Pulmonary Interstitial Fibrosis

By

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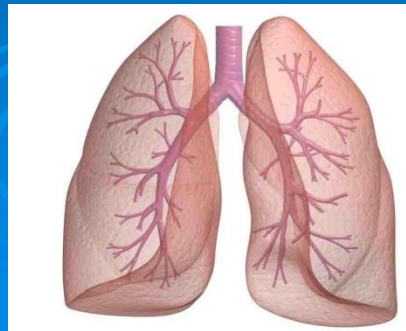


Interstitial Lung Diseases

Definition

Classification

Pathogenesis

Diagnosis

Treatment

Complications

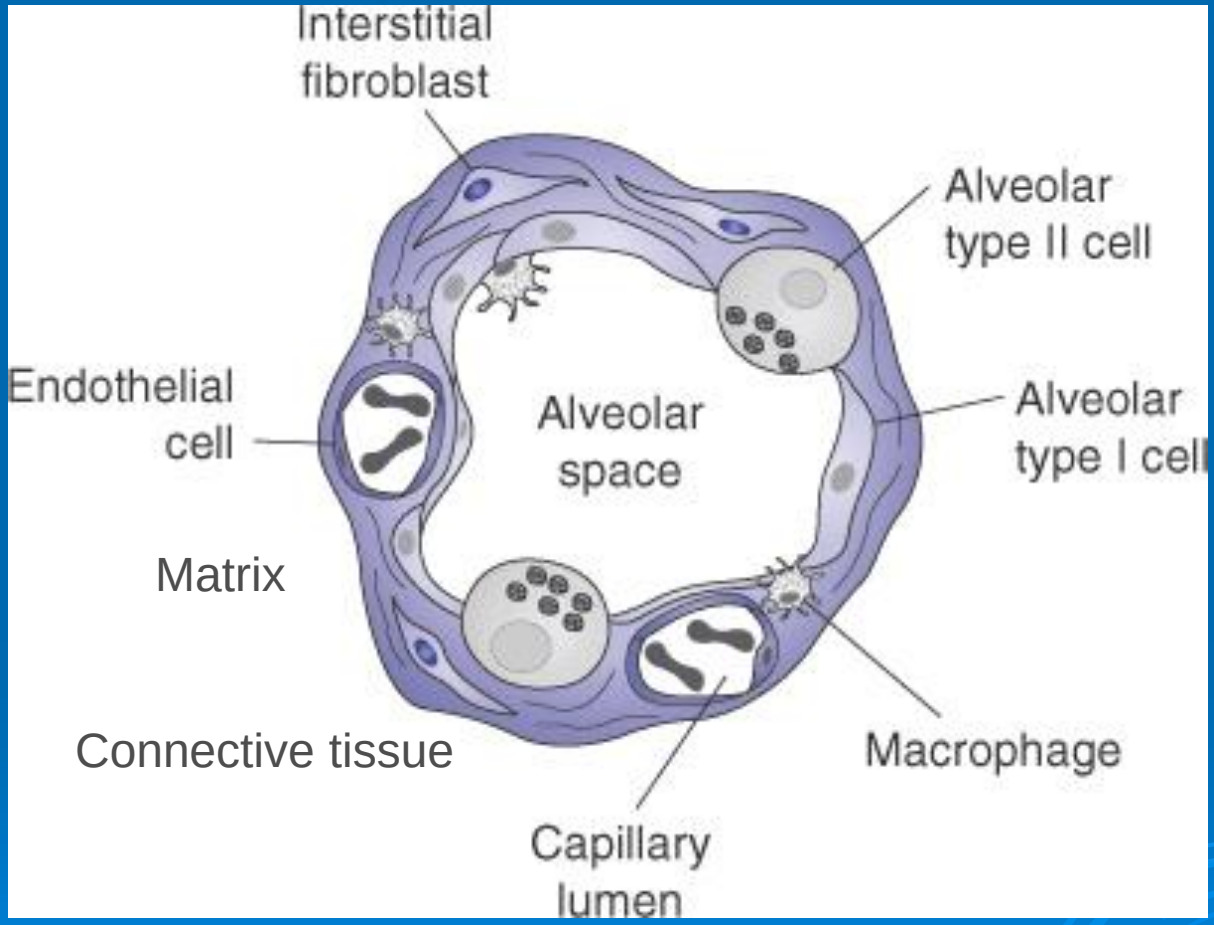
Prognosis

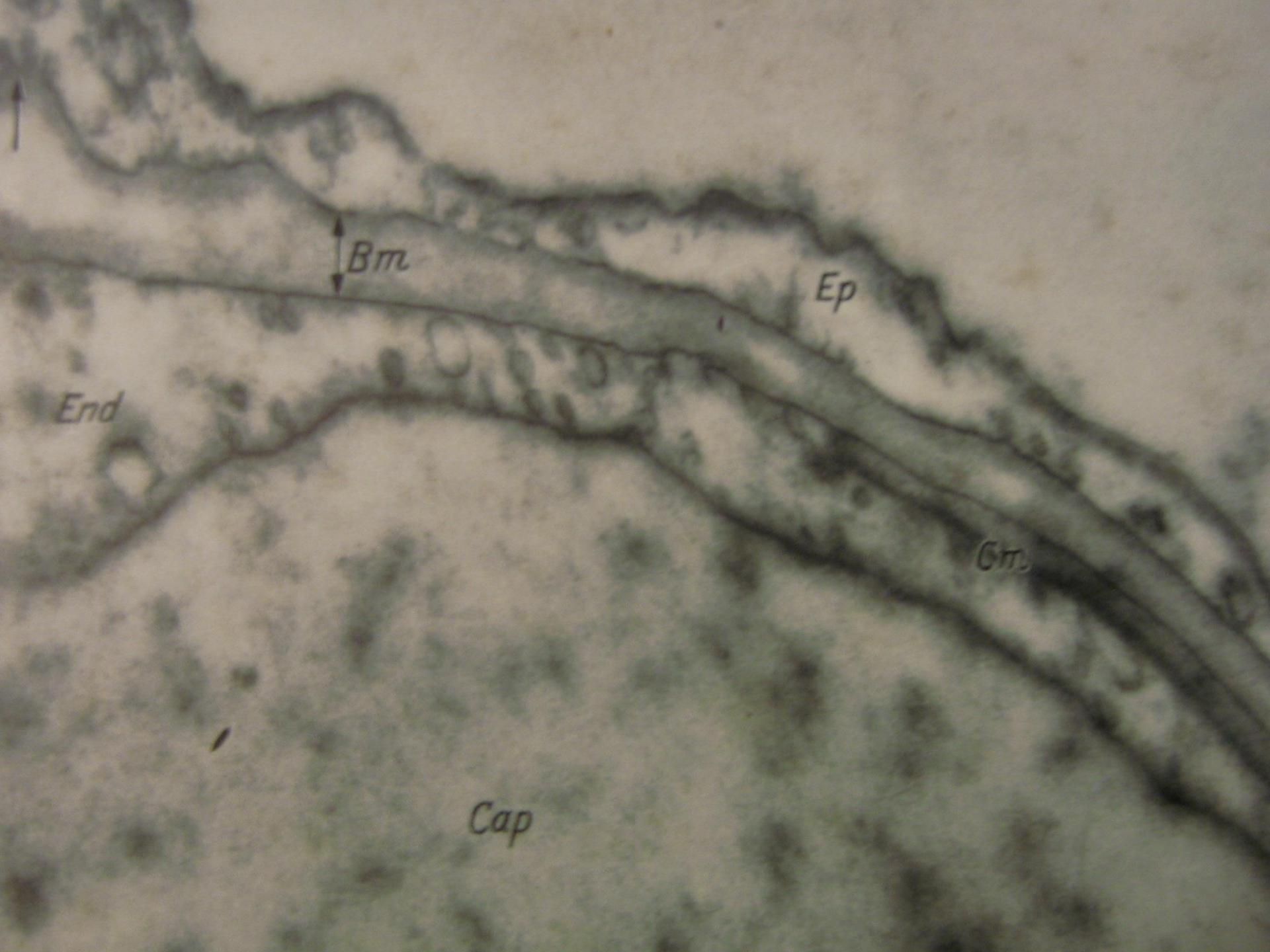
- **HAMMAN and RICH** were the first to describe (in 1935 and 1944) four patients who died of rapidly progressive lung disease characterized by diffuse interstitial pneumonia and fibrosis.

Interstitium

- Refers to the microscopic anatomic space bounded by the basement membrane of epithelial and endothelial cells.
- Within this interstitial space, fibroblast like cells (mesenchymal and connective tissue cells) and extracellular matrix components (interstitial collagens, elastin, proteoglycans) are present

Alveolar/Interstitial Space




Bm
Ep
End
Cap

WHAT DOES THE TERM “INTERSTITIAL’ MEAN?

