, which affects lower lobes).
- Lobular areas of decreased attenuation and vascularity (mosaic attenuation), suggestive of small airway disease.

- Air trapping: Diffuse or patchy, best appreciated on expiratory imaging; its presence with fibrosis strongly supports HP.
- Centrilobular nodules may persist but are less prominent.
- **Honeycombing:** May be present but is usually patchy and less extensive than in IPF.

The triad of fibrosis, air trapping, and mosaic attenuation in a mid-upper lobe predominance is highly suggestive of chronic fibrotic HP [9-13].

2.5.7.3. Radiologic Differential Diagnosis

Radiologic differentiation between HP and other ILDs is essential:

Condition	Key Differentiating Features
IPF	Lower lobe and subpleural fibrosis, extensive honeycombing, absence of air trapping or centrilobular nodules.
NSIP	More homogeneous ground-glass opacities, basal predominance, fewer nodules, and less air trapping.
Sarcoidosis	Perilymphatic nodules, mediastinal lymphadenopathy, upper lobe fibrosis but with more peribronchovascular involvement.
Respiratory bronchiolitis-ILD	Centrilobular nodules in smokers, but without air trapping or mosaic perfusion.

2.5.7.4. Role of Expiratory Imaging

Expiratory HRCT scans are essential for assessing air trapping, a hallmark of small airway involvement in HP. The presence of mosaic attenuation with expiratory air trapping in areas of unaffected lung parenchyma is a strong radiologic clue pointing toward HP, particularly in the chronic form.

2.5.7.5. Quantitative and Emerging Imaging Techniques

Recent advances include:

- **Quantitative CT analysis:** Using software to quantify the extent of fibrosis, air trapping, and emphysema.
- **Radiomics and machine learning:** Experimental tools being developed to improve diagnostic accuracy and predict outcomes based on imaging features.
- **PET-CT imaging:** Limited utility in HP but may help assess disease activity or rule out mimics such as malignancy.

2.5.7.6. Prognostic Implications of Imaging Findings

HRCT findings correlate with disease stage and prognosis:

- Greater extent of fibrosis, traction bronchiectasis, and honeycombing are associated with worse outcomes.
- The preservation of lobular architecture, patchy air trapping, and absence of extensive honeycombing suggest a more favorable prognosis and responsiveness to antigen avoidance or immunosuppressive therapy.
- Radiologic progression despite therapy may indicate a need to consider lung transplantation in advanced fibrotic HP.

Radiological evaluation—particularly with high-resolution CT—is indispensable in the diagnosis and management of hypersensitivity pneumonitis. The identification of key features such as centrilobular nodules, ground-glass opacities, mosaic attenuation, and air trapping enables early diagnosis and helps differentiate HP from other fibrosing ILDs. Chronic HP is best characterized by a combination of airway-centered fibrosis and small airways disease, with specific patterns that guide both diagnosis and prognostication [9-13].

