
بسم الله الرحمن الرحيم

Interstitial lung Diseases (ILD)

BY

Dr. Haggagy Mansour

Lecturer of Chest Diseases

South-Vally University

OBJECTIVES

- Know the definitions of ILD, IIP, and IPF
- Understand the pathogenesis of IPF
- Appreciate the clinical features
- Realize how the diagnosis of IPF is made
- Know current therapies
- Be able to summarize current thinking about IPF

Definition:

Interstitial lung diseases (ILDs) represent a heterogeneous group of acute and chronic lung disorders with variable degrees of pulmonary inflammation and fibrosis affecting the supporting framwork of the lung *(the interstitium).*

Primary bronchus

Secondary bronchus

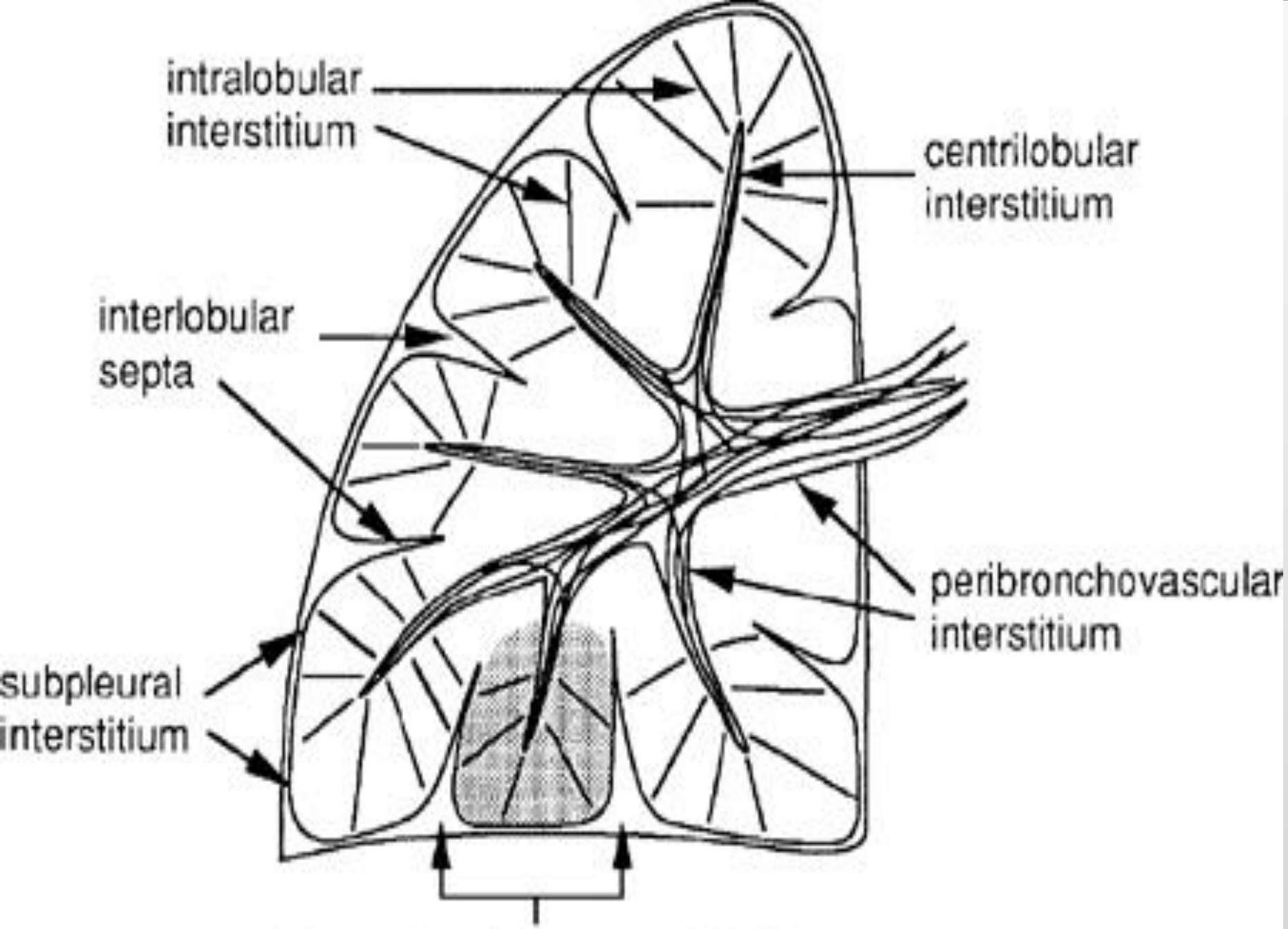
Tertiary bronchus

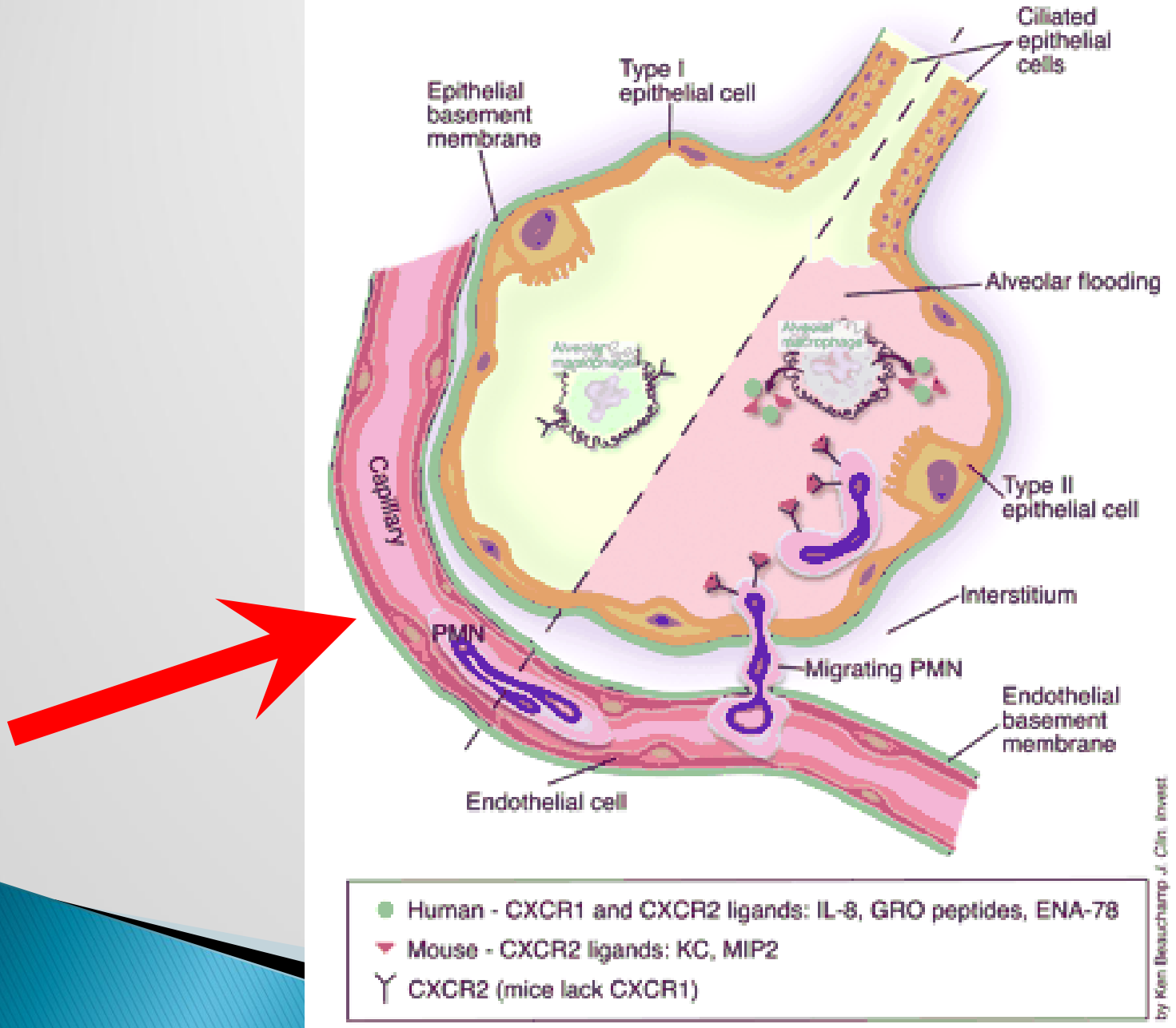
Bronchiole

Terminal bronchiole

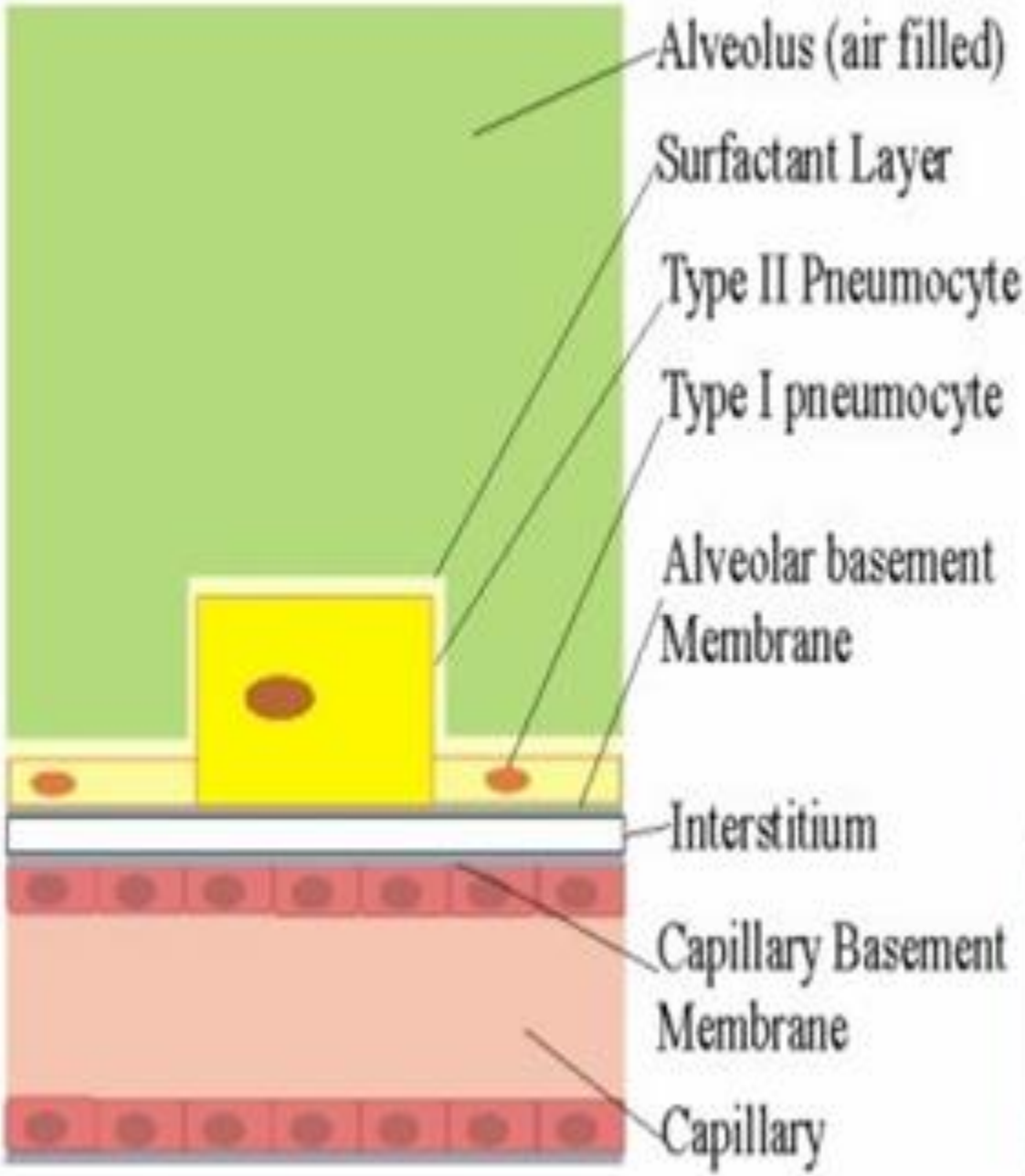
Alveoli

Alveoli enlarged

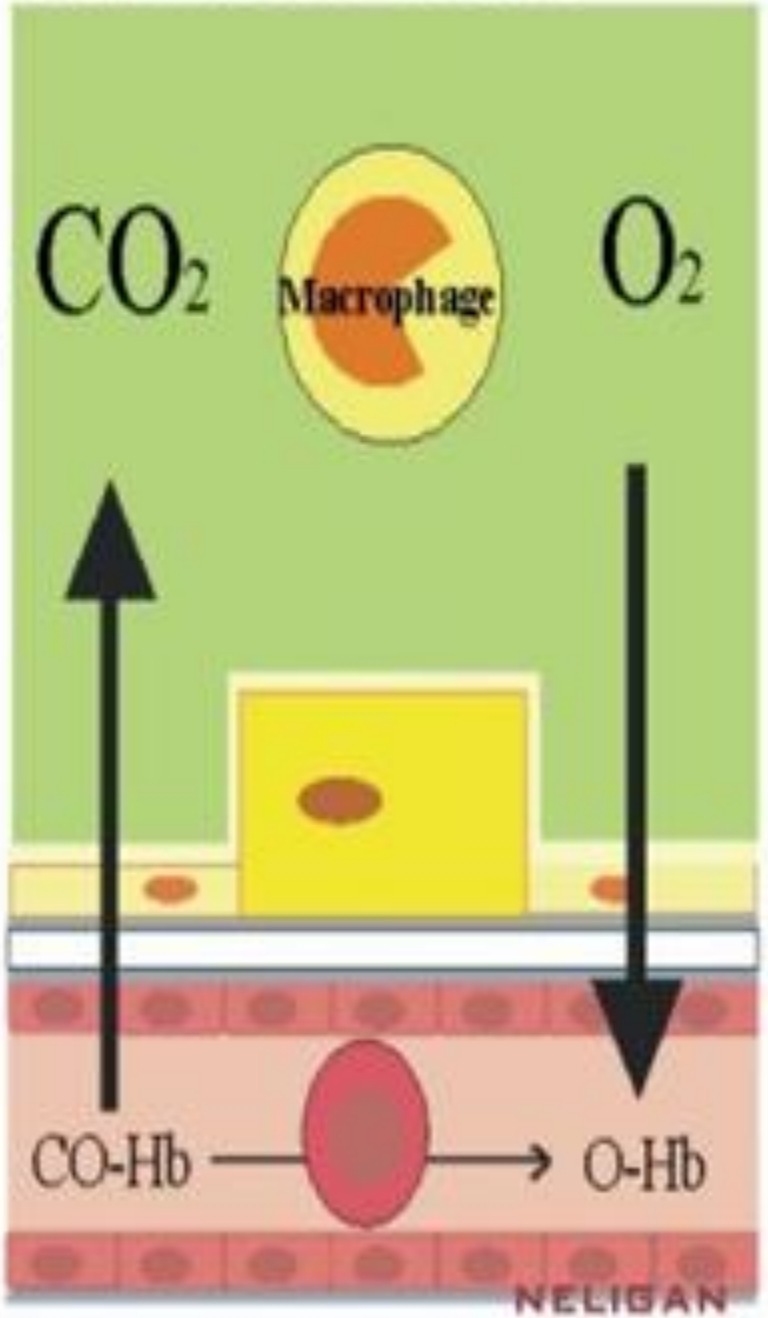

intralobular
interstitium
centrilobular
interstitium
interlobular
septa
peribronchovascular
interstitium
subpleural
interstitium
Secondary Pulmonary Lobule


Ciliated epithelial cells
Type I epithelial cell
Epithelial basement membrane
Alveolar flooding
Capillary
Type II epithelial cell
Interstitium
PMN
Migrating PMN
Endothelial basement membrane
Endothelial cell
Human - CXCR1 and CXCR2 ligands: IL-8, GRO peptides, ENA-78
Mouse - CXCR2 ligands: KC, MIP2
CXCR2 (mice lack CXCR1)
by Ken Beauchamp J. Clin. Invest.

