ILD AND PULMONARY FIBROSIS – a summary for the general pulmonologist

Interstitial lung disease (ILD)
Refers to those conditions that affect the interstitium of the lungs diffusely.

- With or without fibrosis
- May or may not be limited to the lungs
- May or may not have an established cause

Pulmonary fibrosis
Refers to ILD with HRCT findings that include lung infiltrates associated with traction bronchiectasis or honeycombing.

Idiopathic pulmonary fibrosis (IPF)
Refers to pulmonary fibrosis with the following characteristics:

- It is usually progressive
- Occurs spontaneously without an apparent cause
    - Negative lab tests
        - Absence of domestic or professional environmental exposure or use of drugs known to cause ILD
        - Absence of clinical characteristics of other illnesses associated with ILD such as connective tissue diseases (CTD)
- It is associated with a usual interstitial pneumonia (UIP) pattern in HRCT and lung biopsy
    - The UIP pattern is characteristic of IPF but can be seen in other ILDs
        - CTDs
        - Asbestosis
        - Hypersensitivity Pneumonitis
        - Sarcoidosis
        - Drugs known to cause ILD
        - Infections
            - UIP was the most common pathologic pattern found in patients who developed pulmonary fibrosis after COVID

Progressive pulmonary fibrosis (PPF)
Refers to non-IPF pulmonary fibrosis with progression defined as presence of 2 out 3 of the following criteria within one year:

- Worsening clinical symptoms
- Decreased FVC ≥5%
- Decreased DLCO ≥ 10%

ILD DIAGNOSIS

- Should be suspected in patients who develop progressive dyspnea and or dry cough. Once suspected, diagnosis of ILD and the type of ILD should be confirmed usually with a combination of:
    - Clinical history
    - HRCT
    - PFTs
    - Lab tests
    - Biopsy
- However, there is no unique characteristic to any specific ILD and histopathologic and HRCT findings overlap exists between different ILDs.
- Therefore, the recommended approach to ILD diagnosis is a multidisciplinary assessment with a team consisting of pulmonologists, radiologists, and, where necessary, pathologists and rheumatologists.

CLINICAL HISTORY

- Progressive dyspnea and or dry cough
- Inspiratory-Velcro type crackles in IPF

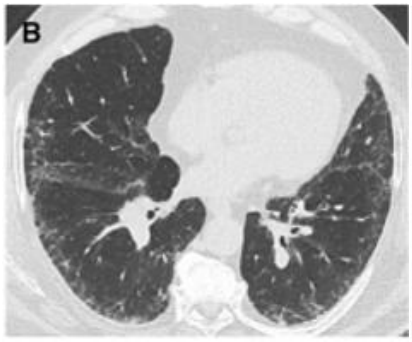
- Domestic and occupational environmental exposure
- Drugs known to cause ILD
- Sign and symptoms of diseases known to be associated with ILD such as CTD
    - Most patients with ILD due to CTD are diagnosed with CTD before developing respiratory symptoms related to ILD
    - However, ILD can be the first manifestation of systemic autoimmune disease in a small proportion of patients, most commonly in patients with idiopathic inflammatory myopathy

HRCT

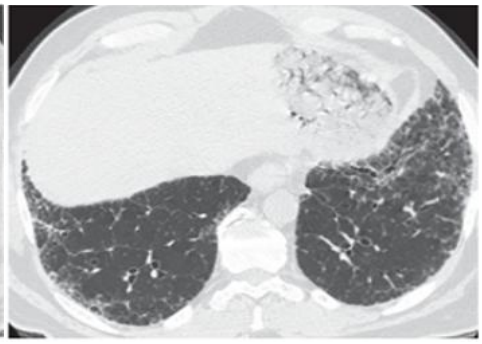
Pulmonary findings commonly seen in ILD include the combination of:

- Reticular infiltrates
- Ground glass infiltrates
- Traction bronchiectasis/ bronchiolectasis
- Honeycombing
- Consolidation

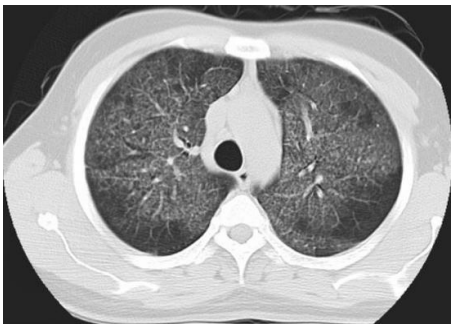
Reticular infiltrates



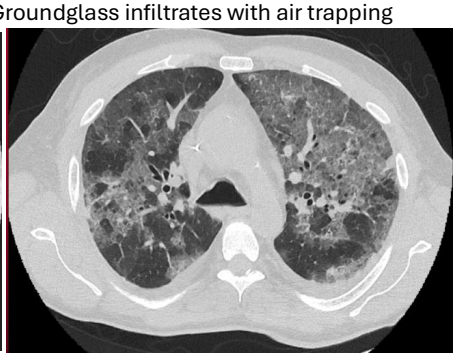
Reticular infiltrates and traction bronchiectasis