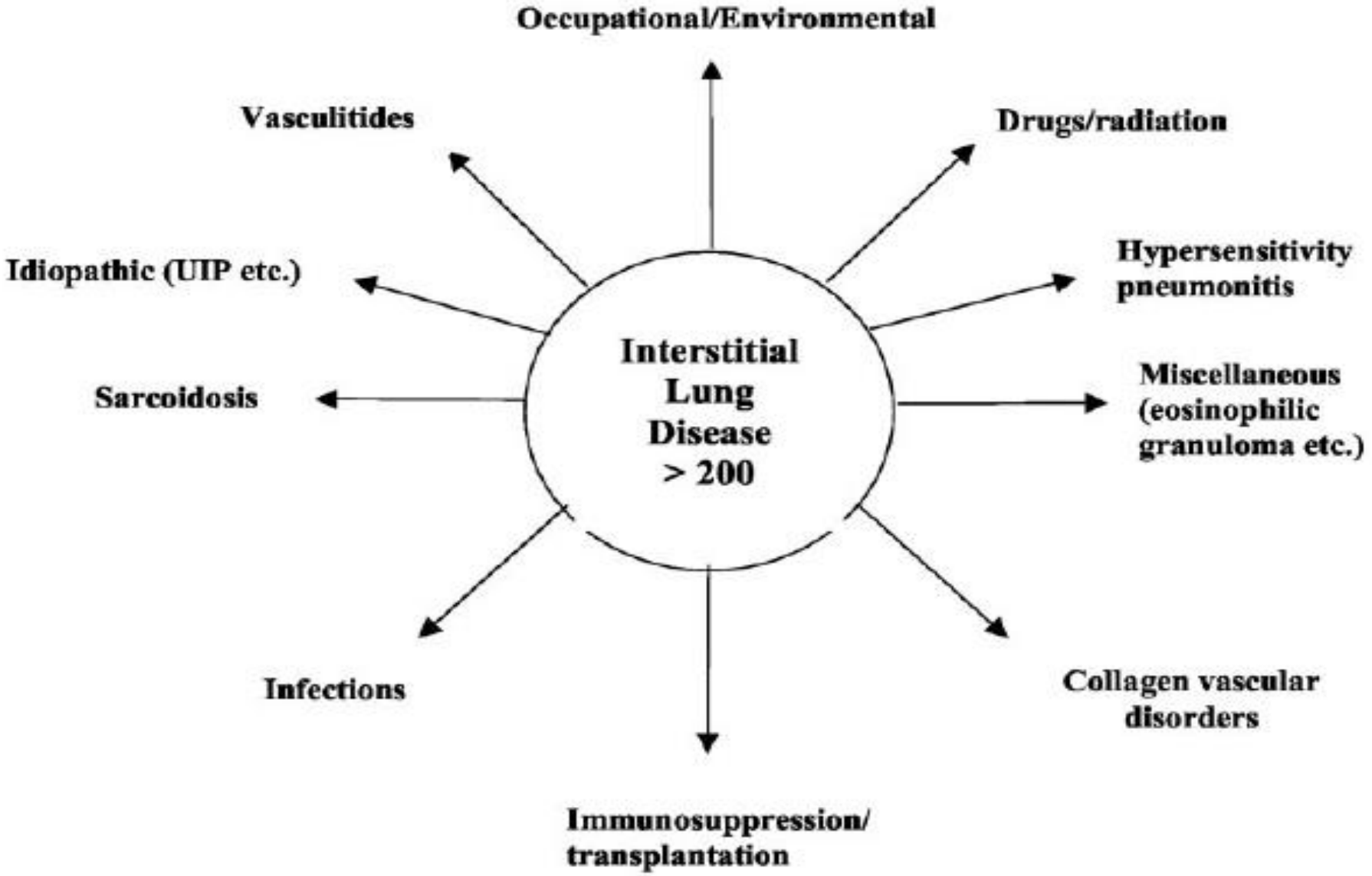
- It implies that the inflammatory process is limited specifically to the area between the alveolar epithelial and capillary endothelial basement membranes.
- This group of pulmonary disorders frequently involves:
  1. alveolar epithelium
  2. alveolar space
  3. pulmonary microvasculature
  4. respiratory bronchioles

Definition

Inflammatory-fibrotic infiltration of the interstitium resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells, producing a disease with similar clinical, radiographic, and physiologic features

EPIDEMIOLOGY

- Interstitial lung disease in was considered to be rare in the past but not now.
- ILDs constitute about 10% to 15% of the patients with respiratory diseases.
- About 50%of the ILDs are idiopathic in origin while others are associate with identifiable diseases, most commonly connective tissue disorders
- UIP, also known as IPF is the most common form of ILD



Classification of ILD

Clinical Classification

- Occupational
- Connective Tissue Diseases
- Idiopathic Disorders
- Drug-induced
- Unclassified

CTD

Scleroderma
Polymyositis
Dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis**
Mixed connective tissue disease
Ankylosing spondylitis
Behcet's
Sjogren's syndrome

Occupational

Inorganic dusts

Silica

Asbestos

Aluminum

Coal dust.

Beryllium.

Mixed dusts

Hard metal : Titanium oxide, tungsten cadmium.

Organic dusts :

Farmer lung

Bagassosis

Humidifier lung, air cond.

Bird breeder’s lung

Chicken handler’s disease

Aspergillosis

Sauna-taker’s disease

Detergent workers lung

Wood-dust worker’s disease

Coffee worker’s disease

Gases, Fumes, Vapors :

Gases : Oxygen, sulfur dioxide, chlorine gas.

Fumes : Oxides of zinc, copper.

Vapors : Mercury

Drugs

Chemotherapeutic agents : bleomycin, cyclophosphamide, methotrexate, procarbazine.

Antibiotics :

Nitrofurantion, sulfonamides, penicillin.

Others :

Amiodarone, procainamide, gold salts methysergide, practolol, carbamazine.

Radiotherapy

Idiopathic

Acute interstitial pneumonitis (Hamman-Rich syndrome)