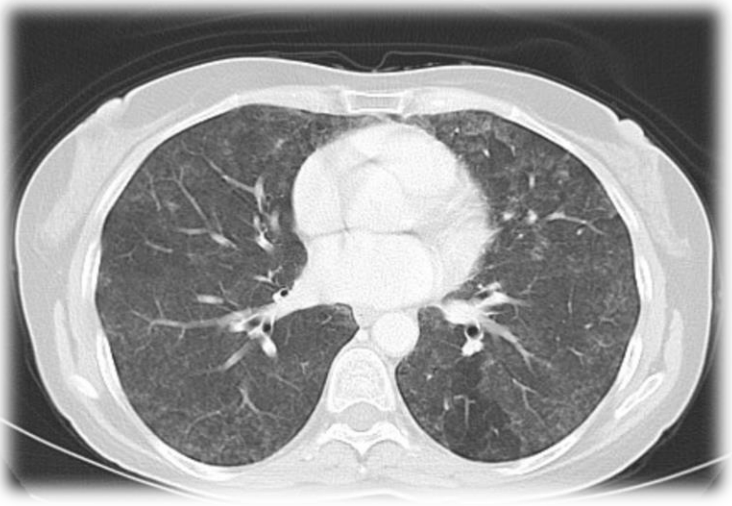

Figure1. Acute HP

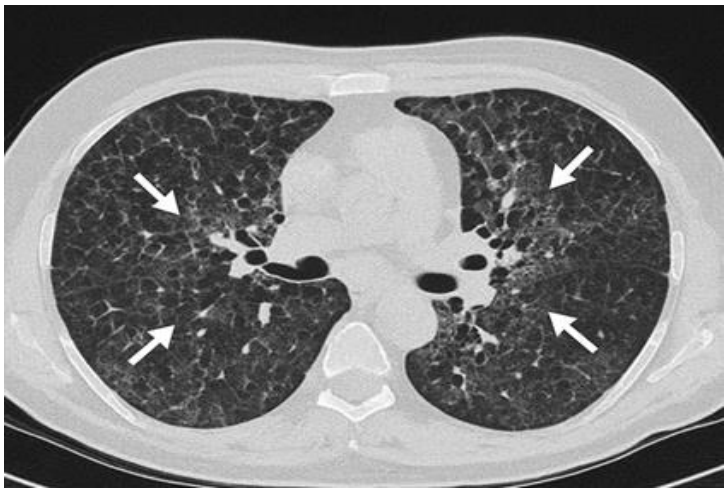

Figure 2. Chronic HP

2.6. Management and Treatment of Hypersensitivity Pneumonitis

2.6.1. Antigen Identification and Avoidance

- First-line intervention in all forms of HP.
- Perform a detailed environmental and occupational history.
- Use specific IgG testing or environmental assessments to identify the causative antigen.

- Remove the patient from the exposure environment (e.g., change in workplace, removal of pets or molds from home).

2.6.2. Corticosteroid Therapy

Used primarily in acute and subacute HP or during inflammatory exacerbations of chronic HP.

Prednisone dosing:

- **Initial dose:** 0.5–1 mg/kg/day (typically 30–60 mg daily) for 2–4 weeks.
- **Tapering:** Gradual taper over 2–3 months, depending on clinical response and radiologic or functional improvement.
- **Monitoring:** Watch for side effects: hyperglycemia, osteoporosis, infections, etc.

Note: In fibrotic HP, corticosteroids have limited efficacy but may help manage inflammatory flares.

2.6.3. Immunosuppressive Therapy

Used in chronic HP or when corticosteroids are contraindicated or not well tolerated.

Common agents:

- **Azathioprine**
    - **Starting dose:** 1–2 mg/kg/day
    - Monitor liver function and blood counts.
- **Mycophenolate mofetil**
    - **Starting dose:** 500–1000 mg twice daily
    - Better gastrointestinal tolerance than azathioprine in many cases.
- **Cyclophosphamide** (rare, severe progressive cases)

Note: These drugs are typically used as steroid-sparing agents.

2.6.4. Antifibrotic Therapy

In progressive fibrotic HP, similar to idiopathic pulmonary fibrosis (IPF), antifibrotic agents can be considered:

- **Nintedanib** (approved for chronic fibrosing ILDs including fibrotic HP)
    - **Dose:** 150 mg twice daily
    - Slows functional decline but does not reverse fibrosis.
- **Pirfenidone** (less evidence, not widely used for HP)

2.6.5. Supportive Treatment

- Supplemental oxygen for patients with resting or exertional hypoxemia.
- Pulmonary rehabilitation to improve exercise capacity and quality of life.
- **Vaccinations:** annual influenza and pneumococcal vaccines.
- Smoking cessation if applicable.

2.6.6. Lung Transplantation

Lung transplantation represents a therapeutic option for patients with fibrotic hypersensitivity pneumonitis (f-HP) who develop advanced, progressive disease despite optimal medical management. In the fibrosing form of HP, ongoing antigen exposure, delayed diagnosis, or suboptimal response to corticosteroids and immunosuppressive agents can lead to irreversible architectural distortion of the lungs, with loss of function and increasing respiratory insufficiency. In these cases, lung transplantation may be the only life-prolonging intervention.

The decision to refer a patient for transplant evaluation is typically made when there is evidence of significant physiological decline, such as a forced vital capacity (FVC) below 50–60% of predicted, a DLCO under 40%, or when the patient becomes oxygen-dependent at rest or with minimal exertion. Additional indicators include rapidly worsening symptoms, declining quality of life, or radiologic progression with honeycombing and extensive fibrosis.

Although the prognosis of f-HP can be variable, patients with progressive fibrotic changes often exhibit a disease trajectory similar to idiopathic pulmonary fibrosis (IPF), for which lung transplantation is a well-established treatment. Referral should not be delayed, as waitlist times and transplant candidacy evaluation can be lengthy. Importantly, outcomes after transplantation in patients with HP are generally comparable to those in other interstitial lung diseases, with median post-transplant survival ranging from 5 to 7 years, depending on comorbidities and center experience [14].

