DM SEMINAR
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IDIOPATHIC INTERSTITIAL PNEUMONIAS - UPDATE

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HEADINGS

- INTRODUCTION
- CLASSIFICATION
- APPROACH TO PATIENT WITH IIP
- CLINICAL-RADIOLOGICAL-HISTOPATHOLOGICAL FEATURES OF INDIVIDUAL IIPS
- TREATMENT

INTRODUCTION

INTRODUCTION

- 1892 - Osler initially described chronic interstitial pneumonia as ‘cirrhosis of the lung’
- 1944 - Hamman and Rich described 4 cases of diffuse interstitial fibrosis that were acute in onset and rapidly progressive → ‘Hamman - Rich Sydnrome’ for any acute onset diffuse idiopathic fibrotic lung disease

INTRODUCTION

WHAT ARE IIPs?

- Heterogenous group of clinicopathologic entities
- Broadly classified under Diffuse Parenchymal Lung Diseases (DPLDs)
- Non-neoplastic in nature
- Can be differentiated from other DPLDs by clinical symptoms and signs, chest radiology, laboratory investigations and histopathological examination

INTRODUCTION

- Idiopathic = Unknown
- Interstitial pneumonia = Involvement of lung parenchyma by varying combinations and patterns of inflammation and fibrosis
- Primary site of injury – Intersititum (Space between epithelial and endothelial basement membranes)
- Airspaces, peripheral airways and vessels along with their respective epithelial and endothelial linings also frequently involved

CLASSIFICATION

CLASSIFICATION

- 1969 - Initial classification given by Liebow and Carrington:

1. Usual Interstitial Pneumonia (UIP) including acute form (Hamman-Rich Syndrome)
2. Desquamative Interstitial Pneumonia (DIP)
3. Bronchiolitis Obliterans Interstitial Pneumonia (BOOP) and Diffuse Alveolar Damage (DAD)
4. Lymphoid Interstitial Pneumonia (LIP)
5. Giant Cell Interstitial Pneumonia

CLASSIFICATION

- 1998 – Katzenstein and Meyers proposed:

1. UIP
2. DIP & RB-ILD (Respiratory Bronchiolitis - associated Interstitial Lung Disease)
3. Acute Interstitial Pneumonia (AIP) – formerly Hamman-Rich Syndrome
4. Non Specific Interstitial Pneumonia (NSIP)

- LIP and Giant Cell Interstitial Pneumonia removed because no longer considered idiopathic (lymphoproliferative disorder and hard metal pneumoconiosis respectively)

CLASSIFICATION

- 1997 – Muller and Colby – similar to Katzenstein/Meyers (addition of BOOP)
- 2001 – ATS/ERS International Multidisciplinary Consensus Classification - reasons for new classification → improvement in understanding of clinical, radiological and histological patterns of IIPs with increasing use of HRCT and VATS-Lung Bx.
- CRP (clinico-radiologic-pathologic diagnosis) and histologic patterns for each of the CRP.

CLASSIFICATION

CRP Diagnosis

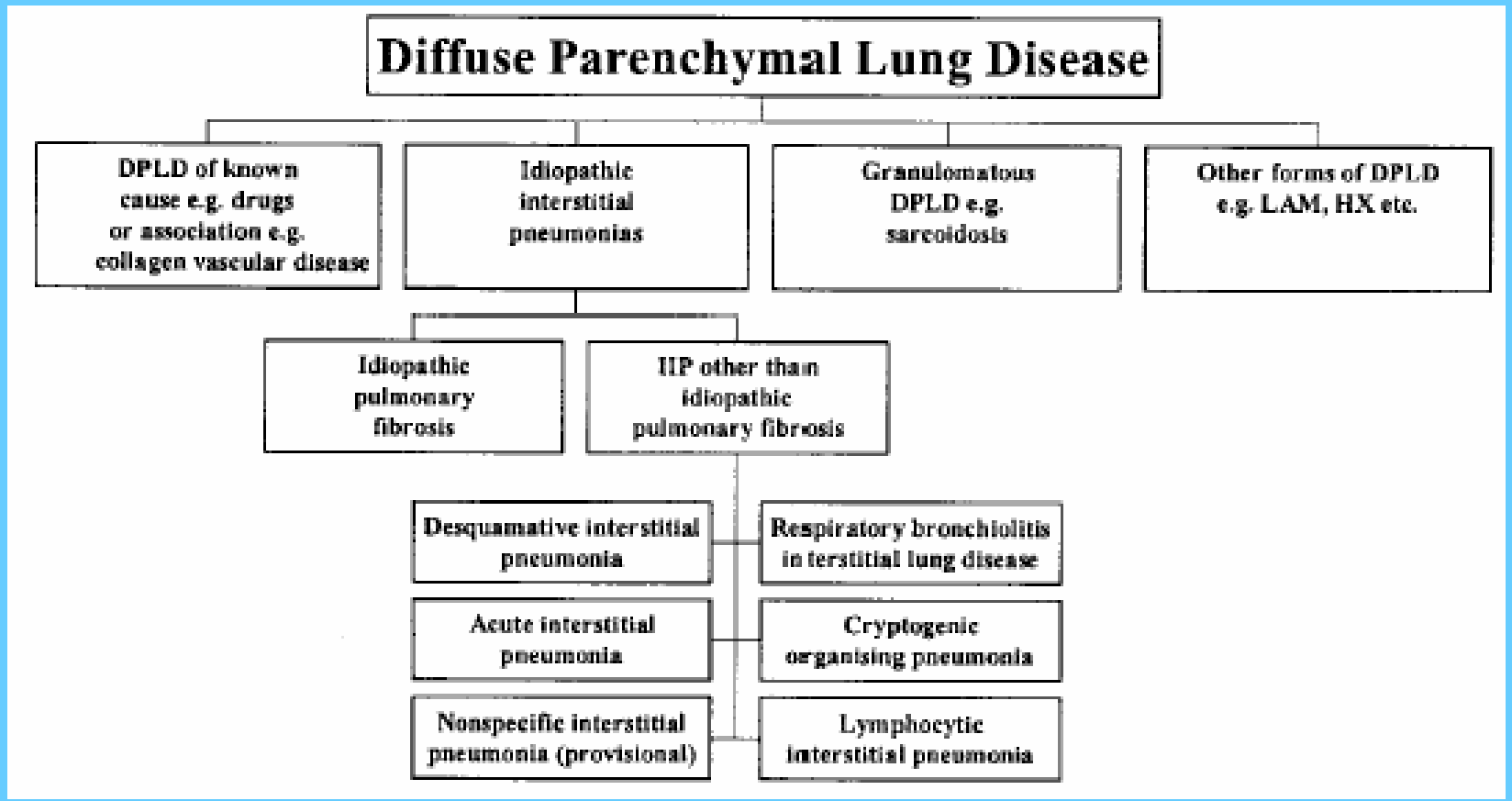
- IPF/CFA
- NSIP (Provisional)
- COP/BOOP
- AIP
- RB-ILD
- DIP
- LIP