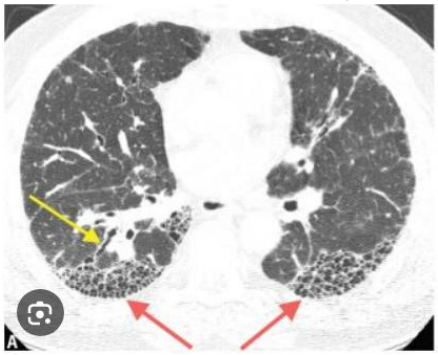
Groundglass infiltrates

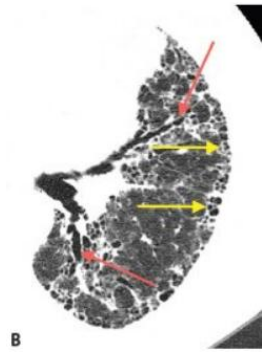


Groundglass infiltrates with air trapping

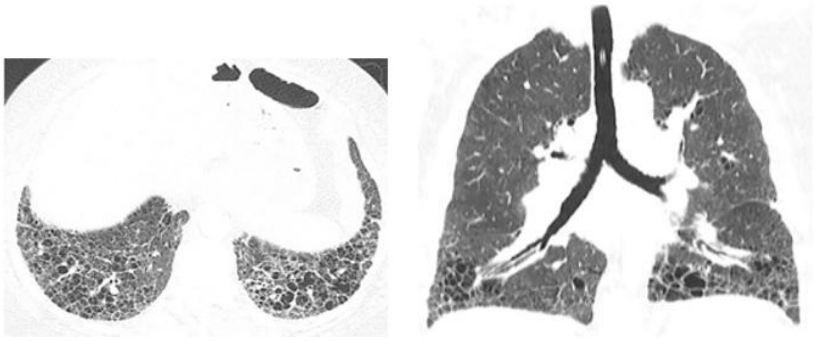


Traction bronchiectasis and honeycombing

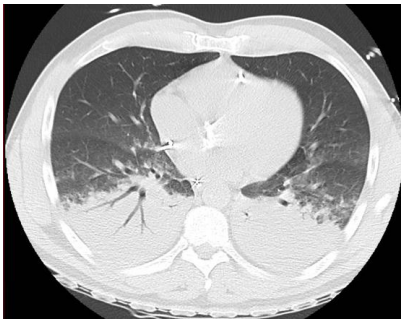




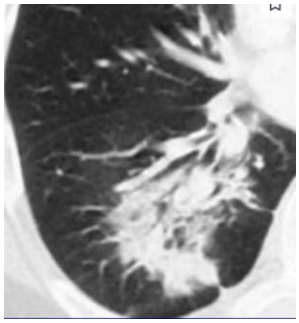
Honeycombing



Consolidation



Consolidation

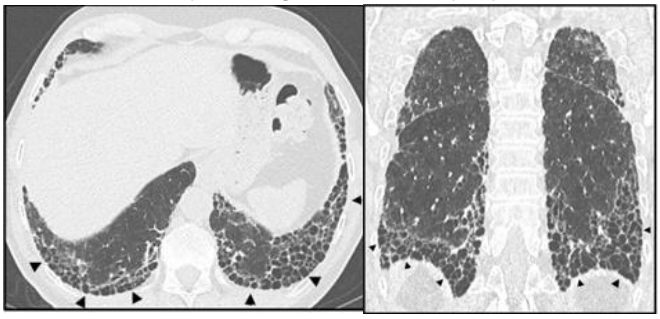


The characteristics and distribution that can be observed in the HRCT is indispensable not only for the diagnosis of ILD but also to distinguish the different types.