Usual Interstitial pneumonitis

Desquamative interstitial pneumonitis

Respiratory bronchiolitis

Cryptogenic organizing pneumonia

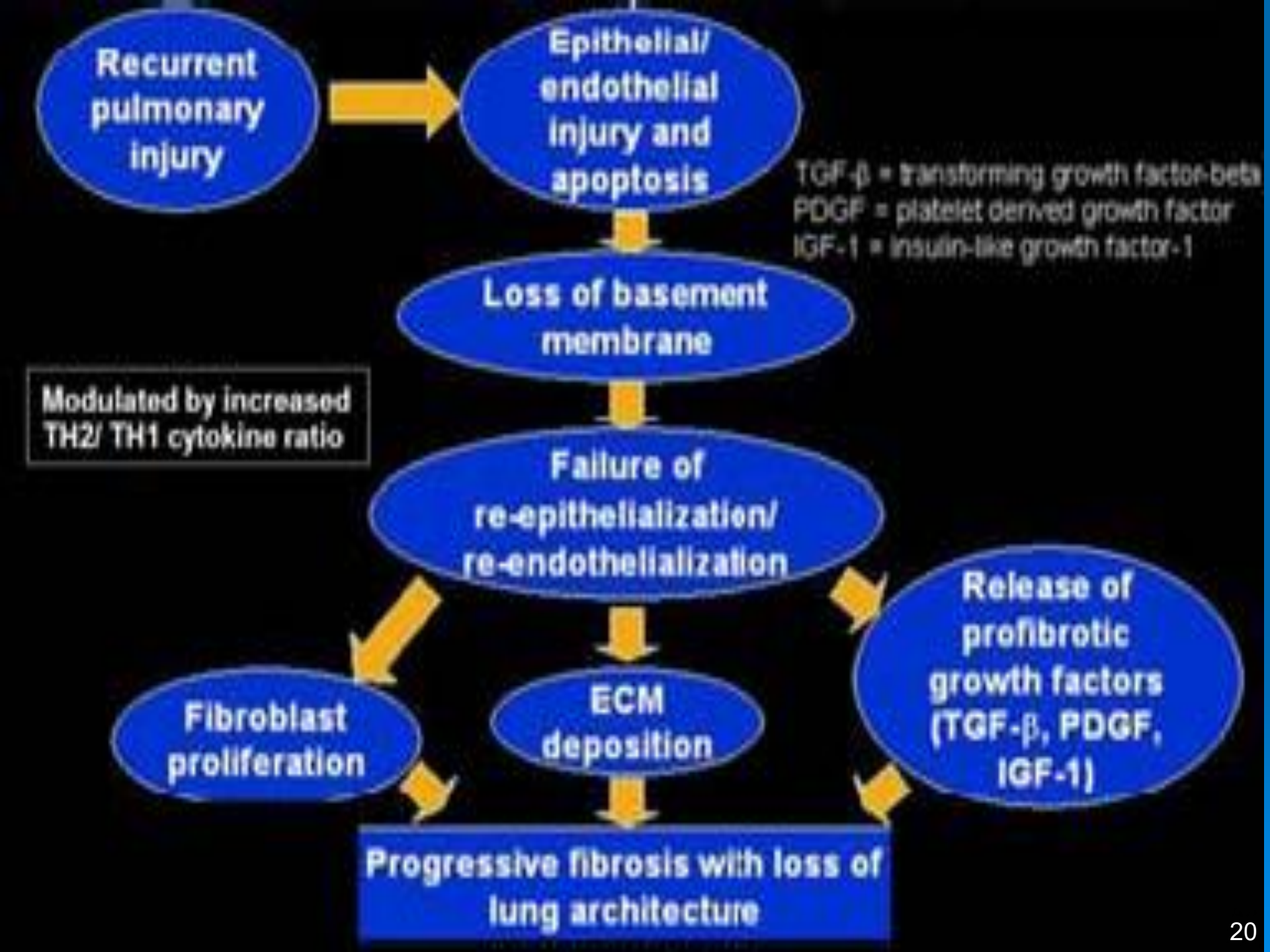
Nonspecific interstitial pneumonitis

Lymphocytic interstitial pneumonia

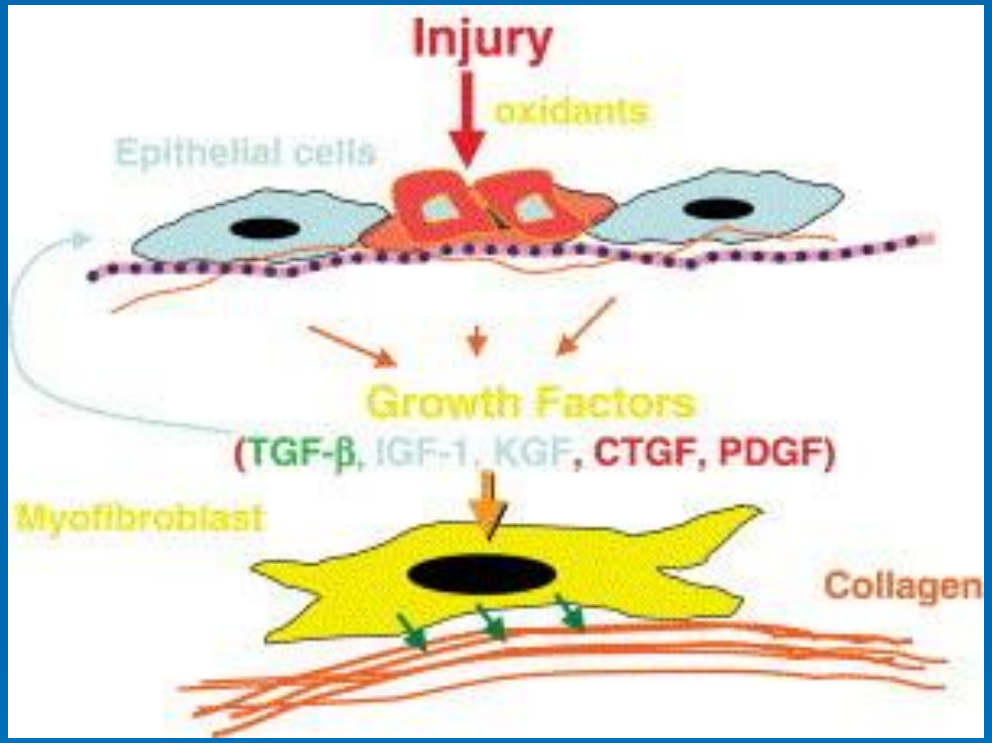
Unclassified

- Sarcoidosis.
- Histiocytosis-X.
- Goodpasture's syndrome.
- Idiopathic pulmonary haemosiderosis.
- Wegner's granulomtosis
- Churg-Strauss syndrome

PATHOGENESIS


Recurrent pulmonary injury
Epithelial/ endothelial injury and apoptosis
TGF-β = transforming growth factor-beta
PDGF = platelet derived growth factor
IGF-1 = insulin-like growth factor-1
Loss of basement membrane
Modulated by increased TH2/ TH1 cytokine ratio
Failure of re-epithelialization/ re-endothelialization
Release of profibrotic growth factors (TGF-β, PDGF, IGF-1)
Fibroblast proliferation
ECM deposition
Progressive fibrosis with loss of lung architecture

Pathogenesis

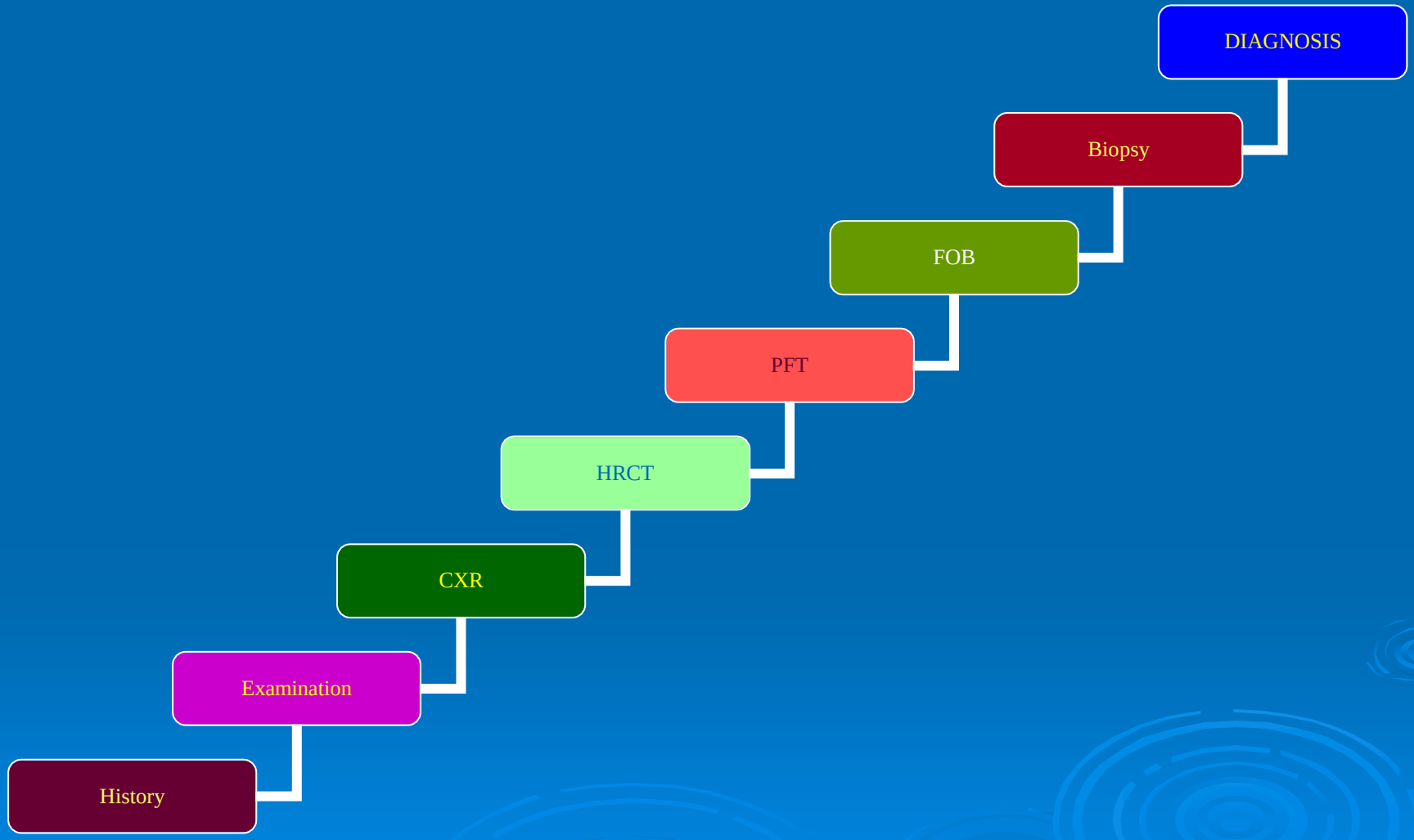


Epithelial cell apoptosis with loss of basement membrane integrity: production of growth factors in response to alveolar epithelial injury with hyperplastic type II cells and myofibroblast recruitment

