HYPERSENSITIVITY
PNEUMONITIS

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Introduction

• Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an immune mediated lung disease.

• This uncommon disease is caused by inhalation of and sensitisation to antigens derived from protozoa, molds, animals, insects, bacteria, chemicals, and other organic materials.
Introduction

• The presentation of HP is with systemic and respiratory symptoms, but the mechanism is **distinctly different** from IgE mediated allergy.

• A complex interaction between exposure to antigens, susceptibility and immune response of the host and genetic factors are involved in the pathogenesis of HP which contribute to the presentation of the disease as **acute, subacute or chronic forms**.
Definition

Hypersensitivity pneumonitis is an allergic disease of the lung parenchyma with inflammation in the alveoli and interstitial spaces induced immunologically by acute or chronic inhalation of a wide variety of inhaled materials.

Several different immune pathways appear to operate separately or concurrently in this condition, but the most compelling evidence favors allergen-specific cell-mediated hypersensitivity as the mechanism of pathogenesis.
Historical background

• A disease resembling HP was reported in grain sifters and measurers by Ramazzini in the early part of the 18th century. He associated the disease with decay, weevils, and mold in the grain.

• Farmer’s lung, the first classic and well-studied example of HP was described in England in 1932. This was followed by reports of increased numbers of hypersensitivity lung diseases caused by a variety of antigens.

• These syndromes include bagassosis, mushroom worker’s lung, pigeon breeder’s disease, ventilation system induced lung diseases, and those caused by aerosols from industrial dusts, chemicals, and drugs.
# Allergen associated with HP

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Source</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
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<tr>
<td>Thermophilic actinomycetes</td>
<td>Contaminated hay or grains</td>
<td>Farmer's lung</td>
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<td></td>
<td>Contaminated bagasse</td>
<td>Bagassosis</td>
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<td></td>
<td>Mushroom compost</td>
<td>Mushroom worker's lung</td>
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<td><em>Bacillus subtilis</em></td>
<td>Contaminated walls</td>
<td>Domestic hypersensitivity pneumonitis</td>
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<tr>
<td><em>Streptomyces albus</em></td>
<td>Contaminated fertilizer</td>
<td><em>Streptomyces</em> hypersensitivity pneumonitis</td>
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<tr>
<td>Fungi</td>
<td>Source</td>
<td>Disease</td>
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<tr>
<td><em>Aspergillus</em> spp</td>
<td>Moldy barley</td>
<td>Malt worker's lung</td>
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<td></td>
<td>Moldy tobacco</td>
<td>Tobacco worker's lung</td>
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<td></td>
<td>Compost</td>
<td>Compost lung</td>
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<tr>
<td><em>Aureobasidium, Graphium</em> spp</td>
<td>Redwood bark, sawdust</td>
<td>Sequoiosiosis</td>
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<td>Contaminated sauna water</td>
<td>Sauna worker's lung</td>
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<td></td>
<td>Contaminated humidifier</td>
<td>Humidifier lung</td>
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<tr>
<td><em>Cryptostroma corticale</em></td>
<td>Maple bark</td>
<td>Maple bark disease</td>
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<td><em>Penicillium casei</em></td>
<td>Moldy cheese</td>
<td>Cheese worker's lung</td>
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<td><em>Sacchoromonospora viridis</em></td>
<td>Dried grass</td>
<td>Thatched roof disease</td>
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<tr>
<td>Various undetermined puffball spores</td>
<td>Moldy dwellings</td>
<td>Domestic hypersensitivity pneumonitis</td>
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<td>Mold in cork dust</td>
<td>Suberosis</td>
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<td>Lycoperdon puffballs</td>
<td>Lycoperdonosis</td>
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<tr>
<td><em>Trichosporon cutaneum</em></td>
<td>House dust (reported in Japan)</td>
<td>Summer-type hypersensitivity pneumonitis</td>
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<tr>
<td>Category</td>
<td>Cause</td>
<td>Industry</td>
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<tr>
<td><strong>Insects</strong></td>
<td><em>Sitophilus granarius</em> (wheat weevil)</td>
<td>Infested flour</td>
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<tr>
<td><strong>Organic chemicals</strong></td>
<td>Isocyanates</td>
<td>Various industries</td>
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<tr>
<td><strong>Miscellaneous</strong></td>
<td>Pituitary snuff</td>
<td>Medication</td>
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<td></td>
<td>Coffee bean protein</td>
<td>Coffee bean dust</td>
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<td></td>
<td>Rat urine protein</td>
<td>Laboratory rats</td>
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<td></td>
<td>Animal fur protein</td>
<td>Animal pelts</td>
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<tr>
<td></td>
<td>Unknown</td>
<td>Contaminated tap water</td>
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</tbody>
</table>
Genetic factor

• HP is more common in males than females with an overrepresentation of middle-aged individuals.