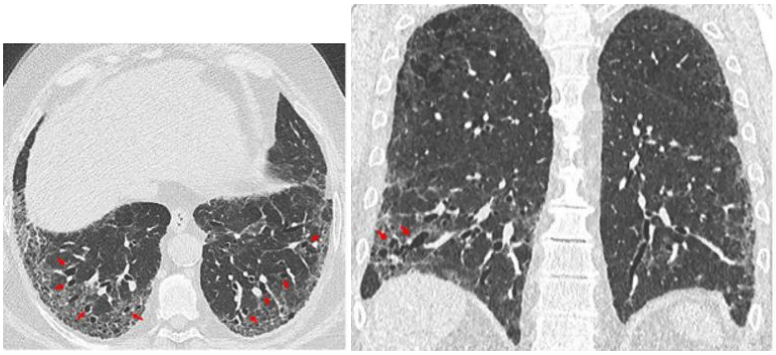
Four HRCT patterns are recognized

- **Usual interstitial pneumonia (UIP)**
  - Heterogenous reticular infiltrates and traction bronchiectasis with peripheral and basal predominance
  - Ground glass infiltrates can be seen but are not prominent
  - Honeycombing is present
- **Probable UIP**
  - Heterogenous reticular infiltrates and bronchiolectasis/traction bronchiectasis with peripheral and basal predominance
  - Absence of honeycombing
- **Indeterminate for UIP**
  - Reticular infiltrates with or without ground glass with peripheral and basal predominance
  - Findings in the HRCT do not secure a specific cause
- **Alternative diagnosis**
  - Findings consistent with another diagnosis

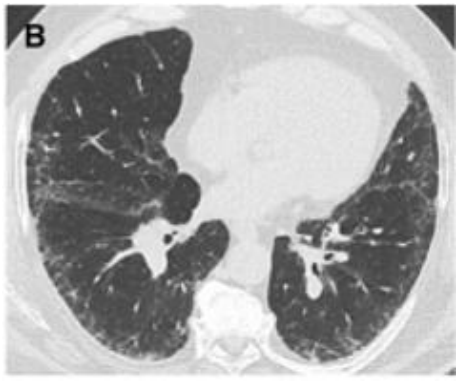
UIP Pattern: honeycombing with basal and peripheral distribution



Probable UIP: reticular infiltrates and traction bronchiectasis with basal and peripheral distribution

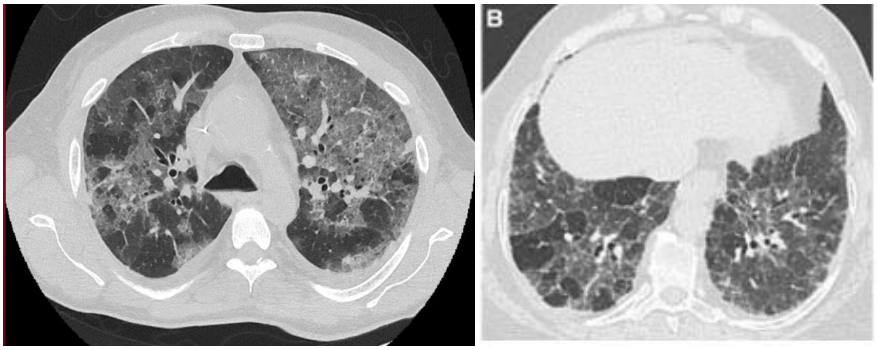


Indeterminate for UIP: reticular infiltrates with basal and peripheral distribution

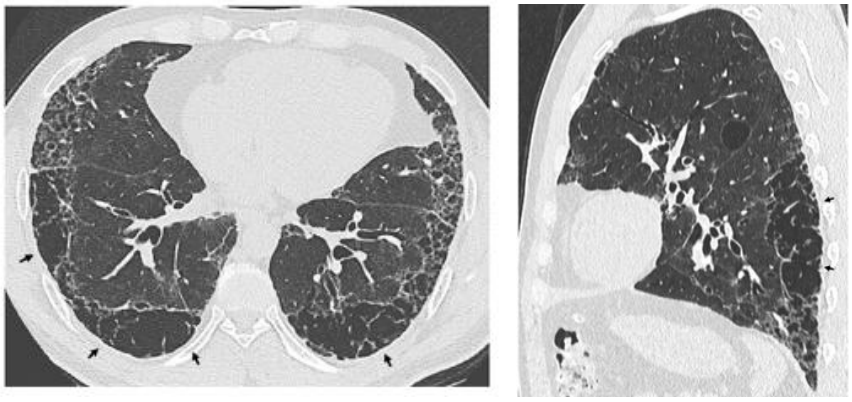


Alternative diagnosis:

Groundglass infiltrates with air trapping characteristic of hypersensitivity pneumonitis (HP)



Smoking-related emphysema and interstitial fibrosis



Figures above taken from Am J Respir Crit Care Med 2022; 205: e18–e47) and Am J Respir Crit Care Med 2018; 198: e44–e68