Histologic Pattern

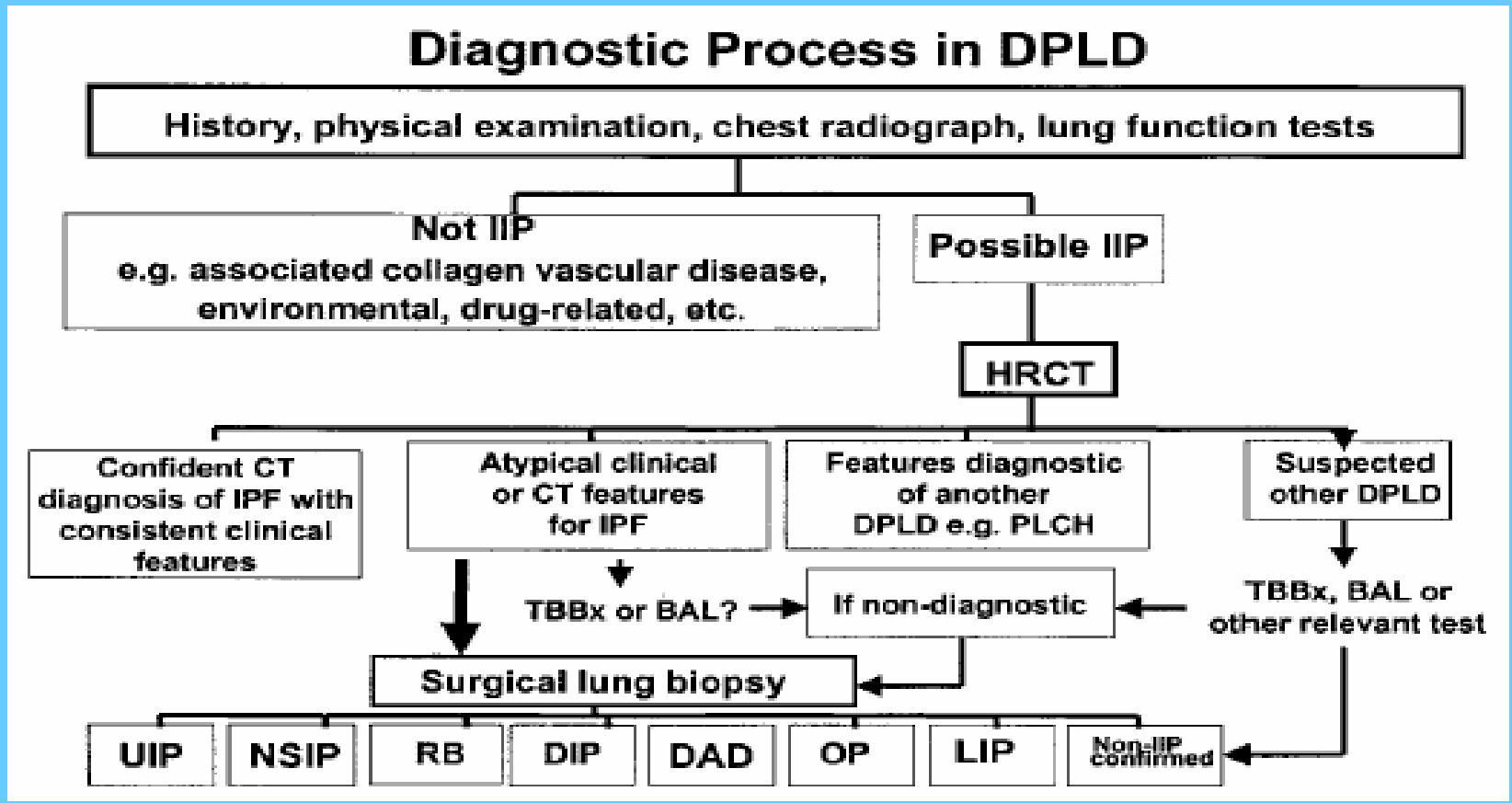
- UIP
- NSIP
- Organizing pneumonia
- DAD
- RB
- DIP
- LIP

DIAGNOSTIC APPROACH

DIAGNOSTIC APPROACH



DIAGNOSTIC APPROACH



DIAGNOSTIC CRITERIA - IPF (NO OPEN LUNG Bx)

Major criteria

- Exclusion of known causes of interstitial lung disease, such as drug toxicity, exposure to environmental respiratory hazards and the presence of connective tissue disease
- Evidence of restrictive lung disease such as reduced vital capacity, impaired gas exchange with an increased alveolar–arterial oxygen gradient, decrease in partial arterial pressure of oxygen at rest or during exercise, decreased carbon monoxide gas transfer
- High-resolution CT showing bibasilar reticulonodular opacities with minimal or no ground-glass appearance
- A transbronchial biopsy or bronchoalveolar lavage findings that would not support other diagnosis such as sarcoidosis, hypersensitivity pneumonitis, malignant disease, infection, cryptogenic organizing pneumonia or pulmonary alveolar proteinosis

Minor criteria

- Age > 50 yr
- Insidious onset of dyspnea with no discernible cause
- Duration of symptoms > 3 mo
- Bilateral inspiratory crackles