Noble, et al. Clinics in Chest Med, Dec 2004

Diagnosis

Diagnosis



Approach to the Diagnosis of ILD

Clinical

- History
- Physical
- Laboratory
- PFTs

Radiology

- Chest X-ray
- HRCT

Pathology

- Surgical lung biopsy

Evaluation of ILD

EXTENSIVE HISTORY

AGE, GENDER, DRUGS, SMOKING, OCCUPATIONAL HISTORY

DURATION OF SYMPTOMS

PHYSICAL EXAM

LABORATORIES

IMAGING

SPIROMETRY, LUNG VOLUMES AND DLCO

Laboratories

LFTs, CBC

ANA, RF, ANCA, anti-GBM

CRP, ESR

Pulmonary function

Spirometry

Lung volumes

Diffusion capacity

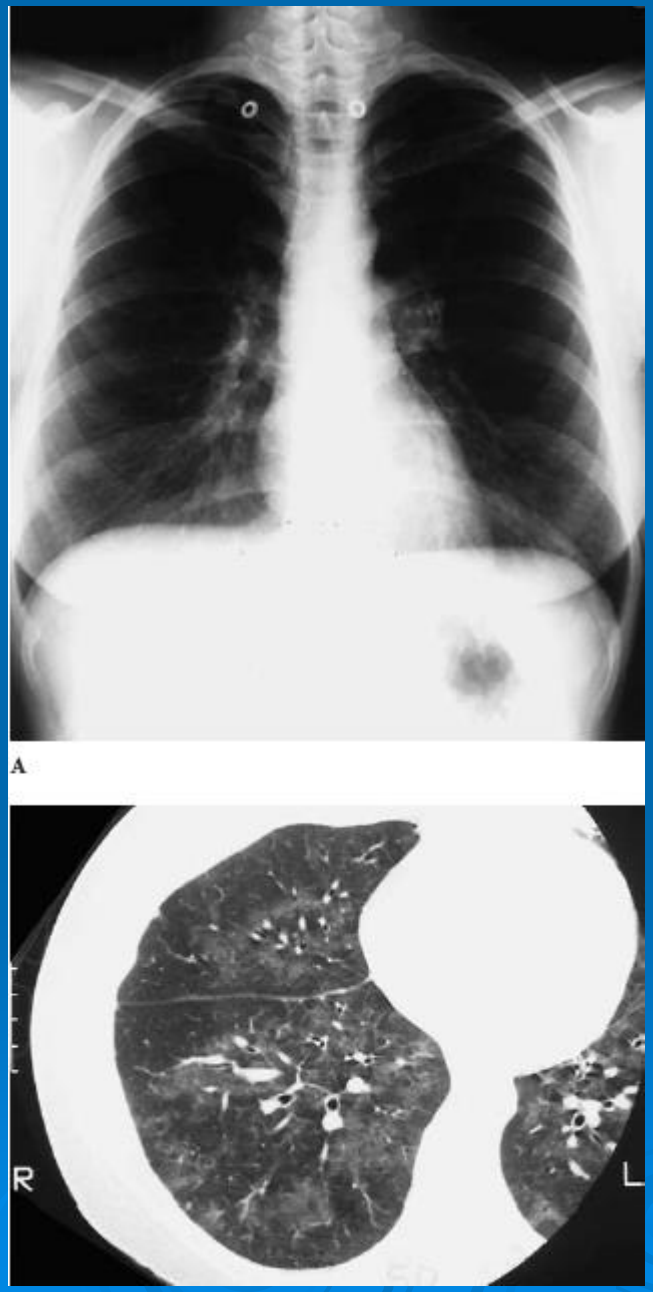
ABG

Imaging

PA/LAT CXR

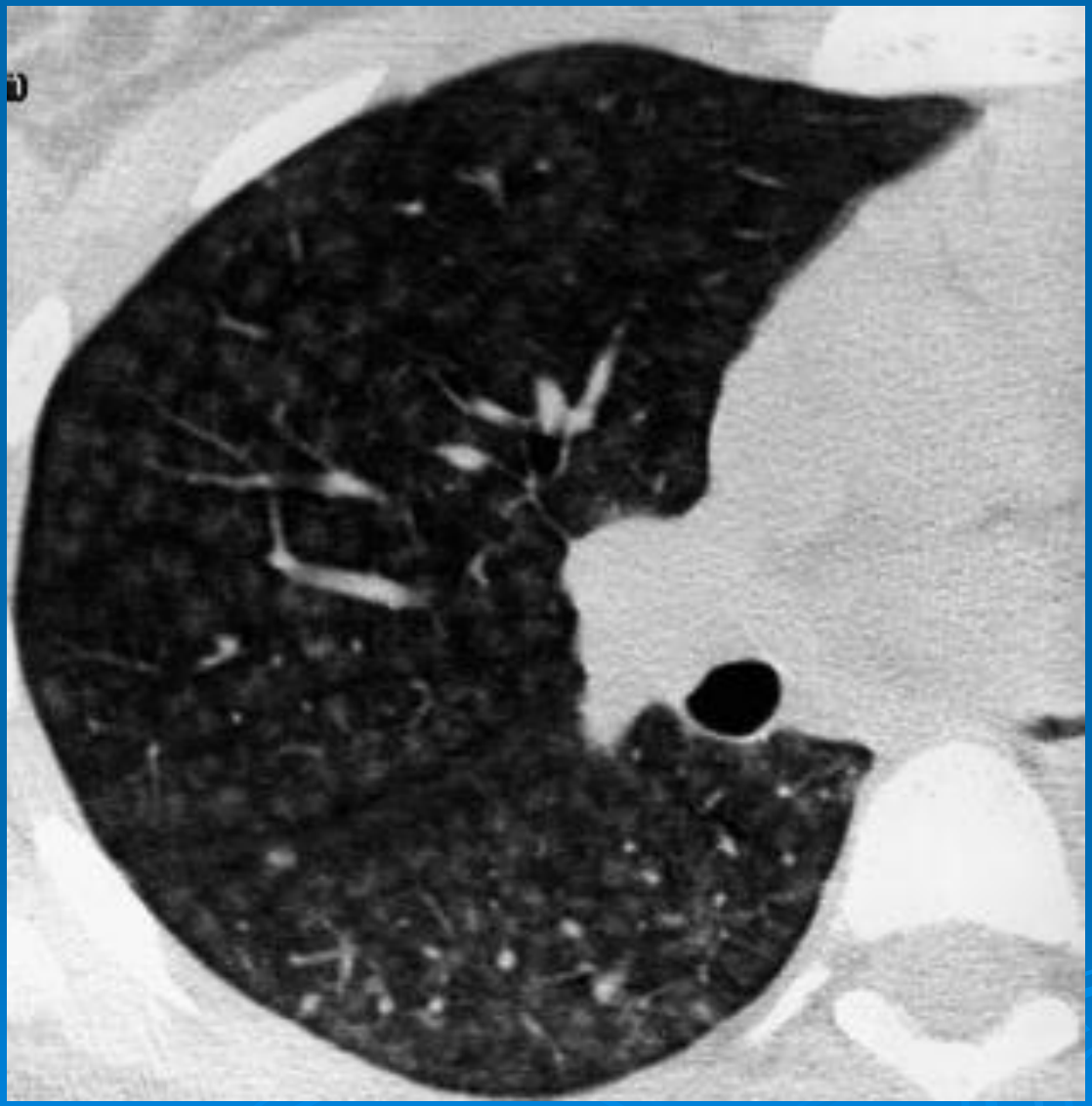
HRCT

GROUND GLASS



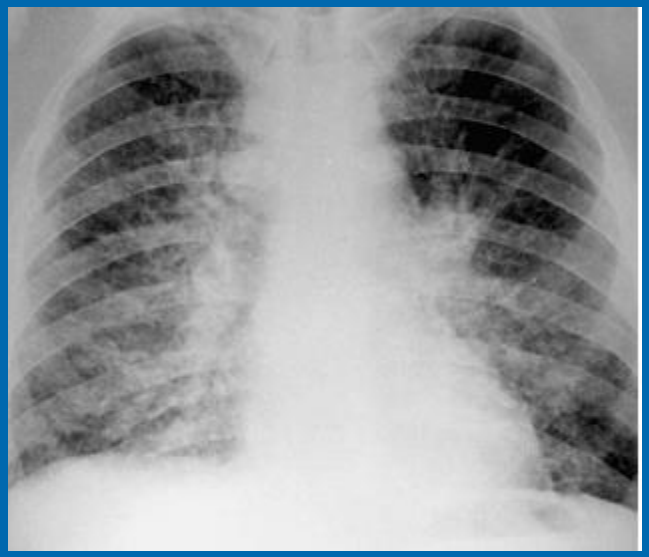
Schwarz, ILD, 2003, RB

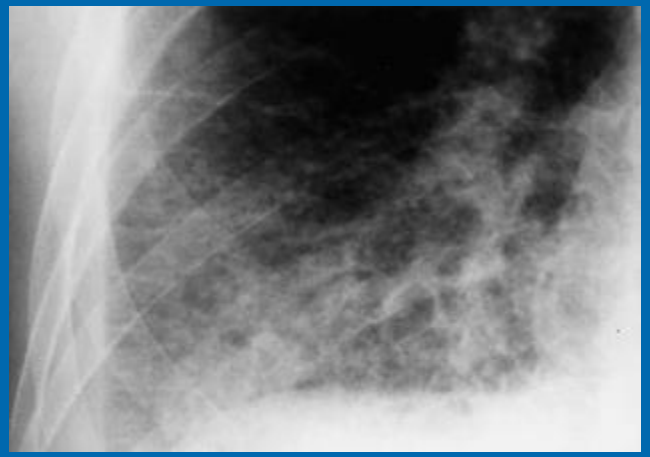
NODULAR GROUND GLASS

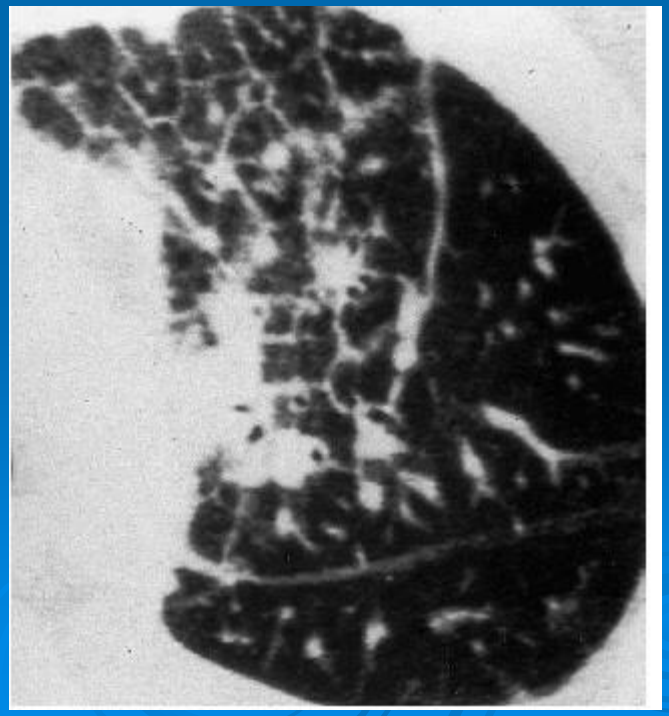


Schwarz, ILD, 2003, HP

INTRALOBULAR SEPTAL THICKENING

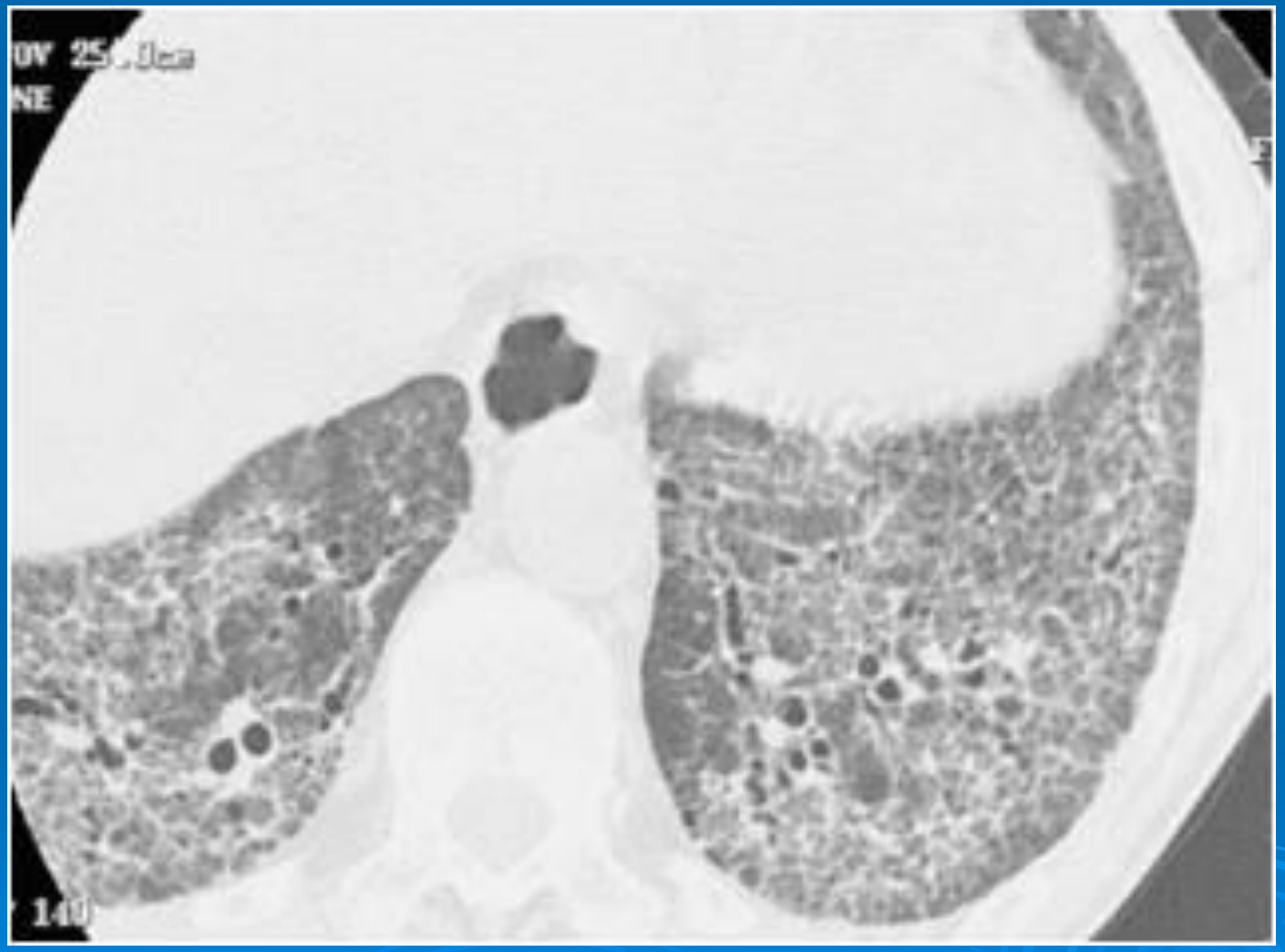