PFTs

- Confirmation of a restrictive pulmonary process
    - Decreased FEV1 and FVC with normal FEV1/FVC ratio
    - Decreased TLC
    - Decreased DLCO
        - Isolated decreased DLCO with normal spirometry and lung volumes can be an early manifestation of ILD
            - Other common conditions associated with isolated decreased DLCO include combined obstructive and restrictive process and pulmonary vascular abnormalities such as pulmonary hypertension (PH) and hepatopulmonary syndrome (HPS)

LAB TESTS

- Negative in IPF
    - Up to 30% of IPF patients have positive ANA tests but the titers are usually not high
        - High titers may indicate the presence of autoimmune diseases
- Useful in other ILDs, particularly autoimmune diseases

LUNG BIOPSY

Currently, less than 10% of patients with ILD undergo lung biopsy.
Usual indication for lung biopsy

- New diagnosis of ILD
- Patient with good lung reserve
- Indeterminate pattern on HRCT or findings suggestive of an alternative diagnosis
    - The diagnostic confirmation of IPF with biopsy is usually unnecessary in patients with UIP or probable UIP patterns without an apparent cause

Patients with progressive dyspnea and or cough, inspiratory crackles, PFTs showing a restrictive process with decreased DLCO, and HRCT with UIP or probable UIP patterns without an apparent cause does not need lung biopsy.

When the decision is to proceed with lung biopsy is made, there are three options

- Bronchoscopy
    - Traditional transbronchial lung biopsies (TLB)
    - Transbronchial lung cryobiopsy (TBLC)
- Surgical lung biopsy (SLB) – VATS

Transbronchial lung cryobiopsy (TBLC)

- Compared to SLB-VATS is an acceptable alternative to diagnose ILD of undetermined cause because has a similar diagnostic accuracy with lower complications
- Compared to TLB has a better diagnostic yield (larger size) but higher bleeding risk (usually performed with bronchial blocker unless done through robotic bronchoscopy with peripheral airway wedging)