• Beryllium lung disease - HLA-DPB1 Glu-69

• HLA DR7 - pigeon fancier's lung in a Mexican

• HLA B8 - farmer's lung and pigeon fancier's lung in Caucasians

• HLA-DQw3 - Japanese summer-type HP

• high-producing TNF-a genotype being associated with farmer's lung and pigeon fancier's lung
Environmental factor

• antigen concentration
• Duration of exposure
• frequency of exposure
• particle size, antigen solubility
• use of respiratory protection
• variability in work practices
• Seasonal variation- peak in antibody production during late summer
Immunopathogenesis

• Although HP is an immunologic disorder, the exact mechanism involved in the disease are not yet fully understood. Both cellular and humoral pathways have been suggested in the disease process.

• Serum precipitating antibodies specific to the antigen can be found in most patients.

• Lesions are initiated by inhalation of large amounts of particulate organic dust antigens.

• Initial nonspecific activation of the alternative pathway of complement provides the necessary stimulus for increased vascular permeability and chemotactic recruitment of neutrophils.
• Alveolar macrophages are also activated, with release of enzymes and $O_2$ metabolites, IL-1 and other monokines. This results in some acute tissue injury and expansion of lymphocyte populations (IL-2 production).

• Macrophage associated antigen is "presented" to lymphocytes. The specific "local" B-cell antibody response provides an additional stimulus in the form of immune complexes that also bind complement, and activate alveolar macrophages.
• Repeated exposure to antigen results in development of intense T cell mediated (delayed) hypersensitivity.

• Sensitized T cells continue to release interleukin 2, with subsequent expansion of lymphocyte populations. Release of other lymphokines, such as macrophage migration inhibition factor further activates alveolar macrophages.

• Under the influence of genetic factors, populations of suppressor T cells (and possibly macrophages) and their products ultimately expand and dampen or modulate the degree of pulmonary T-cell-mediated granulomatous inflammation.
Type-III Hypersensitivity

1-2 hours

Locally injected antigen in immune individual with IgG antibody → Local immune-complex formation → Activation of FcγRIII on mast cells induces their degranulation → Local inflammation, increased fluid and protein release, phagocytosis, and blood vessel occlusion
Type-IV (cell mediated) Hypersensitivity
Pathology

• The histopathology of hypersensitivity pneumonitis depends on the stage of disease.

  Acute phase: the centrilobular respiratory bronchioles, alveoli, and blood vessels are intensely infiltrated by granulocytes, monocytes, and plasma cells. There is Arthus-like vasculitis of alveolar capillaries. Alveolar wall thickening occurs but without necrosis. Immunofluorescence studies show deposition of immunoglobulins, C3, and fibrin in and around affected blood vessels. Thus, any role of precipitating antibodies causing immune complex deposition and complement-mediated Arthus-like vasculitis, alveolitis, and terminal bronchiolitis
• **The subacute phase**: noncaseating granulomas in the interstitial spaces accompanied by lymphocytes and plasma cells with only occasional eosinophils and no vasculitis.

• **Chronic disease** is characterized by persistence of the subacute pathology. Lymphocytes are present in alveolar walls, and interstitial fibrosis. granulomatous and mononuclear inflammation. No eosinophilia occurs.

**Immunofluorescence** shows no immunoglobulin or complement deposits. Monoclonal antibody reagents reveal the presence of activated macrophages and T lymphocytes, predominantly CD8 cells.
Acute HP

• In the acute form of HP, symptoms may develop 4–6 hours following heavy exposure to the provoking antigen. Symptoms include fever, chills, malaise, cough, chest tightness, dyspnea, and headache. Symptoms resolve within 12 hours to several days upon cessation of exposure.
Subacute HP

• Patients with subacute HP gradually develop a productive cough, dyspnea, fatigue, anorexia, weight loss, and pleurisy. Symptoms are similar to the acute form of the disease, but are less severe and last longer. On chest radiographs, micronodular or reticular opacities are most prominent in mid-to-lower lung zones. Findings may be present in patients who have experienced repeated acute attacks
Chronic HP

• In chronic HP, patients often lack a history of acute episodes. They have an insidious onset of cough, progressive dyspnea, fatigue, and weight loss. This is associated with partial to complete but gradual reversibility. Avoiding any further exposure is recommended. Clubbing is observed in 50% of patients. Tachypnea, respiratory distress, and inspiratory crackles over lower lung fields often are present.
Clinical diagnosis  Diagnostic criteria for hypersensitivity pneumonitis

Major Criteria (Four major criteria need to be present)