Schwarz, ILD, 2003, LC

RETICULAR INFILTRATES



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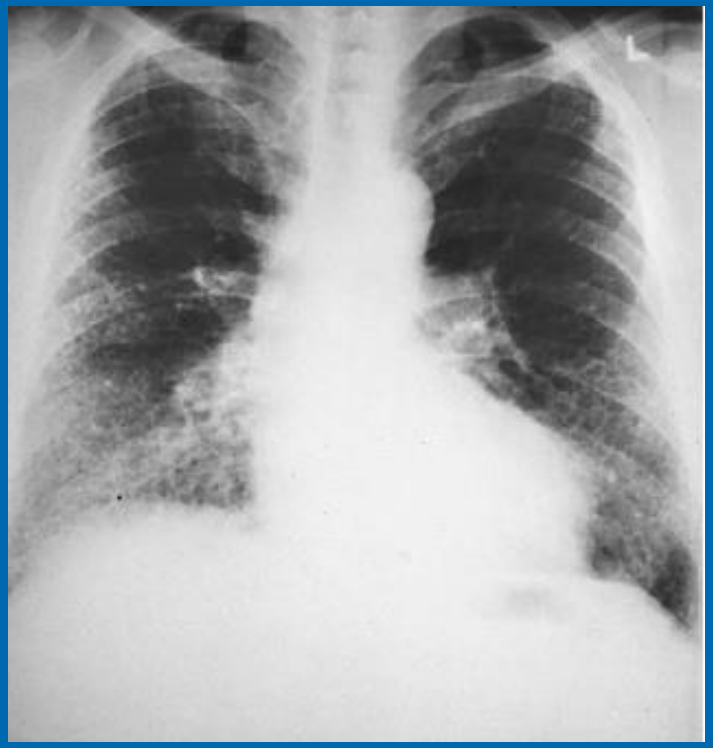
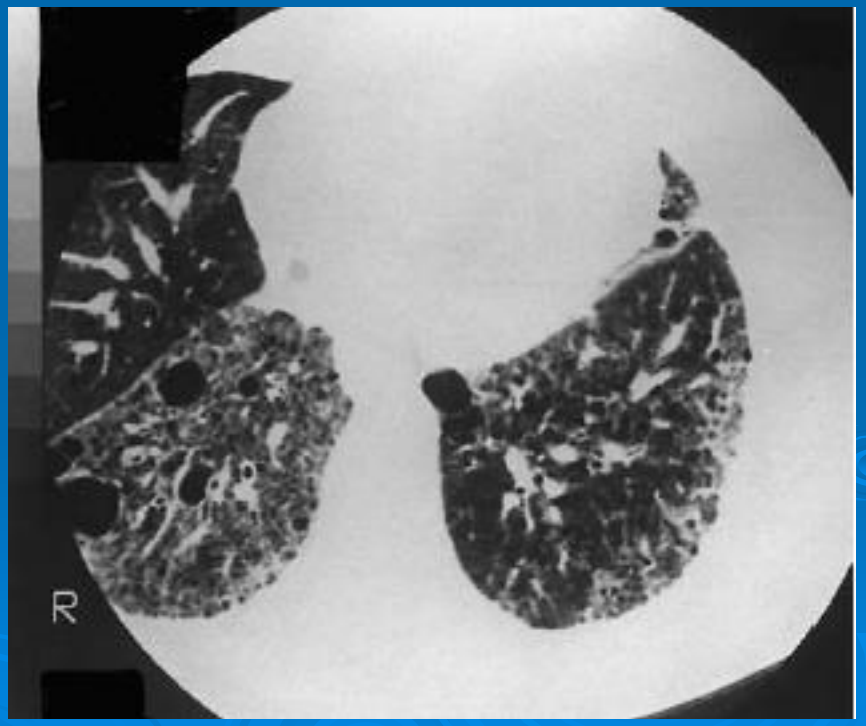
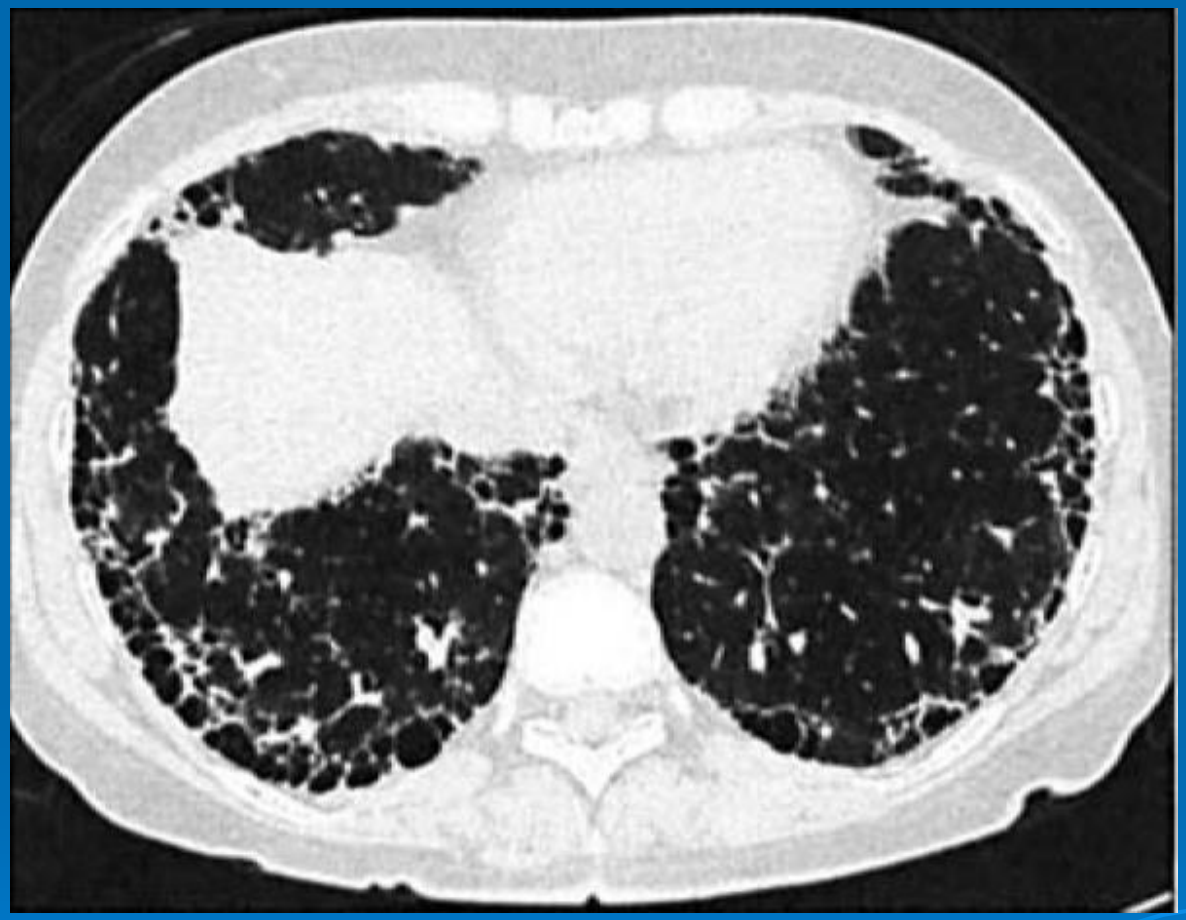


HONEYCOMB LUNG



Schwarz, ILD, 2003

HONEYCOMB LUNG



History

dyspnoea /OE, dry cough +/–, little sputum

Comorbid diseases

CTD – arthritis, rashes, dysphagia

Drugs

Environmental / occupational exposures - with dates & durations

Asbestos, silica

Smoking status

Previous malignancies and treatment

Family history of lung diseases

Examination

Breathless

Cyanosis

Finger clubbing

Skin – rashes, ulcers,

Joint swelling

Leg oedema

P_2

Lung crackles

end-inspiratory

Fine dry or “Velcro”-type

Dyspnoea: The first symptom at first on exercise and then rest.

Wheezing is not a common complaint and may only accompany periods of

Cough is common