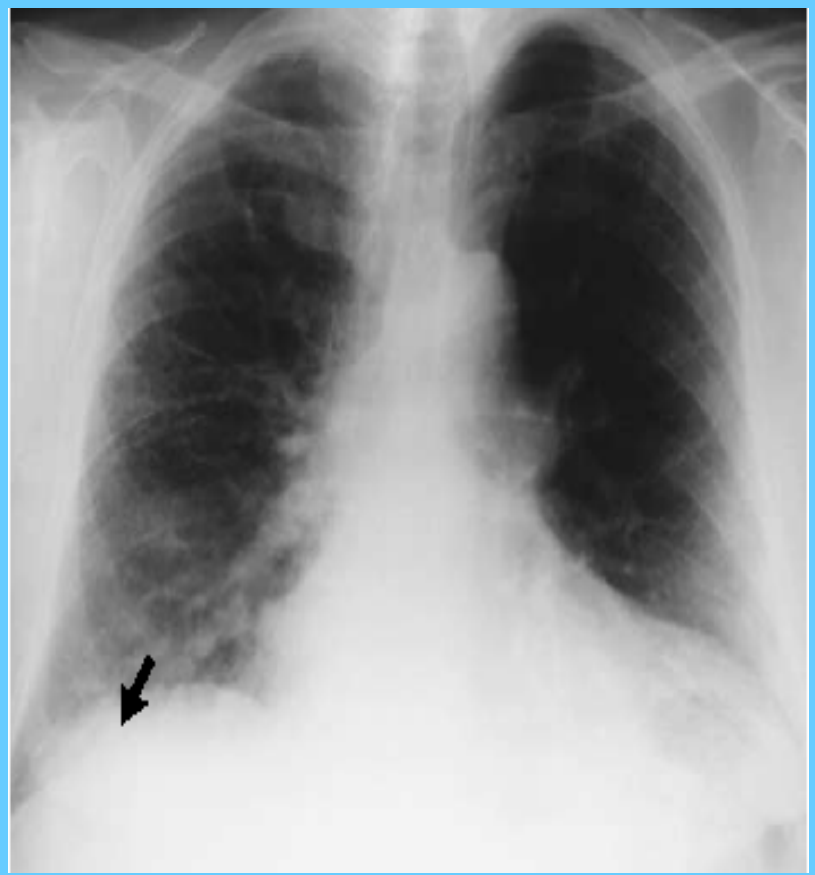
INDIVIDUAL IIPs

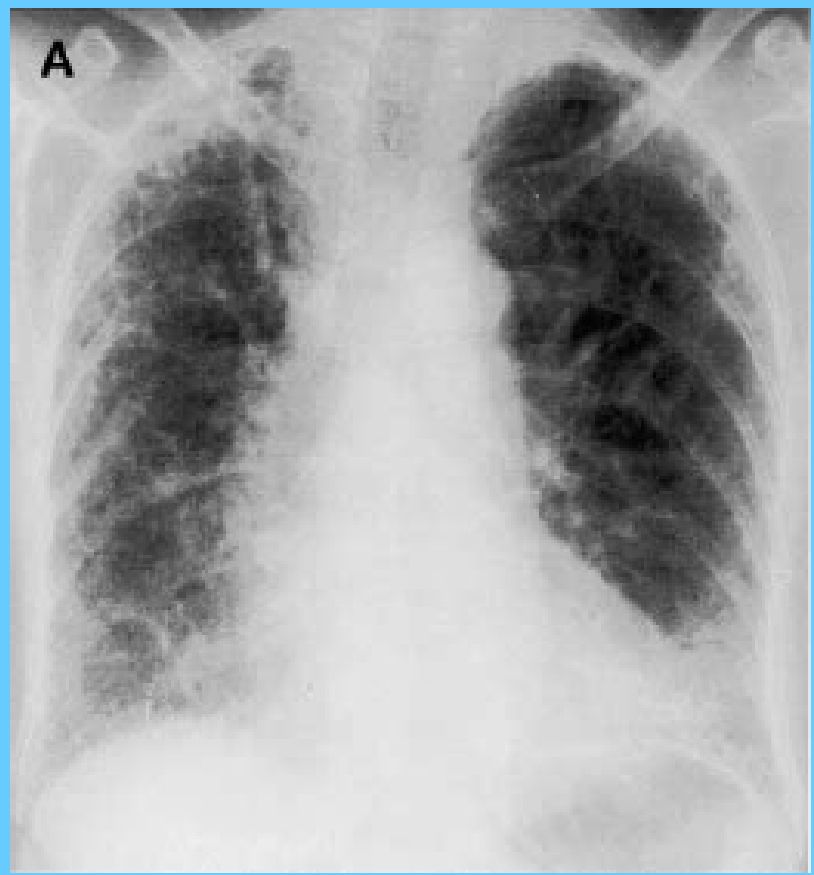
CLINICAL FEATURES - IIPs

	IPF	NSIP	BOOP	AIP	RB-ILD	DIP	LIP
Age	5^{th}-6^{th} Dec	4^{th}-5^{th} Dec	6^{th} Dec	Any (av 50 yr)	4^{th}-5^{th} Dec	4^{th}-5^{th} Dec	5^{th} Dec
Sex	M>F	M=F	M=F	M=F	M:F=2:1	M:F=2:1	F>M
Onset	Insidious	Insidious	Subacute	Acute	Insidious	Insidious	Insidious
Mean duration of symp	> 6 m	1½-2½ yrs	< 3 m	< 3 wk		Wks-Months	3 yrs
Cough	+	+	+ (Sp +/-)	+/-	+	+	+
Dyspnoea	++	+	+	+++	+	+	+
Const symp	N	Y	Y	Y	N	N	Occ
Preceding URI	N	N	Y	Y	N	N	N
Relation to smoking	Y	N	1/Y	N	Y (>30 p yrs)	Y	N
Clubbing	25-50%	25-33%	No	No	No	50%	Late
Lab inv			↑ CRP/ESR, TLC/DLC (N)				Anemia, dysprotenemia
PFT	Restr	Mild restr	Mild-mod Restr	Restr	N/mild restr or obst	N/mild Restr	N/mild restr or obst
DL_{CO}	↓	↓	Mod ↓	↓↓	Mild ↓	Mod ↓	
BAL	↑ N (occ E)	↑ L	↑ TC, L, ↓ CD 4:8	↑ TC, N, RBCs	↑ alv pigm M (occ N)	↑ alv pigm M (occ N)	↑ L
Comments	7 fold risk of ca lung			Usually fulfil criteria for ARDS & req MV			Occ assoc with LNE. Rarely idiopathic