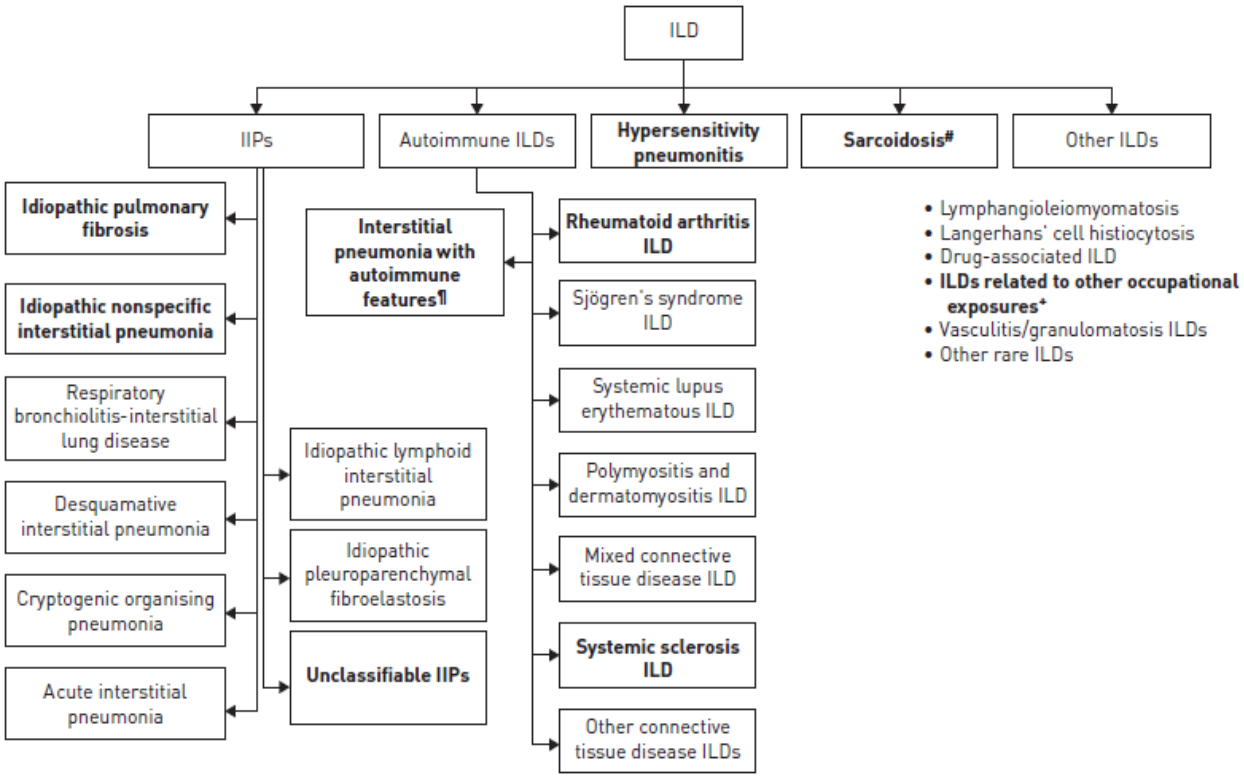
ILD CLASSIFICATION

There are multiple conditions associated with ILD (see graphic below). The most common ILDs are:

- IPF
- CTD
- Hypersensitivity pneumonitis
- Other common causes
    - Smoking related interstitial fibrosis usually associated with emphysema
    - Organizing pneumonia (OP) either idiopathic or associated with other conditions

        - Most common conditions associated with OP
            - Infection
            - Connective-tissue disease
            - Cancer
            - Chronic aspiration
            - Drug-induced
    - Postinfectious (eg, post COVID-19)
    - Drug-induced

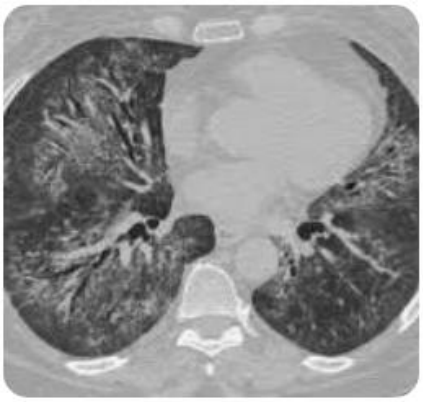
Nevertheless, in up to 15% of patients, the ILD remains unclassifiable even after detailed clinical assessment that includes lung biopsy.



COMMON HISTOLOGIC AND HRCT PATTERNS OTHER THAN UIP

Nonspecific interstitial pneumonia (NSIP)

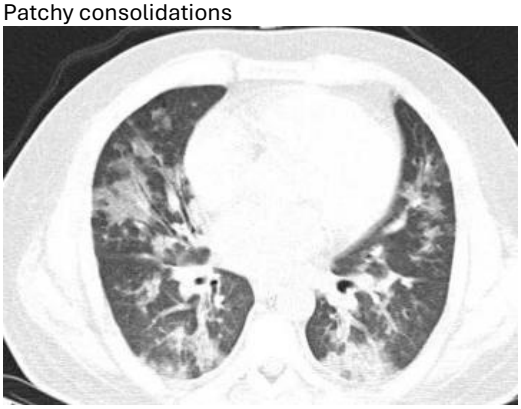
- Frequently associated conditions
    - CTD
    - Drug-induced
    - Smoking-induced
- Intermediate prognosis, if untreated medial survival is 8-10 years
- HRCT findings
    - Predominantly basal ground glass with fine reticulation and traction bronchiectasis
    - Subpleural sparing



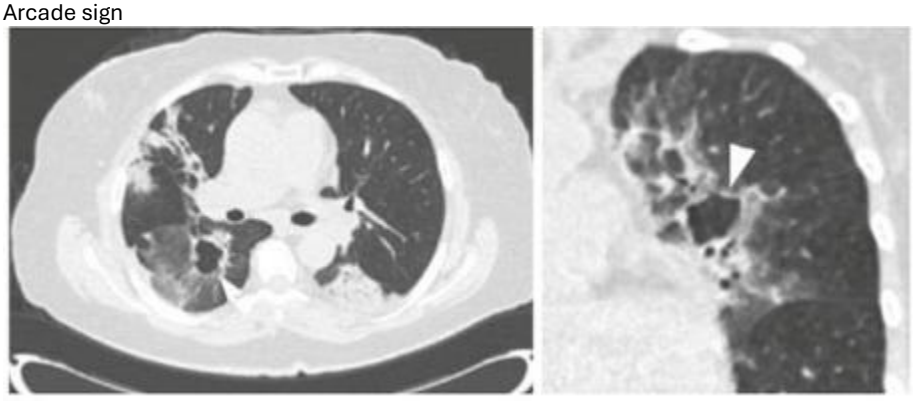
Organizing pneumonia (OP

- Usually good prognosis and response to immunomodulator therapy but can progress to pulmonary fibrosis
- HRCT common findings
    - Patchy consolidation with a predominantly subpleural and/or peribronchial distribution
    - Large nodules or masses
    - Small peribronchial or peribronchiolar nodules
    - Bronchial wall thickening or dilatation in the abnormal lung regions
    - Arcade-like sign of perilobular fibrosis describes an arch pattern in more than half of the patient with COP
    - Ground glass infiltrates
    - The reverse halo sign (atoll sign) is considered to be highly specific, although only seen in ~20% of patients with COP