Digital clubbing is a common finding occurring is not less than 50% of cases, but is rarely associated with hypertrophic osteoarthropathy.

Cyanosis on exercise and later at rest is one of the cardinal features.

Auscultation

Intensity of B.S is normal. Scattered late inspiratory bronchi may be heard. Crepitations are common, fine (Velcro, rale) and sometimes are localized.

Heart , P2 might be accentuated , signs right ventricular hyper-trophy and failure is usual

Investigations

Laboratory studies:

Complete blood count with differential**, eosinophilia**

ESR.

Renal & liver function tests.

Serologic studies: should be obtained if clinically indicated by features suggestive of a connective tissue disease (Antinuclear antibodies, rheumatoid factor), environmental exposure (hypersensitivity precipitin panel), or systemic vasculitis (antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody).

Radiology:

usually abnormal

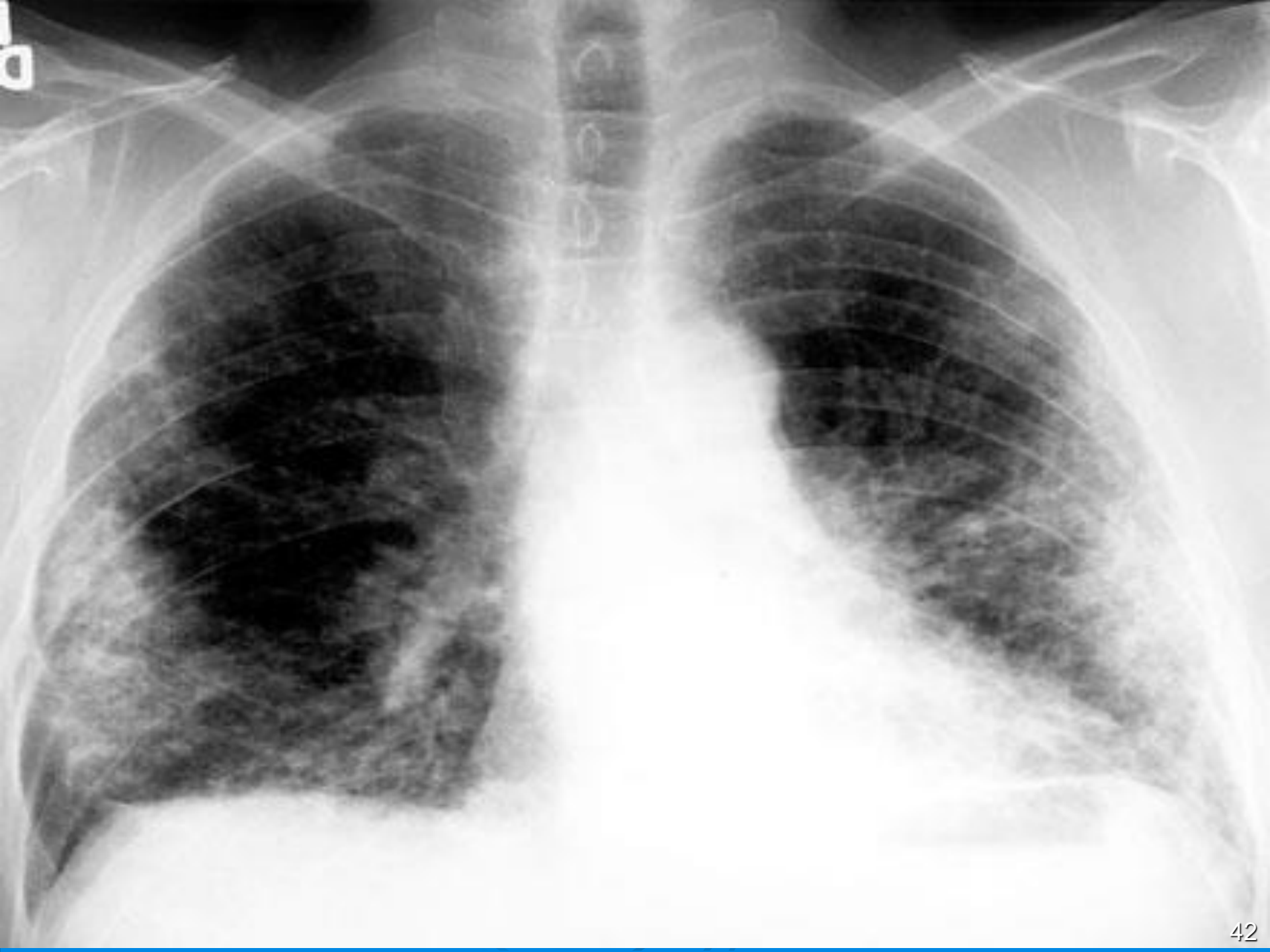
Chest x-ray: normal ~ 10%.