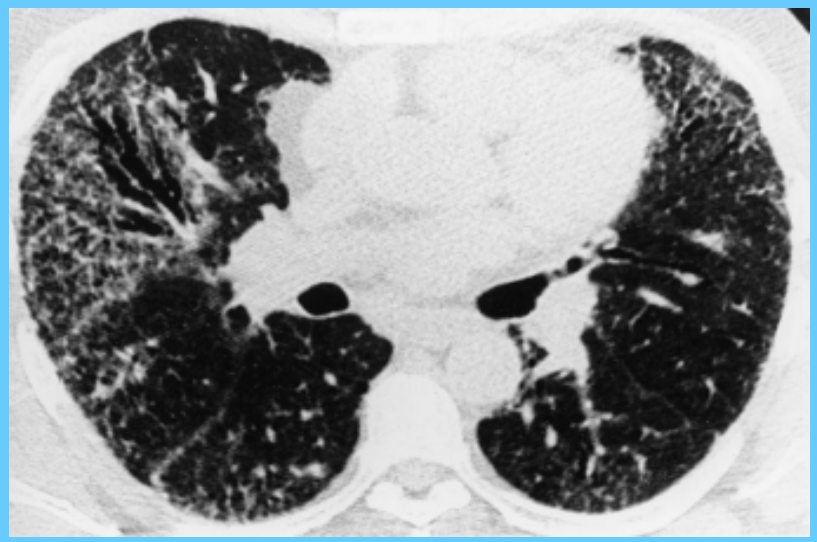
RADIOLOGY - IIPs

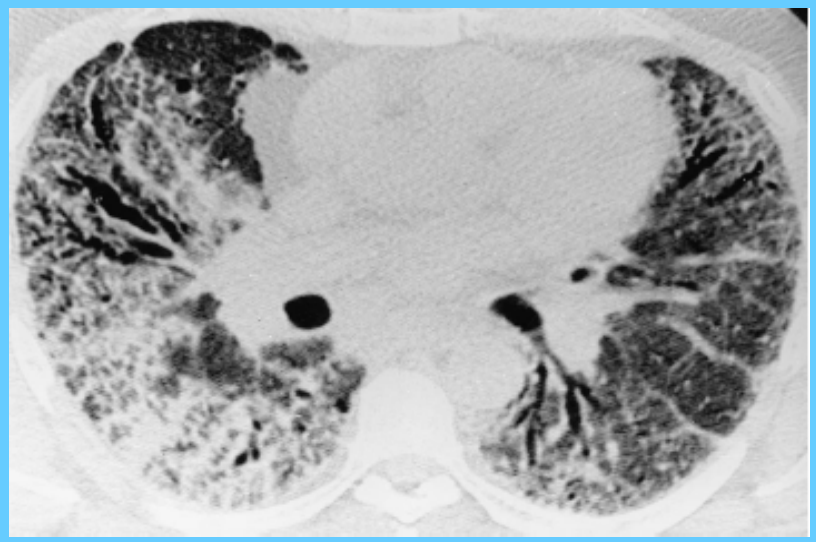
CXR - IPF

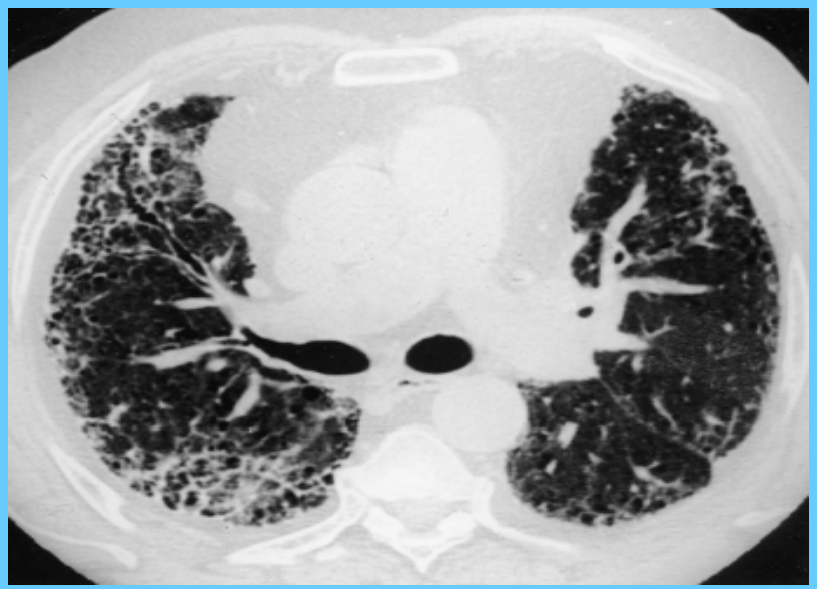


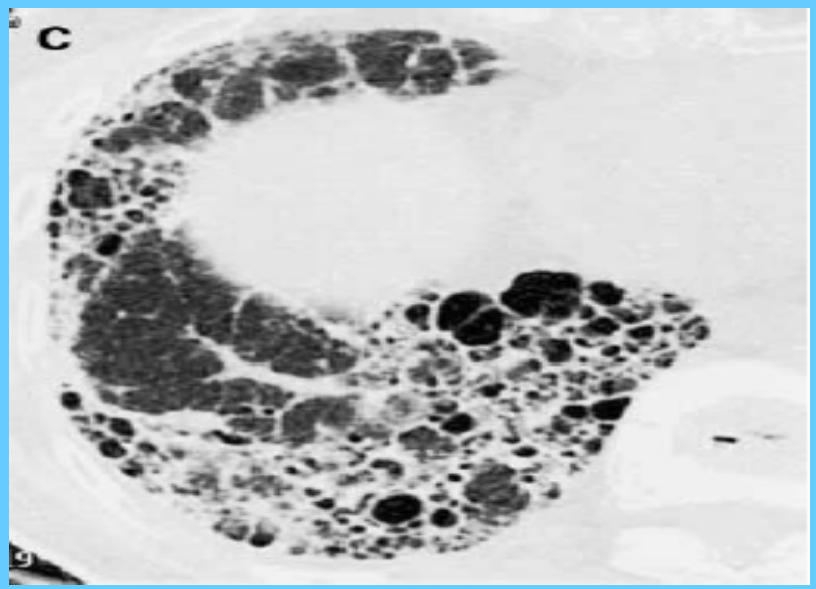


HRCT - IPF







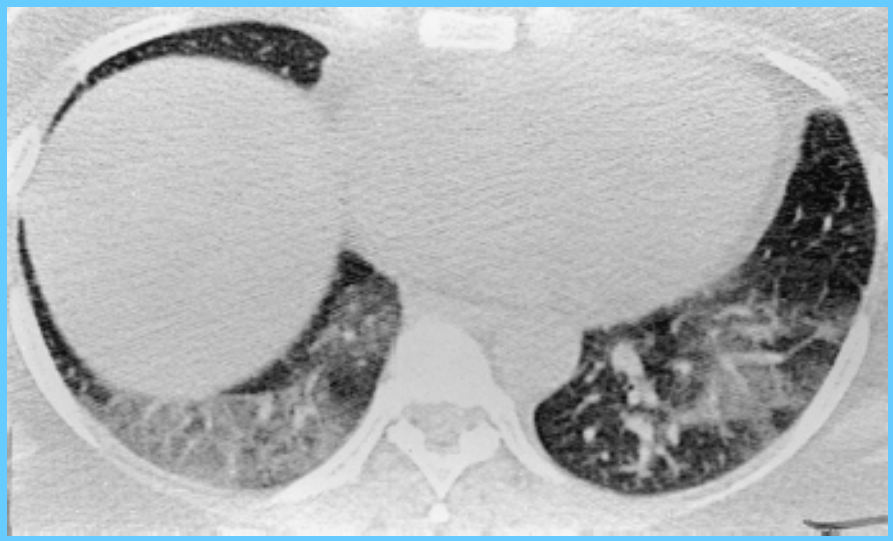


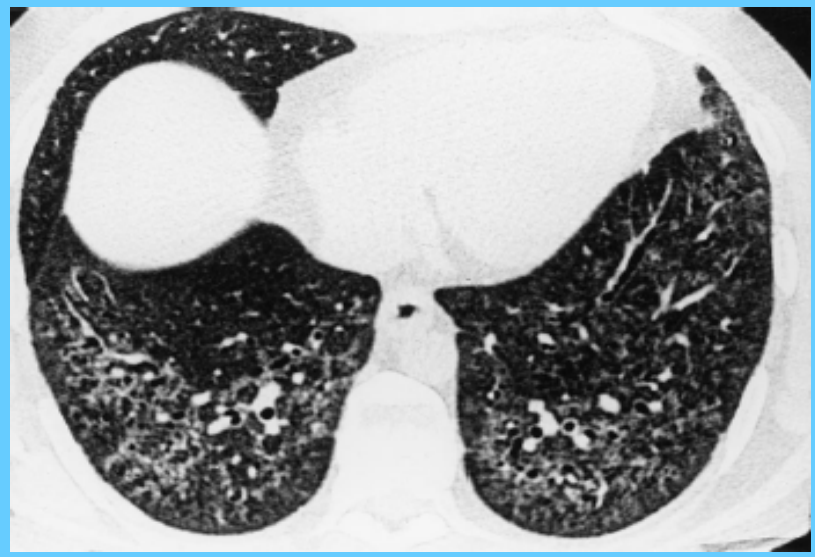
HRCT - IPF

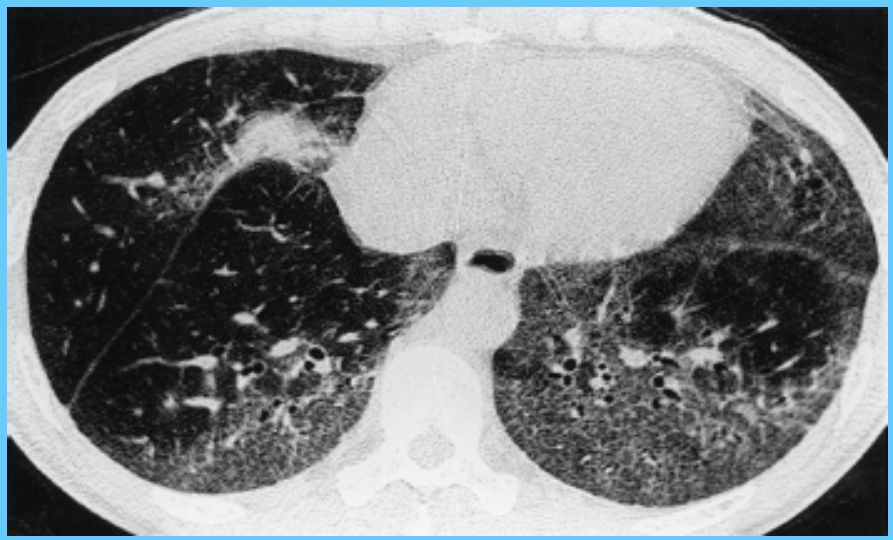
Score	Characteristics
0	No interstitial disease