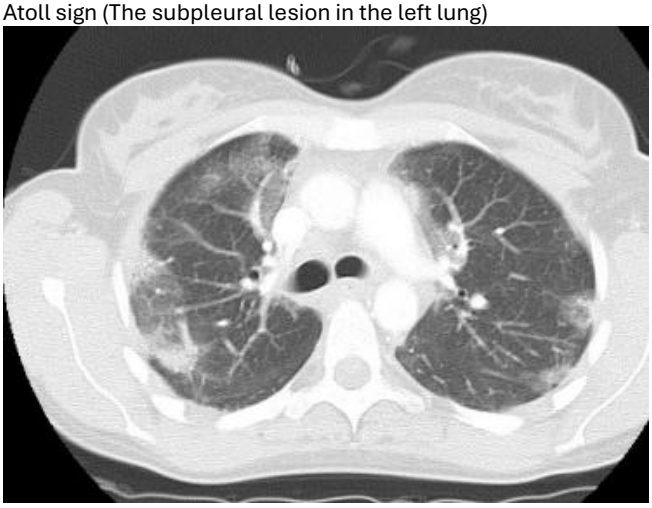
Patchy consolidations



Arcade sign



Atoll sign (The subpleural lesion in the left lung)

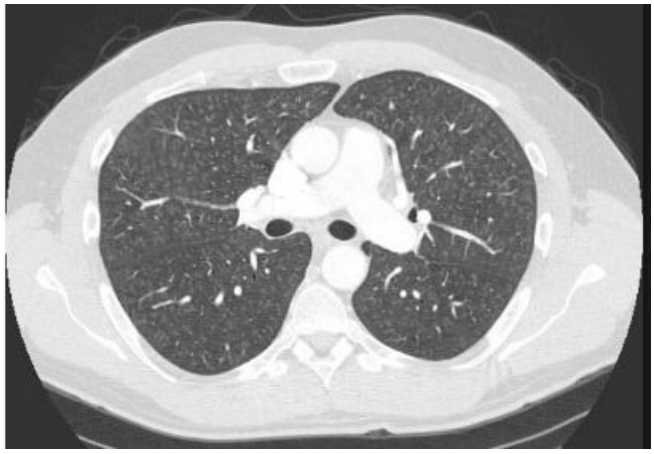


Hypersensitivity pneumonitis (HP)

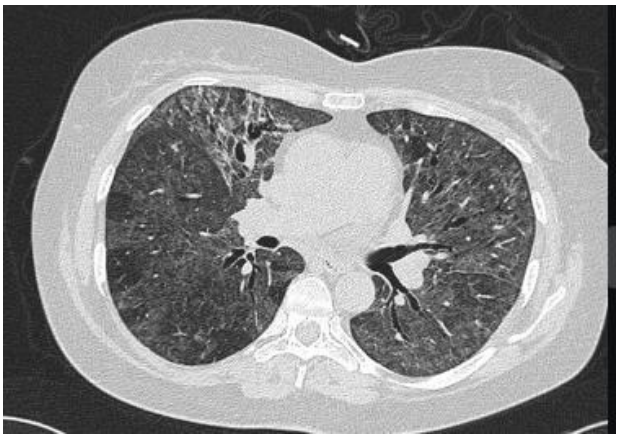
HP is a form of ILD that is precipitated by inhalation of specific antigens, most commonly avian proteins and mold or fungal spores.

- Nonfibrotic (acute and subacute)
- Fibrotic (chronic)

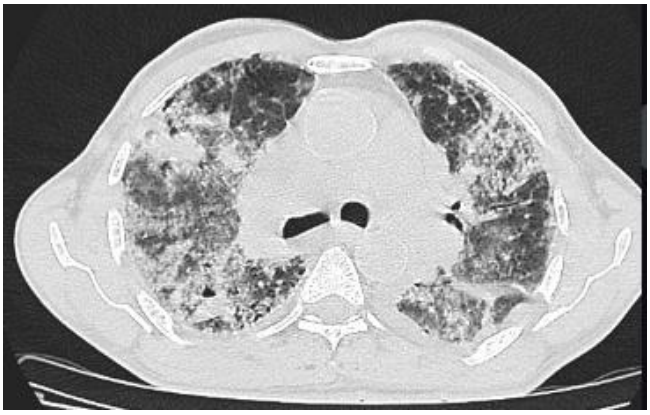
Non fibrotic acute HP



Nonfibrotic subacute HP



Fibrotic chronic HP



Diffuse alveolar damage (DAD)