Careful patient selection, multidisciplinary evaluation, and early referral are essential to optimize timing and maximize the benefits of lung transplantation in f-HP.

3. Results and Discussion

3.1. Clinical Presentation of Non-fibrotic vs. Fibrotic HP

Non-fibrotic HP

In the non-fibrotic form of hypersensitivity pneumonitis, the disease typically presents with acute or subacute symptoms, including cough, dyspnea, and fever. These symptoms are often triggered by recent exposure to an environmental antigen. The clinical presentation is frequently associated with ground-glass opacities on high-resolution computed tomography (HRCT) and mild alterations in pulmonary function, particularly a decrease in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). The diagnosis of non-fibrotic HP relies heavily on a combination of clinical symptoms, exposure history, HRCT findings, and, when needed, bronchoalveolar lavage (BAL) showing lymphocytosis. Fortunately, non-fibrotic HP, when diagnosed early and with antigen avoidance, typically has a favorable prognosis and may resolve completely or show only minimal sequelae [7, 15].

Fibrotic HP

In contrast, fibrotic HP is characterized by more chronic and progressive symptoms. Patients often present with insidious dyspnea, chronic cough, and fatigue, which

worsen over time. Radiologically, fibrotic HP shows evidence of honeycombing, traction bronchiectasis, and reticular opacities, indicative of irreversible fibrosis. Pulmonary function tests (PFTs) reveal significant declines in FVC and DLCO, often indicating advanced disease. The disease progression may lead to respiratory failure in the absence of effective intervention. In these cases, the prognosis is poor, and the management becomes more challenging [3].

3.2. Treatment Approaches for Non-fibrotic vs. Fibrotic HP

Non-fibrotic HP Treatment

The cornerstone of treatment for non-fibrotic HP is antigen avoidance. By removing the source of the triggering antigen (e.g., avoiding mold, bird proteins, or dust), many patients experience significant clinical improvement. In some cases, corticosteroids are used to manage acute inflammation. The typical regimen involves prednisone at a dose of 0.5–1 mg/kg/day for 1–2 weeks, followed by a tapering phase. In cases of recurrent flares or significant symptoms, immunosuppressive agents like azathioprine or mycophenolate mofetil may be considered. However, the need for these medications is generally less frequent in non-fibrotic HP, as early identification and antigen removal often lead to improvement without long-term medication use [9, 10].

Fibrotic HP Treatment

For fibrotic HP, treatment becomes more complex. Corticosteroids remain the first-line treatment, but their efficacy in halting the progression of fibrosis is limited. The initial treatment involves prednisone (0.5–1 mg/kg/day), followed by a gradual taper. However, in patients with advanced fibrosis or those who do not respond to corticosteroids, immunosuppressive therapies such as azathioprine or mycophenolate mofetil may be considered as steroid-sparing agents. Recent studies have suggested that antifibrotic therapies, such as nintedanib, may slow the decline of lung function in chronic fibrotic HP, similar to its role in idiopathic pulmonary fibrosis (IPF). However, the evidence for antifibrotic agents in HP remains limited and warrants further research [11-14].

3.3. Clinical Outcomes and Prognosis

Non-fibrotic HP

Patients with non-fibrotic HP, when diagnosed early and exposed to antigen avoidance strategies, tend to show good clinical outcomes. Symptoms often improve with corticosteroids, and lung function may return to near baseline levels. The long-term prognosis is generally favorable, especially if antigen exposure is completely avoided. However, recurrence of symptoms due to re-exposure remains a risk if the antigen is not thoroughly removed from the environment [8].

Fibrotic HP

In contrast, fibrotic HP has a worse prognosis due to the irreversible nature of fibrosis. Patients with fibrotic HP often require long-term management with corticosteroids and immunosuppressive drugs. Unfortunately, despite these treatments, many patients experience progressive lung function decline and are at risk for respiratory failure. Lung transplantation may be required in advanced cases of fibrotic HP when conservative management fails, offering a potential lifeline for patients who meet transplant criteria.

This format provides a detailed comparison between non-fibrotic and fibrotic HP, addressing clinical presentation, treatment strategies, and prognostic outcomes, which are crucial for the management of these two distinct forms of the disease [6, 7].