1	Interlobular septal thickening; no discrete honeycombing
2	Honeycombing involving up to 25% of the lobe
3	Honeycombing involving 25 to 49% of the lobe
4	Honeycombing involving 50 to 75% of the lobe
5	Honeycombing involving > 75% of the lobe

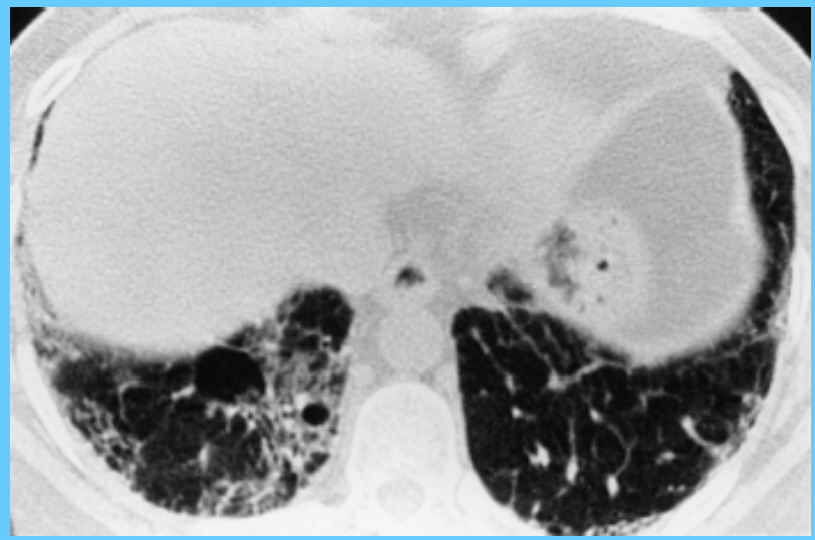
- Scoring system based upon relative qty of honeycombing.
- Final score = mean of scores from each lobe.
- Score > 2 suggestive of increased risk of mortality