DAD is histologically characterized by the presence of hyaline membranes which defines the presence of acute lung injury commonly seen in:

- ARDS
- AIP
- ILD acute exacerbation
- IIM specially DM-MDA5 +

TREATMENT

- Supportive
- Anti-inflammatory depending on the associated etiology
- Anti-fibrotic
- Lung transplant

Supportive treatment

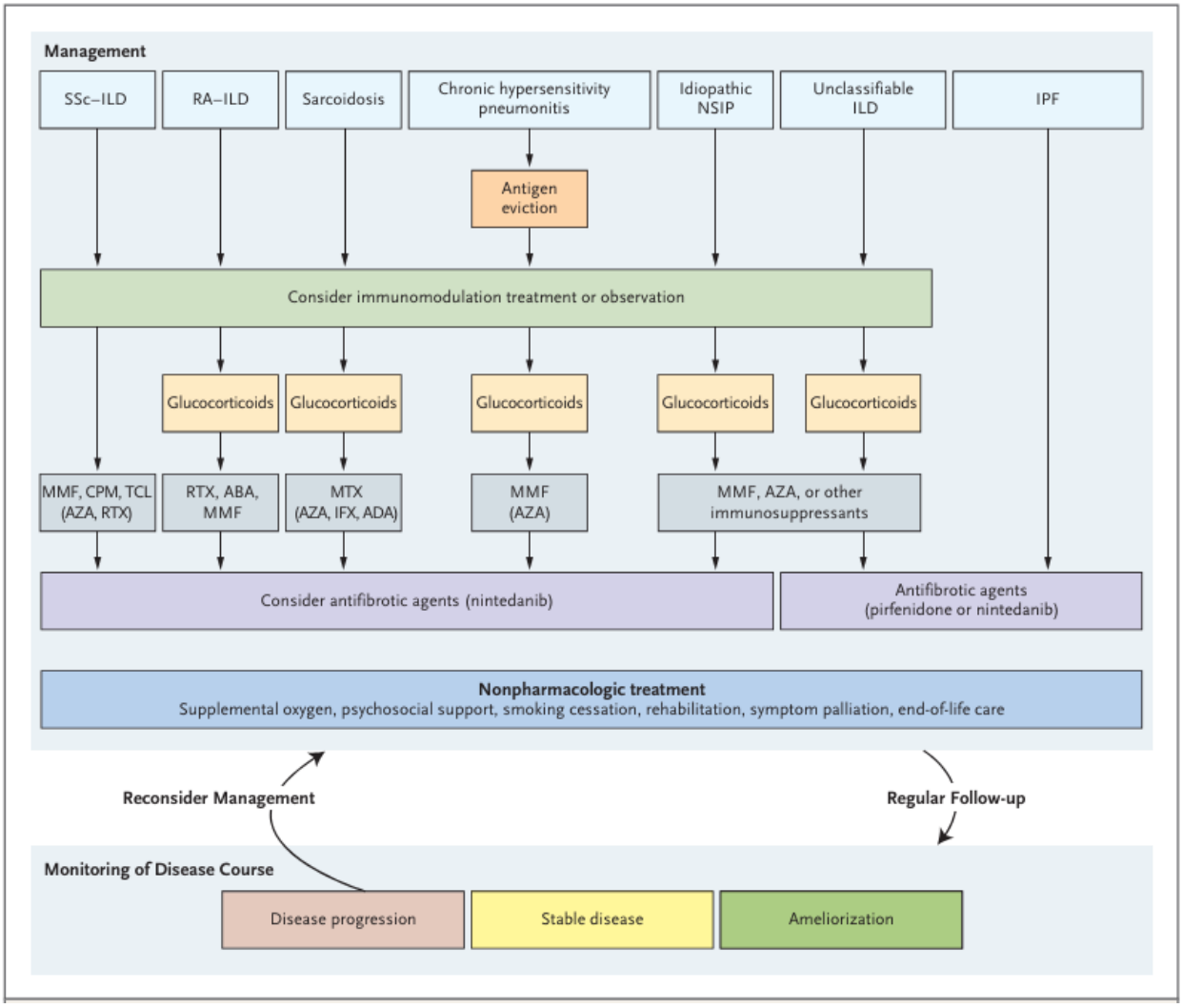
- Supplemental O2 to maintain O2 Sat 90 - 96%
- Pulmonary rehab
- Psychosocial support
- Immunizations – vaccines
    - Pneumonia (PCV21), annual Influenza and RSV, COVID following CDC recommendations
- Early management of respiratory infections
- Cough symptomatic management
    - Benzonatate 100 mg q8h as needed
    - Gabapentin
        - High doses are often required and can limit treatment owing to adverse effects that most commonly include fatigue, dizziness, confusion, ataxia, dry mouth, and nausea
        - 100 mg q8h starting dose; increased the dose by 100 mg every 3 days thereafter until 300 mg q8h or the onset of intolerable drug side effects
    - Codeine or Nalbuphine (an opioid agonist-antagonist) if refractory to treatment of underlying cause and treatment with benzonatate and/or gabapentin
    - Multimodality speech therapy
        - Cough suppression techniques
        - Vocal hygiene
- Dyspnea symptomatic management
    - Short-acting opiates may improve dyspnea in patients with end-stage lung disease
- Psychoeducational counseling to treatment
- Prevention and treatment of associated conditions and complications