Normal Alveolus



Normal Alveolus



Classification of ILDs according to etiology

1. ***Idiopathic interstitial pneumonia (IIP)***
   - **IPF**: idiopathic pulmonary fibrosis (Cryptogenic fibrosing alveolitis)
   - **IP**: acute interstitial pneumonia
   - **NSIP:** non specific interstitial pneumonia
2. ***Occupational and environmental exposures***
   - Chemicals as asbestos silicates and coal
   - Organic dusts and microorganisms causing hypersensitivity pnuemonitis

Classification of ILDs according to etiology

3. Collagen vascular diseases:

- Rheumatoid arthritis
- Systemic sclerosis
- Systemic Lupus erythromatosis

4. Drugs:

- **Cytotoxic**
- **Gold**
- **Nitrofurantion**
- **Pencillamine**
- **salicylates**
- **Amiodarone**

5. ***Inherited disorders:***
   - Tuberous sclerosis
   - Neurofibromatosis
   - Ankylosing spondylosis
6. ***Vasculitis/granulomas:***
   - Churg - Straus syndrome
   - Polyarthritis nodosa
   - Wegner granulomatosis

7. Infections

- Viral pneumonia
- Mycoplasma Pneumpnia
- HIV associated disease

8. Others

- Sarcodosis, Histocytosis X, Lymphangioleiomyomatosis, alveolar protieniosis, oesinophilic pneumonia

Idiopathic Pulmonary Fibrosis /Cryptogenic fibrosing alveolitis

Definition of IPF:

IPF is defined as a specific form of chronic progressive fibrosing interstitial pneumonia of unknown etiology, limited to the lung and associated with the histologic appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy.

Epidemiology:

Incidence and Prevalence

not known

3 to 6 cases per 100,000

Sex and Age

- More males
- 40 and 70 yr

Risk factors:

- *Cigarette smoking*
- *Drugs: as* antidepressants
- *Chronic aspiration: as* secondary GERD
- *Environmental factors:*

  Metal dust and wood dust exposure.

- *Infectious agents*:
  - viruses : EBV, CMV , HIV-l & measles virus.
  - Mycoplasma & legionnaires' disease .
- *Genetic predisposition:*
  - Familial IPF, Association between IPF and other genitic disorders

Pathogenesis:

- The cause of IPF is unknown.
- Viruses, fungi, environmental and toxic agents .
- These blamed agents
  - interact with resident pulmonary immune cells to generate inflammatory mediators or immune responses.
  - These mediators injure epithelial or endothelial cells
- IPF results from the persistent inflammation, tissue injury and repair.
- Chronic inflammation eventually leads to widespread fibrosis


Pathology

Pathology:

- The histologic hallmark of IPF is *Usual interstitial pneumonia (UIP)* which is a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb changes.
- These changes are mainly basal, peripheral subpleural.

- The interstitial inflammation
  - patchy
  - consists of an alveolar septal infiltrate of lymphocytes and plasma cells, hyperplasia of type 2 pneumocytes.
- The fibrotic zones
  - dense collagen
  - scattered foci of proliferating fibroblasts "fibroblastic foci"
- Areas of honeycomb.


Clinical Features

Symptoms:

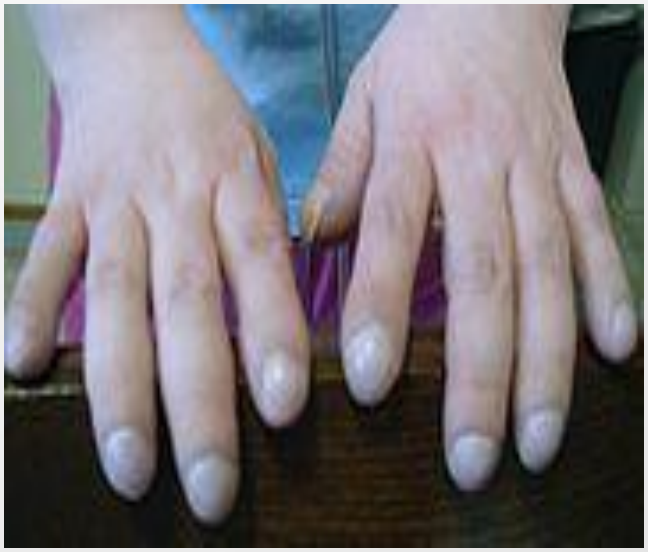
- ***Dyspnea***

  gradual onset, exertional

  progressive > 6 months

- ***Dry cough***

General examination:



- Clubbing in 25 to 50%.
- Central Cyanosis.
- weight loss, malaise, and fatigue may be note

- ***On physical examination***

  Crackles in 80% of cases.

  "dry," fine end-inspiratory crepitations,

  "Velcro" and mainly in lung bases.