HRCT - NSIP

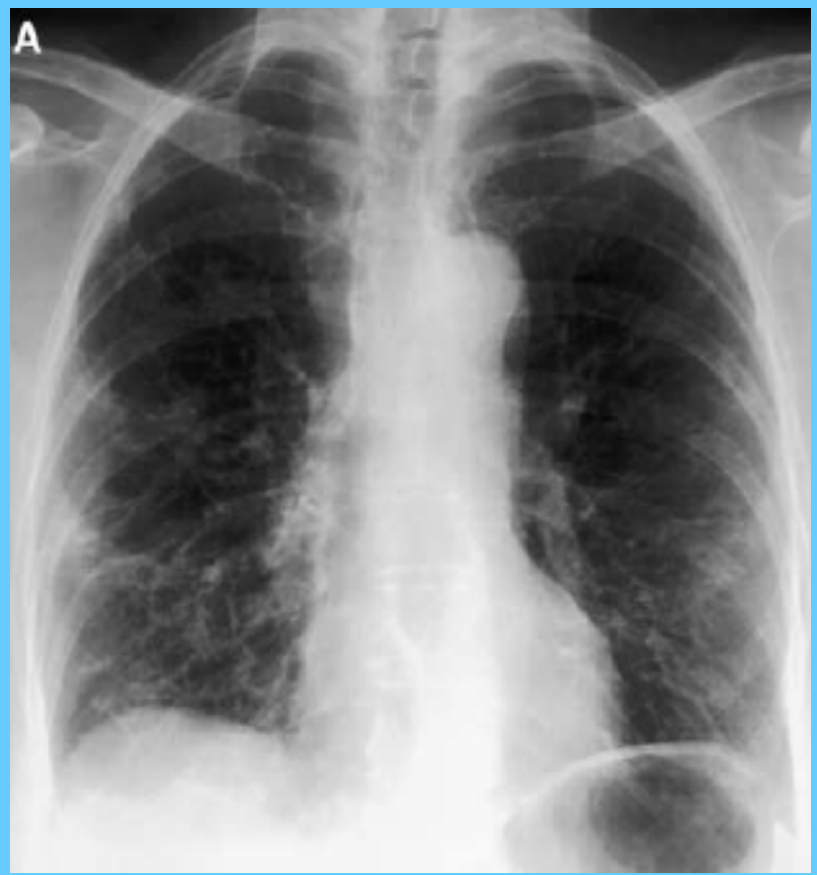


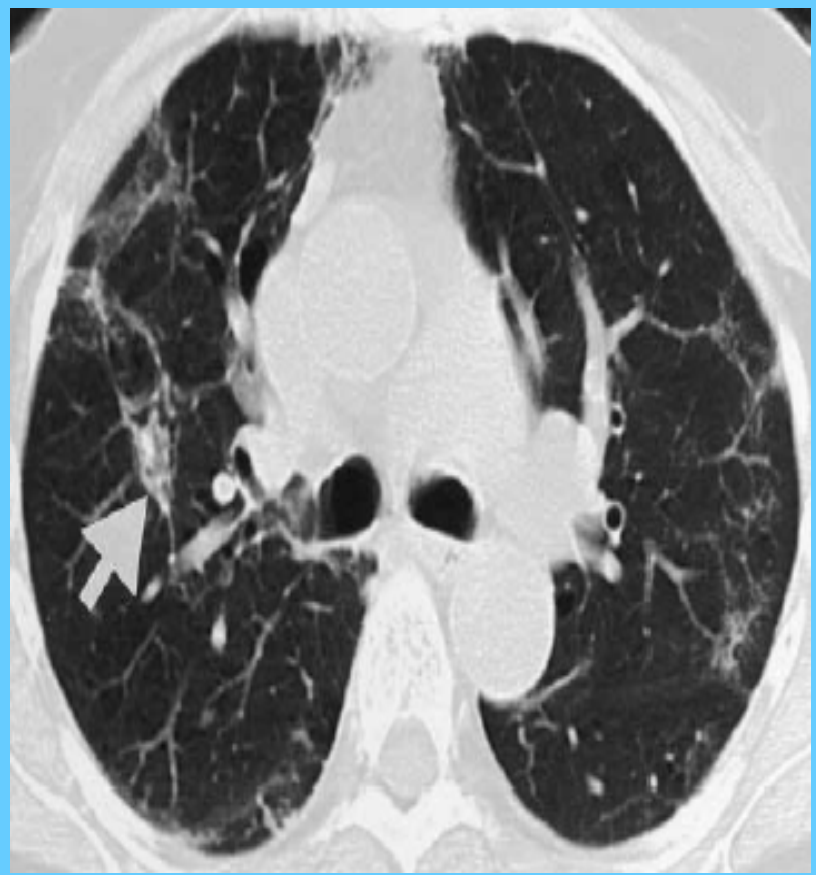




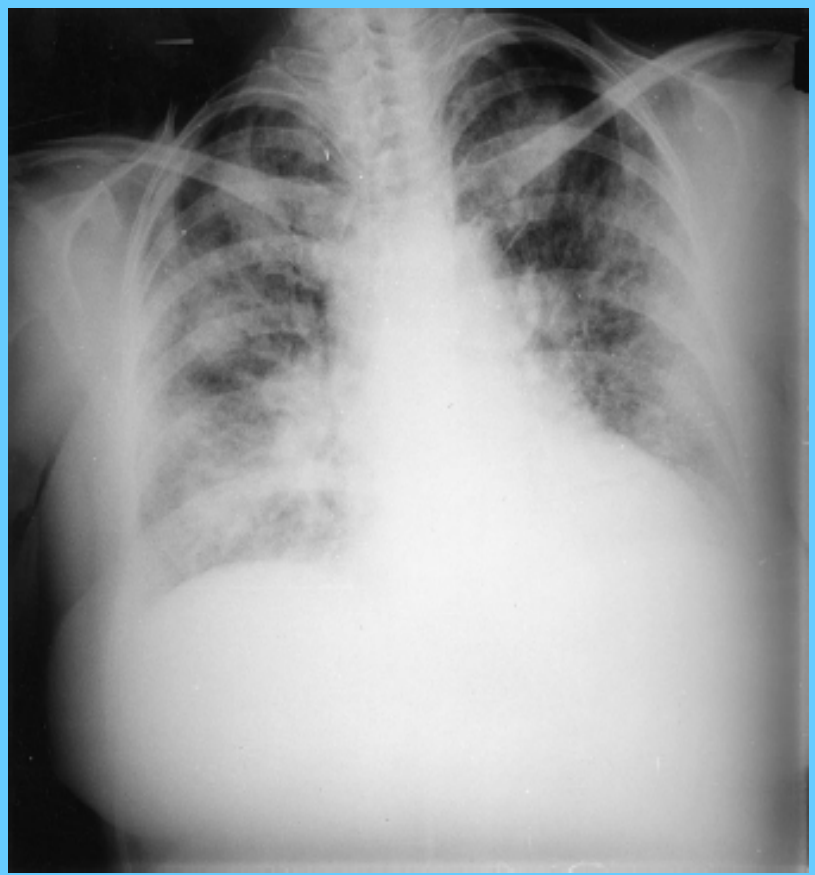


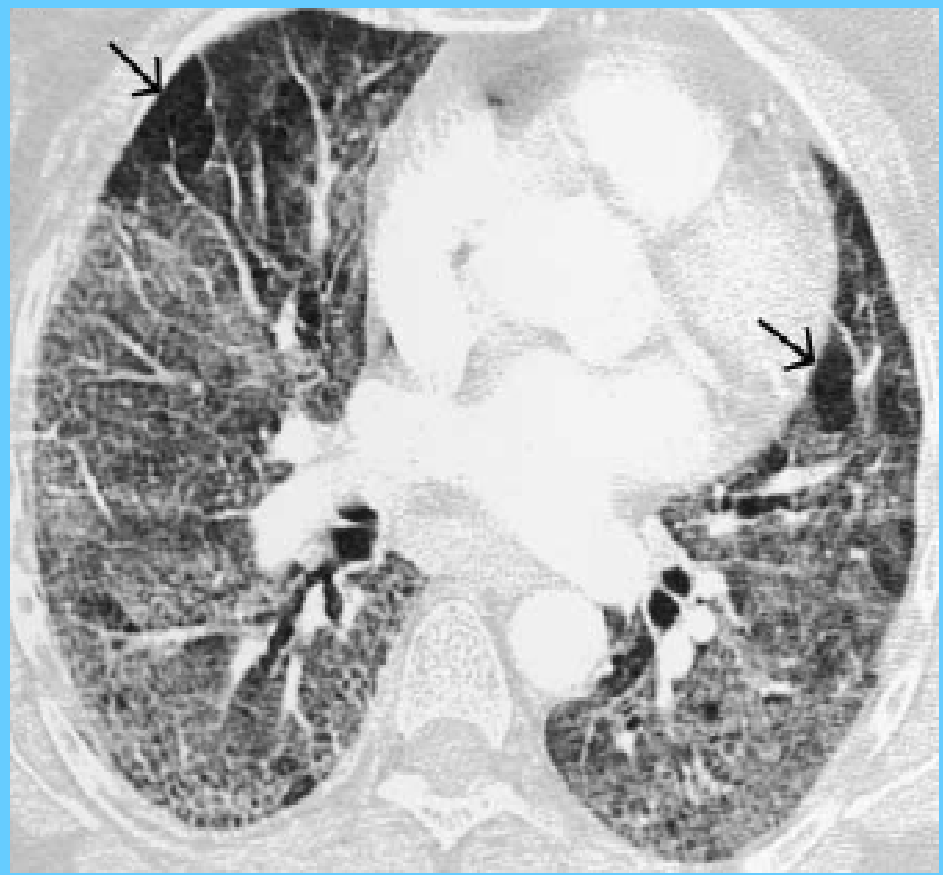