- Acid reflux
- Aspiration
- Pulmonary Hypertension (PH)
  - Pulmonary vasodilators- treprostinil
    - Up to 85% of patients with end-stage fibrotic ILD develop PH
    - Inhaled treprostinil improves walking distance and respiratory symptoms
- Avoiding an identified inciting cause (such as birds or mold) may improve the outcome in patients with hypersensitivity pneumonitis (HP)

- Acute Exacerbation of ILD
  - Management of triggering condition
    - Antibiotics
    - Glucocorticoids
    - Diuretics

Anti-inflammatory treatment

- Usually indicated in patients with non IPF nor with progressive pulmonary fibrosis
- Multiple drugs either alone or in combinations are used depending on the underlying condition including Glucocorticoids, Mycophenolate, Azathioprine, Methotrexate, Rituximab, Tocilizumab, and Cyclophosphamide (see graphic below taken from N Engl J Med 2020; 383: 958-68)



- The American Thoracic Society of systemic sclerosis (SSc/scleroderma – ILD guidelines strongly recommend the use of mycophenolate mofetil for patients with SSc – associated ILD
    - Tocilizumab, nintedanib, cyclophosphamide, rituximab, and the combination of mycophenolate and nintedanib are associated with conditional positive recommendations, however, no specific guideline recommendations have been proposed regarding the ordering of specific medications or the timing of combination therapy
- Corticosteroids and immunosuppressant therapies such as azathioprine and mycophenolate mofetil are frequently prescribed to treat HP and RA – associated ILD. However, none have been tested in RCTs for either disease.
- For RA – associated ILD, observational data suggested that rituximab, abatacept, and tofacitinib are associated with the best pulmonary outcomes, including a lower incidence of ILD and fewer respiratory hospitalizations

Anti-fibrotic treatment

Slows annual FVC decline by approximately 50% in patients with IPF, scleroderma associated ILD, and in those with progressive pulmonary fibrosis of any cause

- Nintedanib
- Pirfenidone (only in IPF)
- Nerandomilast t (JASCAYD) phosphodiesterase 4-PDE4 inhibitor
    - Slowed decline in FVC both as monotherapy and as an add-on to existing antifibrotic agents nintedanib and pirfenidone for IPF but without significant impact on acute exacerbations or mortality
    - 18 mg twice daily which can be reduced to 9 mg twice daily for intolerance, except when used with pirfenidone

Lung transplant referral

- Low threshold for referral to improve quality of life, functional capacity, and survival.
    - The International Society for Heart and Lung Transplantation guidelines recommend that patients with UIP due to any cause should be referred for lung transplant assessment at diagnosis
    - For patients with other forms of ILD, referral for transplant assessment is recommended in patients with the following criteria:
        - Dyspnea – functional limitation
        - Need for supplemental O2
        - Abnormal PFTs
        - FVC <80%
        - DLCO <40%
        - Associated pulmonary hypertension
        - Failure to improve with evidence of PPF after a trial of medical management in the preceding 2 years

PROGNOSIS

- Median survival for IPF is 3 to 3.5 years.
    - In patients who respond to antifibrotic treatment with slowing FVC decline life expectancy improves approximately for 2 years
- After lung transplant, patients with ILD have a median survival of 5 to 7 years.
- End-of-life planning and access to palliative care services are important for individuals with ILD and respiratory failure
- For patients with end-stage disease for whom lung transplant is not an option, intubation and mechanical ventilation should be avoided because they are associated with poor outcome