Triad: Central cyanosis, clubbing and late fine inspiratory crepitations

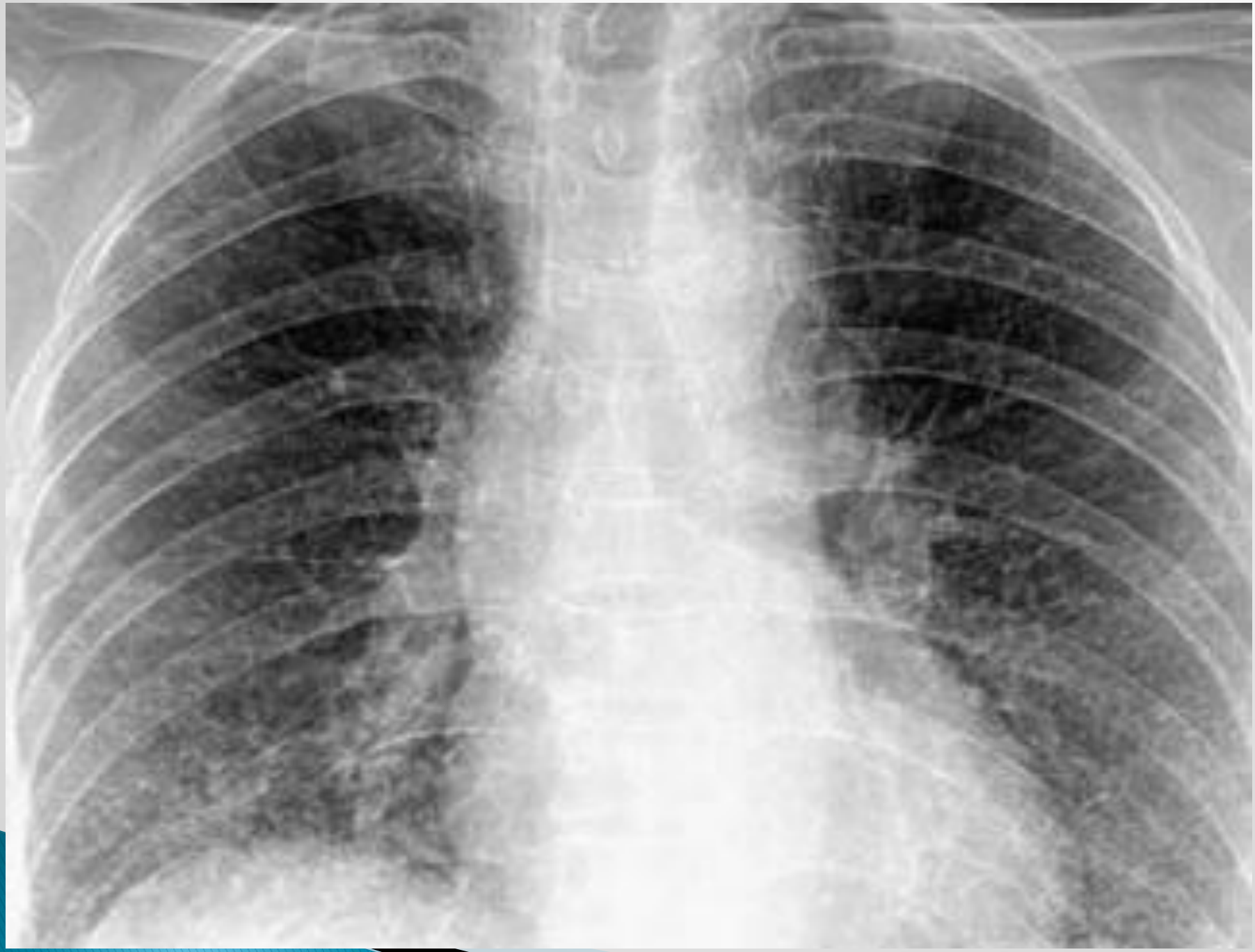

Diagnosis

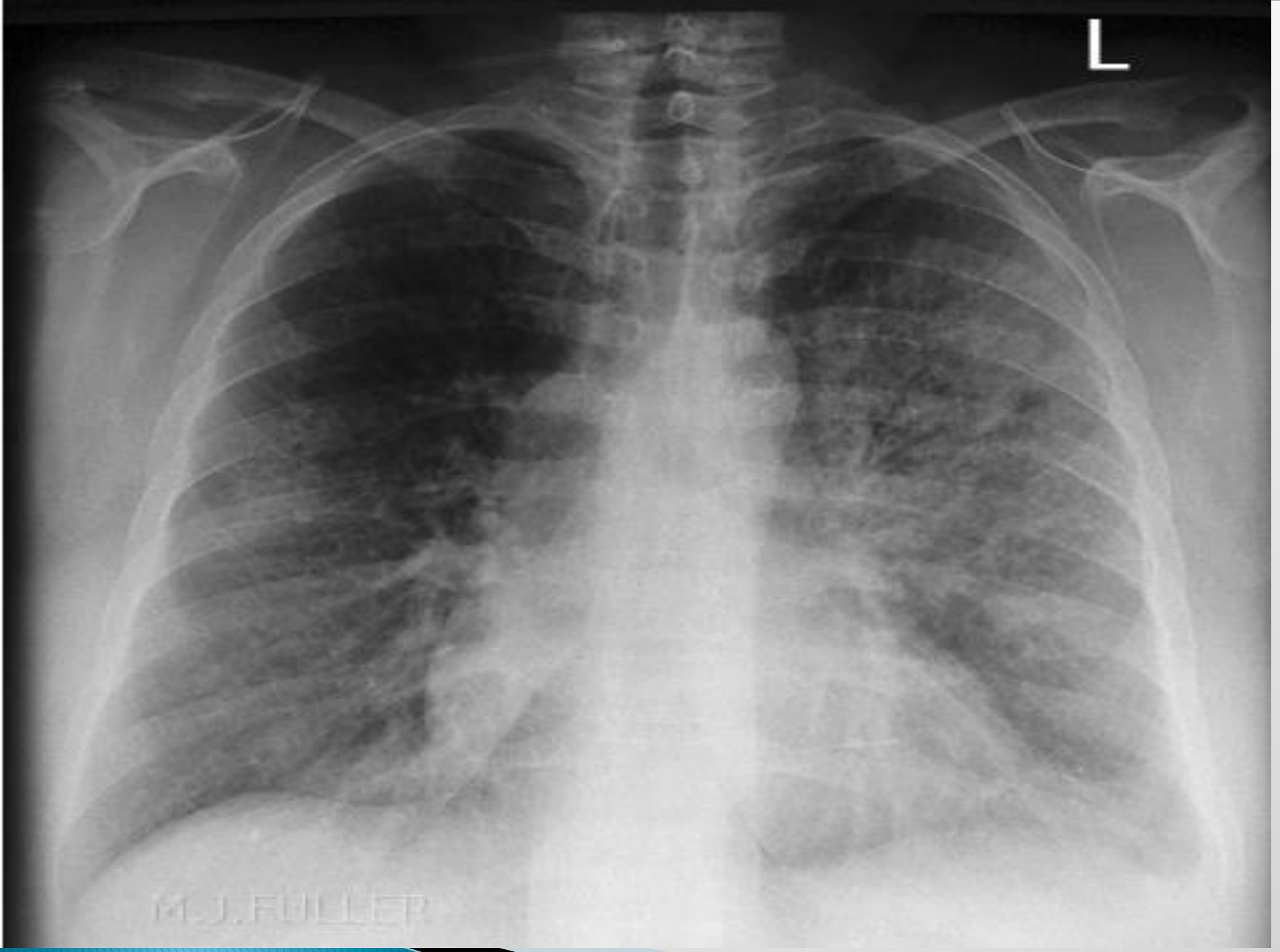
Diagnostic Studies:

I. Chest Radiograph
II. High Resolution CT Scanning
III. Pulmonary function tests
VI. Bronchoalveolar Lavage
VII. Lung Biopsy

I. Chest Radiograph

- Most patients have an abnormal chest X-ray
- A normal chest radiograph cannot be used to exclude microscopic evidence of UIP on lung biopsy .
- Peripheral asymmetrical bilateral reticular opacities at the lung bases.

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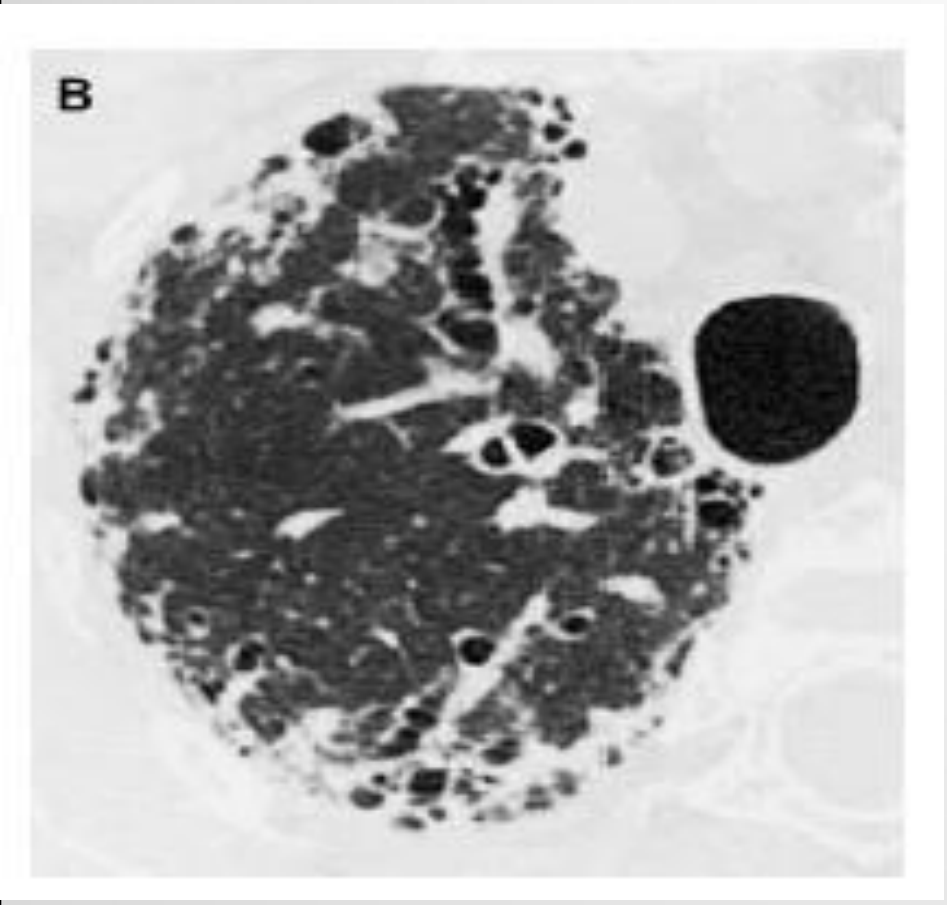