1. History of symptoms compatible with HP
2. Evidence of exposure to the offending antigen by history or through detection in serum or BAL fluid antibody
3. Changes of characteristic HP on chest radiograph (reticulonodular infiltrates, linear opacities) or HRCT of the chest (ground-glass opacities, micronodules, honeycombing, linear opacities, air trapping)
4. Demonstration of BAL fluid lymphocytosis, if BAL is performed
5. Demonstration of histologic changes consistent with HP, if lung biopsy is performed, such as alveolitis, noncaseating granulomas, giant cells, foamy alveolar macrophages, or fibrosis
6. Positive ‘natural challenge’ that produces symptoms and objective abnormalities either through controlled inhalational challenge or after re-exposure to the offending environment
Clinical diagnosis  Diagnostic criteria for hypersensitivity pneumonitis

Minor Criteria (Two minor criteria need to be present)
1. Bibasilar rales
2. Decreased diffusion capacity
3. Arterial hypoxemia, either at rest or with exercise

Clinical Prediction
1. Exposure to known offending antigen
2. Positive precipitating antibody to the offending antigen
3. Recurrent episodes of symptoms
4. Respiratory crackles in physical examination
5. Symptoms occurring between 4 to 8 hours after exposure
6. Weight loss
Laboratory Finding

• In acute disease- Slight leukocytosis without eosinophilia. The erythrocyte sedimentation rate is normal or mildly elevated.

• In chronic disease- serum immunoglobulin levels may be slightly increased.

• **Pulmonary function tests:** In acute disease a reversible restrictive pattern with reduced lung compliance and reduced diffusing capacity.

• **Arterial blood gases:** hypoxemia.

• **The spirometric findings:** Irreversible restriction with or without an accompanying obstructive component due to bronchiolitis obliterans. Bronchial hyperirritability may occur.
Chest radiographic findings: In an acute episode, the presence of multiple bilateral small nodules sparing the apices and bases is the typical pattern. This indicates the presence of interstitial inflammation and an alveolus-filling infiltrate. Less common findings are patchy pneumonia or a normal radiograph.

• In chronic disease a fibrotic linear pattern with or without nodules increases in intensity toward the periphery. A loss of volume that is most marked in upper lobes, honeycombing, and cor pulmonale-induced cardiac enlargement may occur.
Chest X-ray showing opacity of a fibrotic appearance in both lung fields, most exuberant in the middle level of the right lung field.
Immunologic Diagnosis

Large quantities of precipitating antibodies are usually present, especially in early or acute disease, but they may disappear after a prolonged period of allergen avoidance. The more sensitive radioimmunoassay, radioallergosorbent test (RAST), enzyme-linked immunosorbent assay (ELISA), and complement fixation test procedures lack specificity for diagnostic purposes. Serum complement component levels are normal or occasionally increased with acute allergen exposure.
Bronchial provocation testing with allergen extract currently has the highest sensitivity and specificity for diagnosis, but it is an experimental procedure because of technical limitations and danger. It should be done in a hospital with 24-hour monitoring. A reversible restrictive lung defect begins at 4-6 hours, peaks at 8 hours, and resolves by 24 hours. Although the timing of response is similar to a late-phase asthmatic response, the abnormality in pulmonary function is different.
Differential Diagnosis

• Pulmonary mycotoxicosis (atypical farmer's lung)
• Recurrent infectious pneumonias
• other causes of interstitial lung disease
• asthma
• allergic bronchopulmonary aspergillosis
• pneumoconioses
Treatment

• Avoidance of the allergen is the accepted form of treatment and prevention.

• Systemic corticosteroid therapy is indicated for resolution of acute reactions and for terminating and reversing severe or progressive disease. The drug should not be used as an alternative to avoidance of the allergen, but it may be necessary to protect the patient by suppressing inflammation if the allergen source has not been identified. Inhaled corticosteroids are not indicated.
Complications and Prognosis

• Respiratory failure and cor pulmonale may result from chronic disease. Bronchiolitis obliterans may lead to irreversible obstructive pulmonary disease. Death from respiratory failure is possible during any phase of the disease.

• Prognosis for recovery is good in the acute or subacute stages once the cause has been identified and avoided. Some patients with bird handler's disease, however, have progressive pulmonary insufficiency.

• Farmers can continue to have some exposure to thermophilic actinomycetes without progressive illness.
Prevention

- **Avoidance** is the only means of preventing this disease. Effective treatment therefore requires a specific immunologic diagnosis. The purpose of avoidance is prevention of irreversible lung disease.

- **Occupational preventive measures** are obvious for the currently recognized causes. Proper workplace hygiene, filters and masks where appropriate, and other measures should be employed. Diseases caused by allergens in homes, automobiles, and offices are best prevented by physician awareness of the disease.
Thanks a lot for your Kind attention

The End