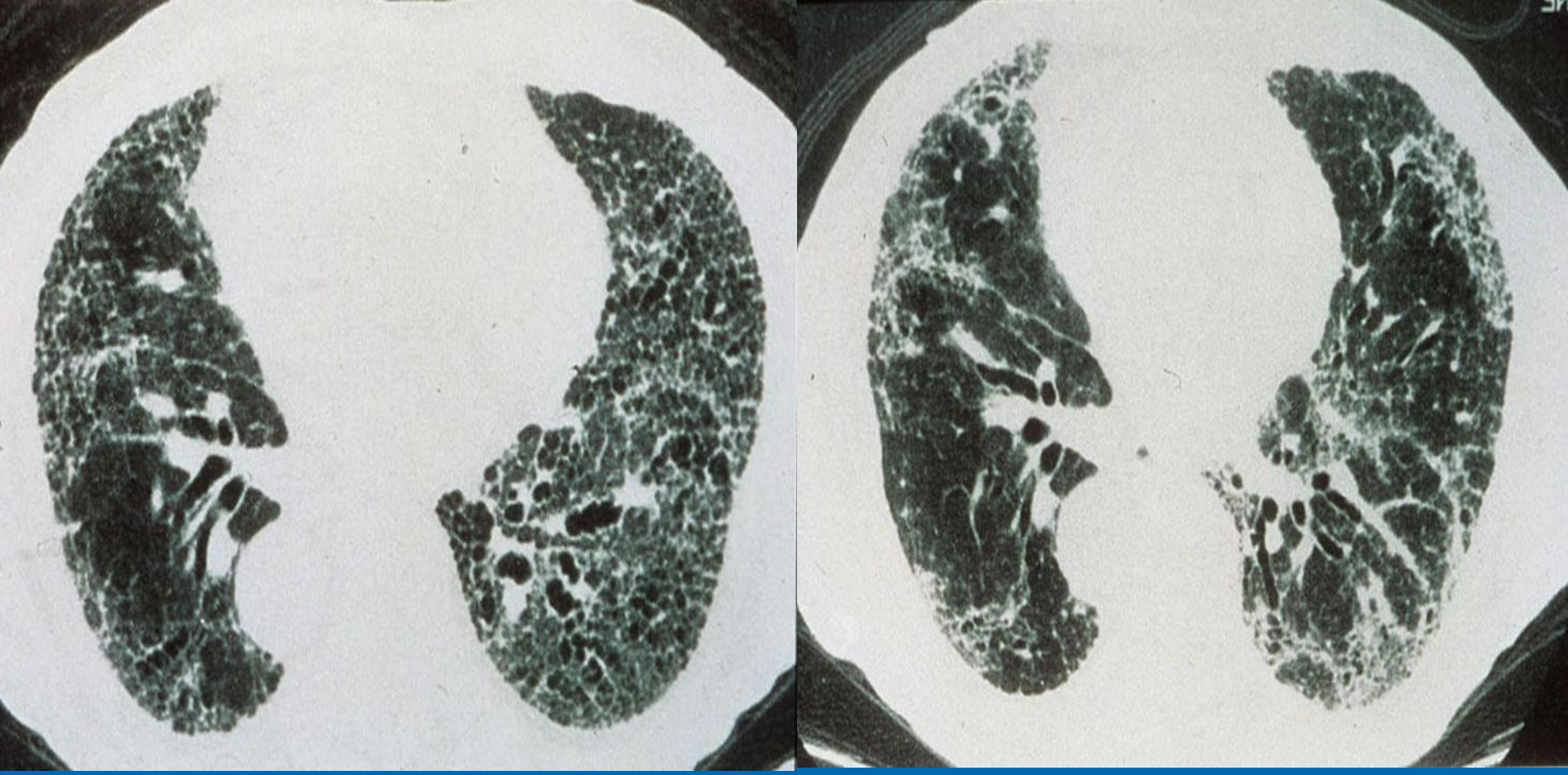
High resolution CT scan chest

Radiological pattern of disease

- **Reticulo / Nodular.**
- **Alveolar shadows**
- **Pleural involvement**
- **Honeycomb**
- **Interlobar septal thickening**
- **Hilar adenopathy**

Anatomical distribution (upper or lower zone)

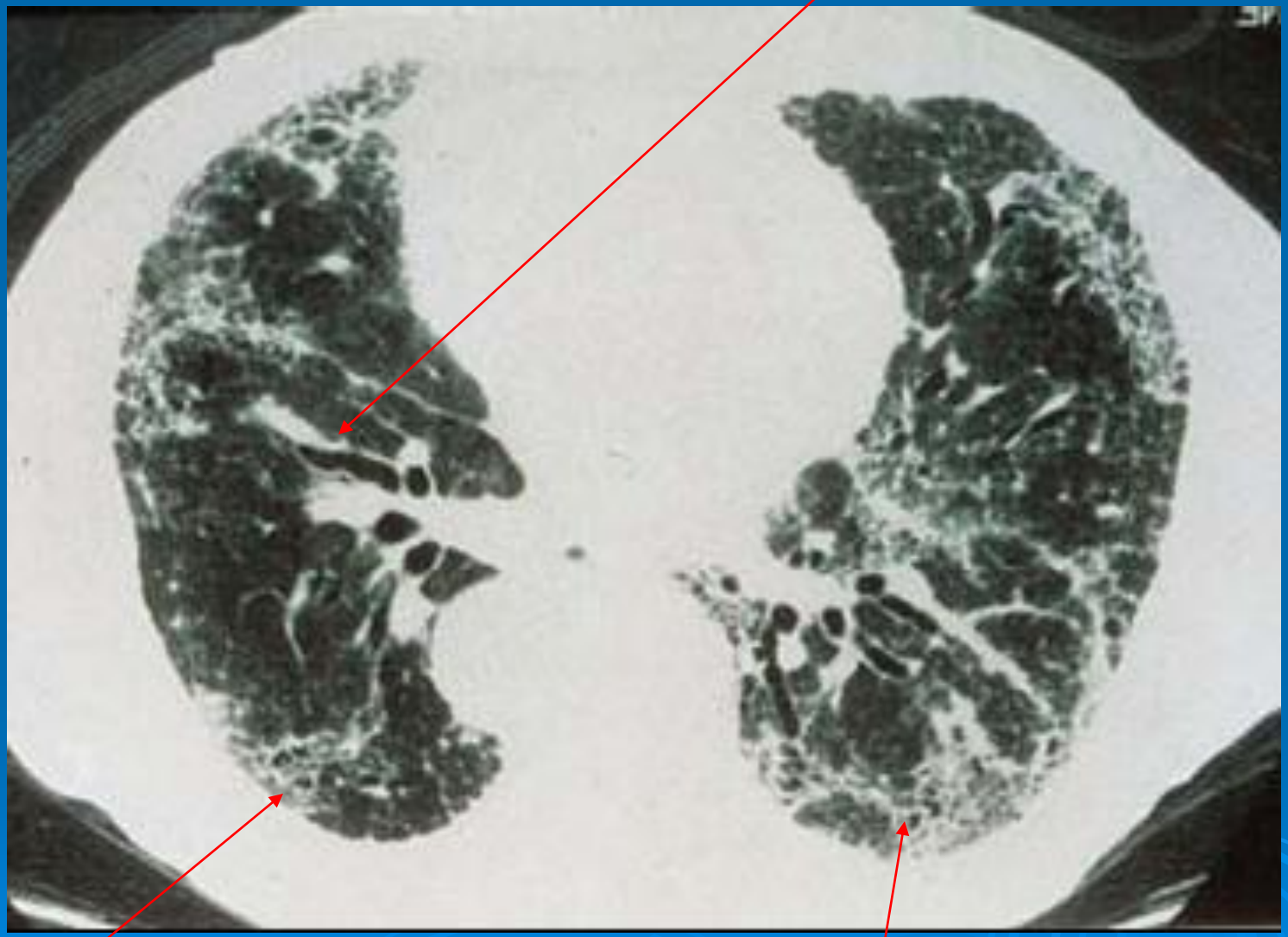




Patchy abnormalities predominate in the periphery of the lung & lower lobes

Reticular and honeycomb changes often associated with ground glass opacification and traction bronchiectasis

Traction bronchiectasis



Honeycomb

Subpleural distribution

PULMONARY FUNCTION TESTING:

Complete lung function testing (spirometry, lung volumes, diffusing capacity)

Measurement of lung function is helpful in assessing the severity of lung involvement in patients with ILD.