RADIOLOGY - BOOP



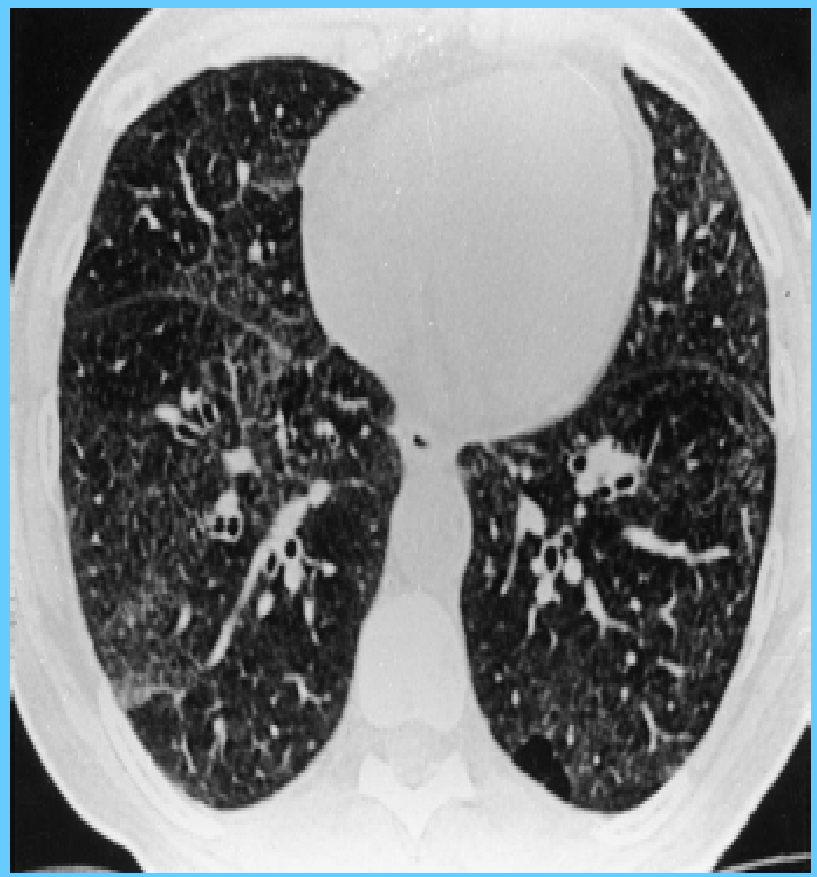


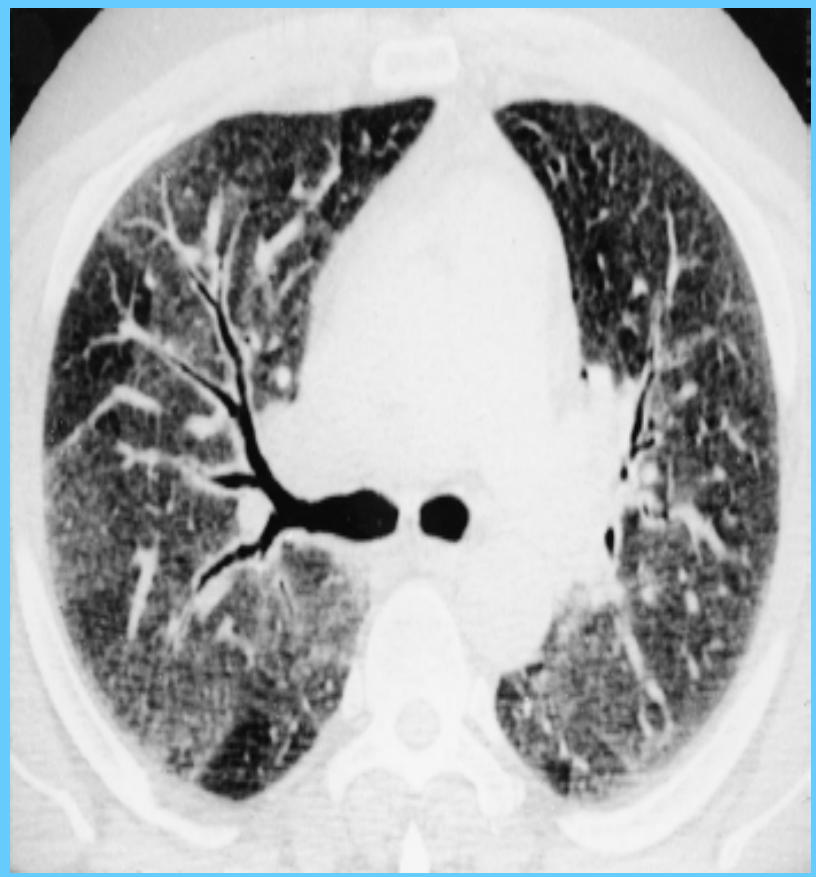
RADIOLOGY - AIP





HRCT – RBILD & DIP