4. Discussion

4.1. Interpretation of Findings from the Literature

In this review, we analyzed various studies on hypersensitivity pneumonitis (HP), focusing on the fibrotic and non-fibrotic forms, and identified both common trends and discrepancies in diagnostic and therapeutic approaches. Most of the studies emphasize the importance of early diagnosis and antigen avoidance in non-fibrotic HP, with a generally favorable prognosis when treatment is promptly initiated. In contrast, the literature indicates that the fibrotic form of HP presents significant

management challenges, as standard treatments, including corticosteroids, are insufficient to prevent disease progression [2-4].

By comparing studies, it was observed that treatment approaches for fibrotic HP have yielded variable results. While some studies suggest a limited benefit from corticosteroids, others discuss the use of immunomodulators and antifibrotic agents as promising alternatives. Overall, there is a consensus on the need for novel therapeutic strategies targeting fibrosis specifically, such as antifibrotic drugs like nintedanib, which show potential in slowing disease progression [12].

4.2. Limitations in Current Understanding

Despite the progress made in understanding and managing HP, several limitations are present in the current body of literature. Many of the studies included in this review are retrospective and involve relatively small sample sizes, limiting the generalizability of the findings. Furthermore, the heterogeneity of the disease and variability in antigen exposures make it difficult to draw definitive conclusions regarding the optimal treatments for all patients. The lack of standardized guidelines for managing fibrotic HP further contributes to inconsistency in treatment approaches. Future research should focus on large, prospective studies to validate current findings and explore additional therapeutic options.

4.3. Clinical Implications and Management

Based on the findings of this review, it is clear that treatment strategies for HP must be individualized based on disease form. In non-fibrotic HP, antigen avoidance and early corticosteroid therapy remain the most effective interventions to prevent disease progression. However, for fibrotic HP, it is evident that standard treatments, such as corticosteroids, are insufficient to halt the progression of fibrosis, highlighting the need for additional therapies, particularly immunomodulators and antifibrotic agents. These emerging treatments, while still under investigation, offer promise for improving long-term outcomes in patients with fibrotic HP [9, 10].

As more evidence accumulates, personalized treatment based on genetic and molecular profiles of patients is expected to play a crucial role in the management

of HP. In addition, regular monitoring of pulmonary function and immune markers will be essential for adjusting treatment regimens and preventing disease progression in a timely manner.

4.4. Future Directions and Research

Future research should focus on prospective studies to evaluate the impact of antifibrotic therapies and other emerging drugs on the progression of fibrotic HP. Additionally, exploring the role of biomarkers and genetics could help identify patients at greater risk for developing fibrotic forms of HP, allowing for earlier interventions. Combination therapies that target both acute inflammation and fibrosis may offer a more effective treatment approach, and these need to be investigated further. Moreover, understanding the genetic susceptibility to HP could lead to personalized medicine strategies, offering more effective treatments tailored to individual patients [6, 7].

5. Conclusion

Hypersensitivity pneumonitis (HP) remains a challenging interstitial lung disease, both in terms of its pathogenesis and clinical management. The disease arises from a complex interplay between genetic predisposition, environmental antigen exposure, and dysregulated immune responses, resulting in a spectrum of lung inflammation and fibrosis. Despite decades of study, HP continues to be underdiagnosed or misclassified, in part due to its heterogeneous clinical presentation and the limitations of existing diagnostic tools.

Accurate diagnosis requires a multidisciplinary approach that integrates clinical history, exposure assessment, high-resolution imaging, bronchoalveolar lavage analysis, and, in selected cases, lung biopsy. Differentiating fibrotic from non-fibrotic HP is critical, as this distinction strongly influences prognosis and therapeutic strategy. While antigen avoidance remains the cornerstone of treatment, immunosuppressive therapies—primarily corticosteroids and, more recently, antifibrotic agents—are increasingly important in managing progressive forms of the disease [14].

Future research must prioritize the identification of reliable biomarkers to improve diagnostic precision and to monitor treatment response. In parallel, the development of standardized clinical criteria and increased awareness among healthcare professionals are essential to minimize diagnostic delays and optimize patient outcomes.

Ultimately, managing HP requires not only clinical vigilance but also a proactive, individualized approach that balances environmental, immunologic, and fibrotic components of the disease. Only through such comprehensive understanding can we hope to improve survival and quality of life for patients affected by this often-overlooked condition [8].

Conflict of Interest

The author declares no conflict of interest. The author is solely responsible for the entire content of this chapter.

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