In addition, the finding of an obstructive versus a restrictive pattern is useful in narrowing the number of possible diagnoses.

Smoking history must be considered when interpreting the functional studies.

Most of the interstitial disorders have a restrictive defect with reductions in total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV).

Flow rates are decreased (FEV1 and FVC), but the changes are in proportion to the decreased lung volumes; thus, the FEV1/FVC ratio is usually normal or increased.

The reductions in lung volumes become more pronounced as lung stiffness worsens with disease progression.

Arterial blood gas:

The resting arterial blood gases may be normal or may reveal hypoxemia (secondary to mismatching of ventilation to perfusion) and respiratory alkalosis. Carbon dioxide retention is rare and usually a manifestation of end-stage disease.

Importantly, a normal resting PaO_2 (or O_2 saturation by oximetry) does not rule out significant hypoxemia during exercise or sleep, which is common in ILD.

However, secondary erythrocytosis is rarely observed in uncomplicated ILD.

Lung biopsy

The procedure of choice in establishing a diagnosis in patients with ILD secondary to suspected idiopathic interstitial pneumonia (IIP).

 The location of the surgical lung biopsy is guided by the distribution of disease on HRCT images

Fiberoptic Bronchoscope:

& histopathological examination.

BRONCHOSCOPY

- It is often the initial procedure of choice.
- Endobronchial lesions:
  - Sarcoidosis
  - Wegener's granulomatosis - Inflammation and stricture of the major airways
- Transbronchial bx:
  - Diagnostic: Sarcoidosis (75-80%)
    Lymphangitic carcinomatosis (80%)
    Eosinophilic pneumonia
    Pulmonary alveolar proteinosis
    Pulmonary histocytosis X
    Good pasture's syndrome

SURGICAL BIOPSY

Video-assisted thoracoscopic lung biopsy is the preferred method of obtaining lung tissue.

contraindications:

- Serious cardiovascular disease
- Radiographic evidence of diffuse end-stage disease (honey combing)
- Severe pulmonary dysfunction

ROLE OF LUNG BIOPSY

- Not required to make the diagnosis in all patient with ILD.
- To reach a definitive diagnosis or to stage a disease without examination of lung tissue.
- Indication for lung biopsy:
  - to assess disease activity
  - to exclude neoplasm or infection
  - to identify a more treatable condition
  - to establish a definitive Dx before starting a treatment with serious side effects
  - to provide a specific diagnosis in patients with:
    >> atypically or progressive pattern
    >> a normal or atypical chest x-ray features

TREATMANT

BASIC PRINCIPLES OF TREATMENT:

- Provide symptom relief
- Slow down disease progression
- Prevent complications
- Improve quality of life
- Prolong survival
- Prevent treatment complications

Lines of Treatment of ILD

Anti-inflammatory drugs Corticosteroids Azathioprine Cyclophosphamide

Anti-fibrotic agents Colchicine Pirfenidone Pentoxyphylline D-Penicillamine TGF-beta antagonist Interferon-gamma

Anti-oxidant agents N-acetylcysteine Nitric oxide synthase inhibition

Supportive and symptomatic treatments* Oxygen Pulmonary vasodilators Diuretics Antibiotics (if infection) *

CORTICOSTEROIDS:

Represent the classic treatment of IF. They are to be given as early as possible, without any time consumption in assessment of progression. They modify adhesion of leukocytes to endothelial surface, reduce level of immune complexes, proteolytic enzymes production, and reduce all cytokine production

Dose: Large dose to maximize effect. 1.0-1.5 mg / kg / D of prednisolone not exceeding 100 mg / D for 8-12 weeks (for chronic progressive cases). If responding, reduce to 0.5-1 mg / kg / D for 12 weeks, than 0.25 mg / kg / D. alternate day therapy is not preferable.

Favorable (or improved) response to therapy is fined by two or more of the following, documented two consecutive visits over a 3-to6-mo period.

A decrease in symptoms, specifically an increase in the level of exertion required before the patient must stop, because of breathlessness or a decline in the frequency or serenity of cough.

Reduction of parenchymal abnormalities on chest radiograph or HRCT scan.

Physiologic improvement defined by two or more of :the following

- ≥10% increase in TLC or VC (or at least ≥200-ml change).
- ≥15% increase in single-breath DI∞ (or at least ≥3ml/ min / mmHg).
- An improvement of normalization of O2 saturation (≥4 percentage point increase in the measured saturation) or PaO2 (≥4- mm Hg increase from the previous measurement) achieved during a formal cardiopulmonary exercise test.

A failure to respond to therapy (e.g., after 6 mo of treatment) is defined as :

-An increase in symptoms, especially dyspnea or cough

-An increase in opacities on chest radiography or HRCT scan, especially the development of honeycombing or signs of pulmonary hypertension .

-Evidence of deterioration in lung function in Two or more of the following :

- ≥10% decease in TLC or VC (or ≥200-ml change).
- ≥15% decrease in single- breath DI∞ (or at least ≥3 ml/min/mmHg change).
- Worsening (greater fall) of O2 saturation (≥4 percentage point decrease in the measured saturation) or rise the AaPO2 at rest or during a formal cardiopulmonary exercise test (≥4 mm Hg increase from the previous measurement).

For acute rapidly progressive cases give 250 mg methyl prednisolone IV/6 hours for 5 days

30% usually have good response. Some fail to continue improvement after the initial duration.

Novel therapies in IPF

- A number of agents that interfere with collagen synthesis have been tested:
- Pirfenidone (A pyridone molecule)
- IFN-γ-1b (A glycoprotein) cost > 50.000$ per patient per year in USA.
- IFN-ß-1a.
- Colchicine
- D-Penicillamine (A chelating agent).
- N-acetylcysteine (Antioxidant).
- Captopril (ACE inhibitor).
- Bosentan (Endothelin-1 receptor antagonist).
- Imatinib mesylate (A protein-tyrosine kinase inhibitor).

Potential alternative treatments

Agents that alter collagen synthesis or fibrosis:

Colichicine: This agent inhibits collagen formation, suppresses the release of alveolar macrophage- derived growth factor & fibronectin.

Its efficacy appears similar to corticosteroids and may be considered as first line therapy or for patients refractory to corticosteroids. 0.6-1.2 mg are given daily either alone or in combination with immuno- suppressive / cytotoxic agents.

2nd line drug or 1st line if there is contraindication to corticosteroids

Cyclophosphamide

Dose: Oral 25-50 mg/ D, increased to 150 mg over 3-6 D.

IV 2 mg / D for 3-5, followed by oral.

Azathioprine

Given with a small dose of conticosroids as a 2nd line. (2 mg / kg / D, not exceeding 200 mg /D)

Penicillamine:

Limited reports about its use. 150 mg / day /

4 weeks, increased to 500 mg.

Cyclosporine:

Very few reports about its use in IF. Dose 5 mg / day increased up to 100 mg .

Other Novel agents:

Glutathions (an effective scavenger of toxic oxidants that suppresses lung fibroblast proliferation in response to mitogenes), taurine (a natural free amino acid), and niacin, inhibit the development of experimental fibrosis (better than either agent alone) in an animal model.

Other Novel agents :

Because epithelial injury in IPF may be mediated by oxygen radicals, it has been suggested that antioxidant strategies might prove beneficial. Possible strategies might include delivery of antioxidant enzymes to the lung parenchyma or even promoting increased genetic expression of antioxidant enzymes

Other antifibrotic agents:

Interferon α & B , relaxin (increased pro-collagenase), pirfenidone, suramin (pro-fibrotic cytokine inhibition)& prosta- glandin E2 (inhibits collagen production).

Other Novel agents :

High –dose N-acetylcysteine, as a glutathione precursor, has been suggested as an adjunct to maintenance immunosuppression therapy in patients with IPF.

Lung Transplantation

Transplantation should be considered for those patients who experience progressive physiologic deterioration despite optimal medical management and who meet the established criteria. Single lung transplantation is currently the preferred surgical operation. Unless specific contraindications exist, patients with sever functional impairment, oxygen dependency, and a deteriorating course should be listed for lung transplantation.

Lung Transplantation

Relative contraindications to lung transplantation include unstable or inadequate psychosocial profile/stability or significant extra-pulmonary disorders (e.g. liver, renal or cardiac dysfunction) that may negatively influence survival. Many centers limit lung transplantation candidates to those <60 years of age.

Complications

Progressive respiratory failure

Pneumonia

Cor pulmonale

Pneumothorax

Bronchial carcinoma

Pulmonary embolism

Drug toxicity

Worse prognosis

- Old age
- Male
- Smoking
- Honeycombing
- 6-MWT – SpO2 < 88%
- Lower DLCO < 40%
- Higher rate of acute exacerbations
- Pulmonary HT

Causes of death in ILD

Coronary artery disease

- Lung cancer
- Infection
- Pulmonary embolism
- Acute exacerbation of IPF


Thank You