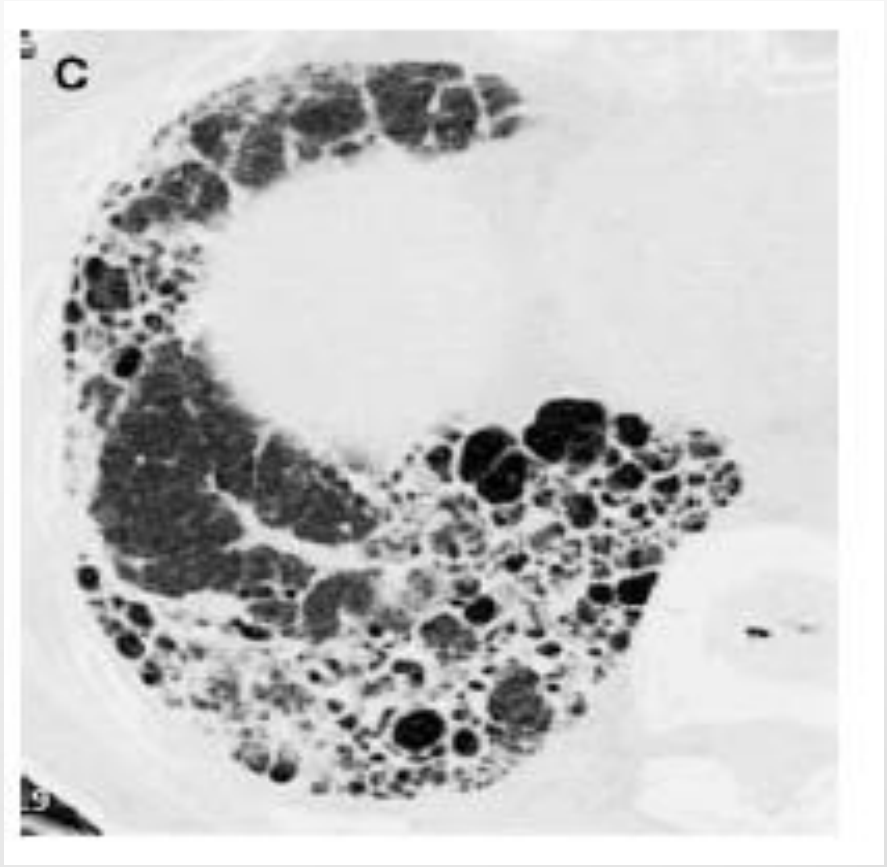
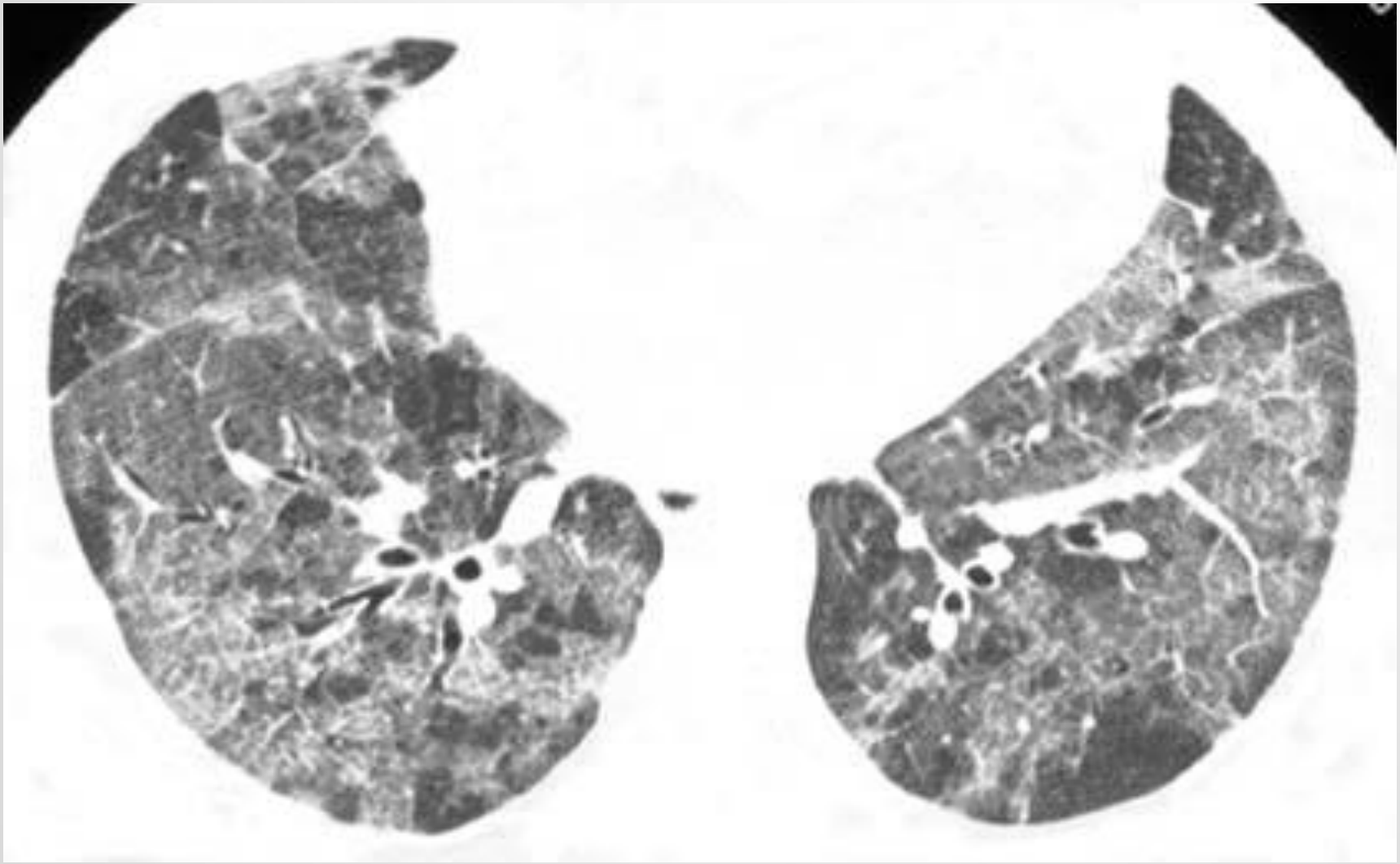
II. High Resolution CT Scanning of chest

- HRCT is more sensitive and specific than X ray.
- provides information about extent and nature of the disease.
- Peripheral, patchy, subpleural, bibasilar reticular abnormalities.
- ground glass opacity is limited (less than 30%).
- Traction bronchiectasis and/or honeycombing.





(B and *C)* CT images show basal predominant, peripheral predominant reticular abnormality with traction bronchiectasis and honeycombing, typical of IPF



Ground glass, not IPF

III. Pulmonary function tests

- Restrictive impairment (reduced vital capacity [VC] and lung volumes as (TLC, FRC and RV).
- Forced expiratory volume in 1 s (FEV1), and forced vital capacity (FVC) are often decreased but the FEV1/FVC ratio is maintained or increased.
- The DLCO is reduced.

- The resting arterial blood gases may be normal initially or may reveal mild hypoxemia and respiratory alkalosis.
- With exercise, the alveolar-arterial O_2 gradient ($AaPO_2$) widens, and the arterial O_2 pressure (PaO_2) and arterial O_2 saturation (SaO_2) fall.
- Pulmonary function tests are useful to assess the extent of the disease and efficacy of therapy

V. Bronchoalveolar Lavage

- Increases in neutrophils, eosinophils, activated alveolar macrophages & their products , cytokines, growth factors for fibroblasts, and immune complexes .
- Increases in neutrophils or eosinophils (or both): worse prognosis .
- BAL lymphocytosis: greater responsiveness to corticosteroid therapy and better prognosis.

VII. Lung Biopsy

- Open lung biopsy: diagnostic gold standard
- Surgical lung biopsy through ***open thoracotomy*** or ***video-assisted thoracoscopy*** is recommended in patients with suspected IPF and who cannot be confidently diagnosed on clinical and radiological ground, and who are without contraindications to surgery .
- **UIP pattern:** Temporal heterogenity with area of end stage fibrosis and honey combing alternating with areas of inflammations with proliferation of fiboblast and myofibrobast

Diagnostic Criteria

The presence of all of the following 4 major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

Major Criteria:

1. Exclusion of other known causes of ILD.
2. Abnormal restrictive pulmonary function studies.
3. Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
4. Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis.

Minor Criteria:

- Age > 50 yr
- Insidious onset of unexplained dyspnea on exertion
- Duration of illness ≥ 3 months
- Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)

Complications:

1. Respiratory failure.
2. Heart failure.
3. Pneumothorax.
4. Pulmonary infections.
5. Pulmonary embolism.
6. Bronchogenic carcinoma.


treatment

- Treatment strategies have been based on eliminating or suppressing the inflammatory component

Conventional Treatment Options

- Corticosteroids
- Immunosuppressive/cytotoxic agents
- Antifibrotic agents Perfinidione and nentidinibe

➢ *Corticosteroids* : *0.5-1 mg/k or 40 to 60 mg daily of prednisone or prednisolone) for 2 to 4 month*, with a subsequent gradual taper to the minimum effective dose. If there is no response, stop treatment and try another treatment option

- *Cytotoxic treatment*.

  azathioprine or cyclophosphamide are used among steroid non responders, patients experiencing serious adverse effects from corticosteroids, and patients at high risk for corticosteroid complications.

- *Combined therapy*

  corticosteroid and either azathioprine or cyclophosphamide and antioxidants.

Monitoring the Clinical Course of IPF(CRP Score)

Patient should have a thorough evaluation 3, 6 and 12 months after initiation of therapy and at least annually thereafter.

- **Assessment of dyspnea**
- **HRCT lung scans**
- **Physiologic testing**
  - **Lung volumes (FVC& TLC)**
  - **DLCO**
  - **Resting arterial blood gases (e.g., $AaPO_2$)**
  - **Cardiopulmonary exercise testing**

Monitor response to therapy & follow up At 6, 12 & 18 months or more

Response	Symptoms	X-ray HRCT	PFT	Blood gases
Improved	Improvement of dyspnea grade	Improvement Radio score	▪ ≥ 10 % increase in TLC or VC ▪ ≥ 15 % increase in DLco	▪ So_2 ≥4% ▪ PaO_2 ≥4mmHg increase.
Stable	Stable dyspnea grade	Stable Radio score	▪ 10% change in TLC or VC ▪ < 15% change in DLco	▪ So_2 < 4% increase ▪ Pao_2 < 4 mmHg increase
Worse	Worse dyspnea grade	Worse Radio score	▪ ≥10% decrease in TLC or VC. ▪ ≥15% decrease in DLco	▪ So_2 ≥4% decrease. ▪ A-aPo_2 increase >4 mmHg.

2 or more, on 2 consecutive visits over a 3- to 6- month period

+ Monitor adverse effects of treatment

ATS/ERS Multidisciplinary Consensus Classification of IIPs. Am J Respir Crit Care Med 2002; 165: 277–304

Other Management Issues

- Supplemental O_2 during exercise.
- Antitussive agents : Severe paroxysms of cough
- Treatment of complications of IPF.
- Pulmonary rehabilitation.

LUNG TRANSPLANT

- **IPF is the most common ILD among referrals for transplant and the 2nd most frequent disease for which lung transplantation is performed**

- **Criteria:** **Evidence of UIP plus any of the following:**
  - **DLCO < 39% predicted**
  - **Decrement in FVC > 10% during 6 months**
  - **Decrease in pulse ox below 88% during 6-minute walk test**
  - **Honeycombing on HRCT**

- **5-year survival for lung transplant in IPF is 40-50%**

Prognosis:

- Unfortunately, the prognosis of IPF is less favorable
- Most cases shows progressive disease despite of optimal treatment

Indicators of longer survival among patients with IPF

- Younger age (< 50 yr)
- Female sex
- Shorter symptomatic period (1 yr)
- Presence of ground glass and reticular opacities on HRCT
- Increased lymphocytes (20 to 25%) in BAL
- A beneficial response or stable disease 3 to 6 m after initial corticosteroid therapy
- Current cigarette smoking at the time of diagnosis


Thank you