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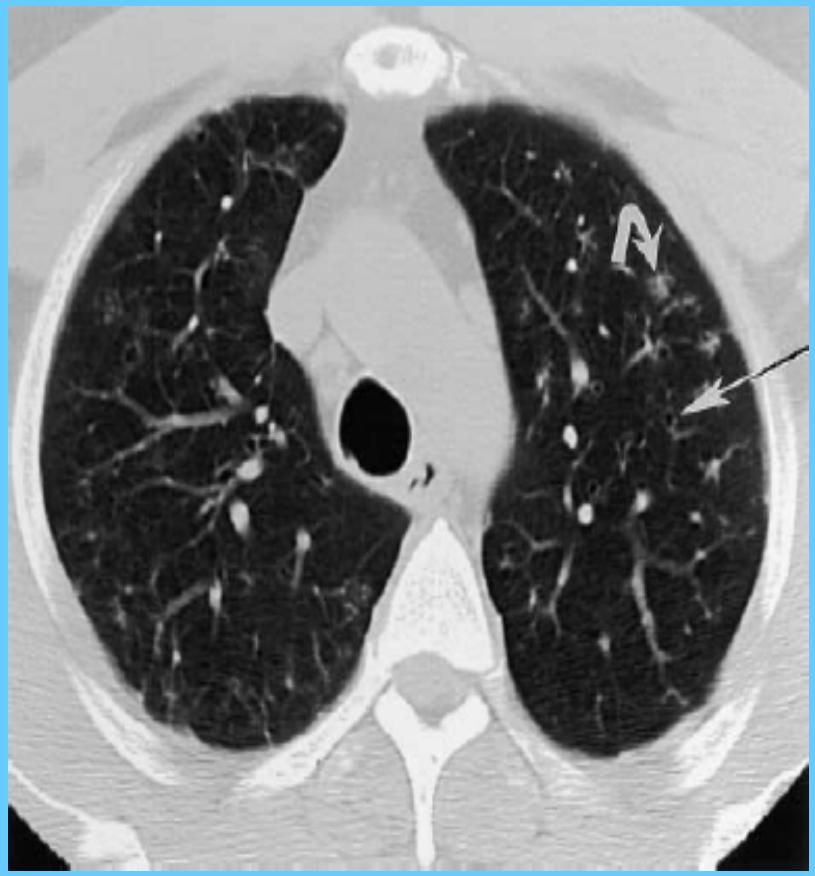
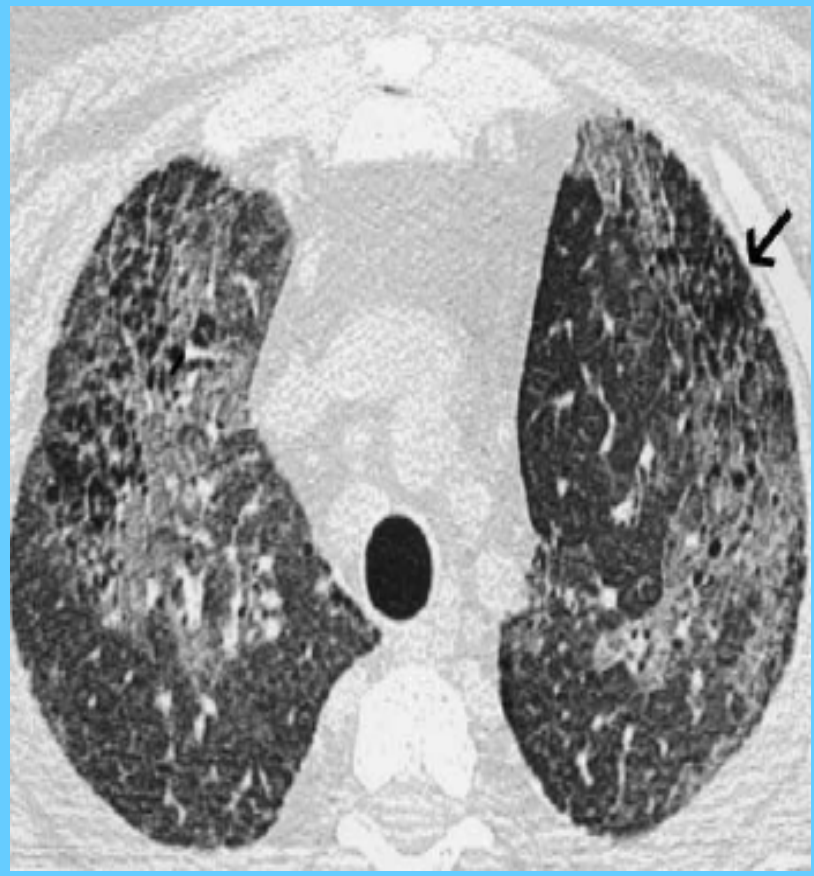
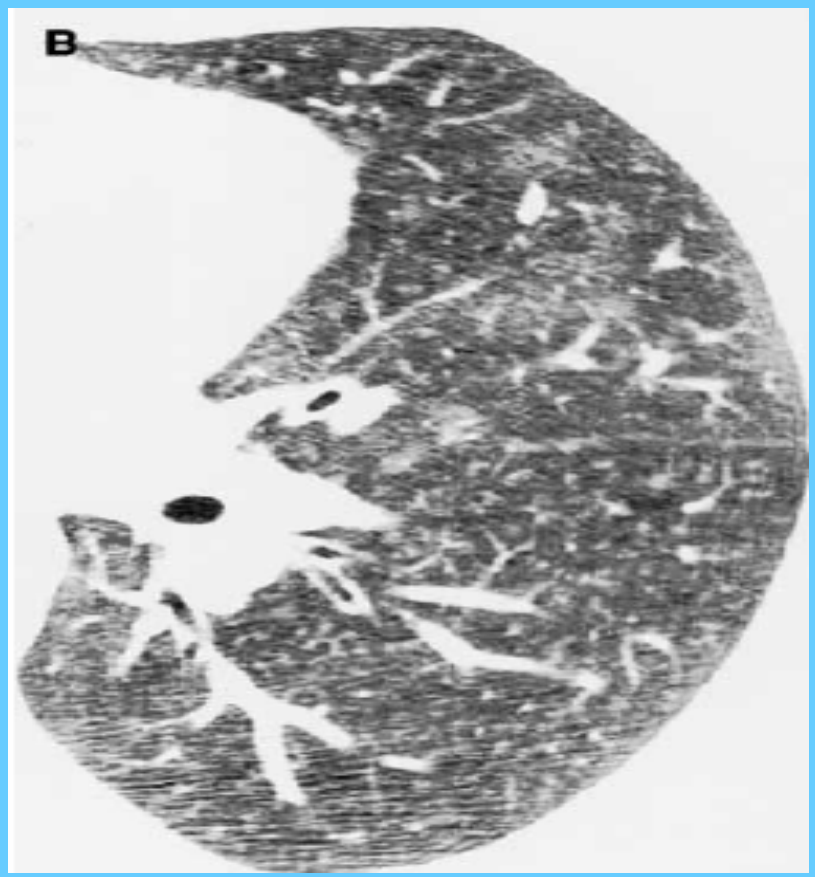
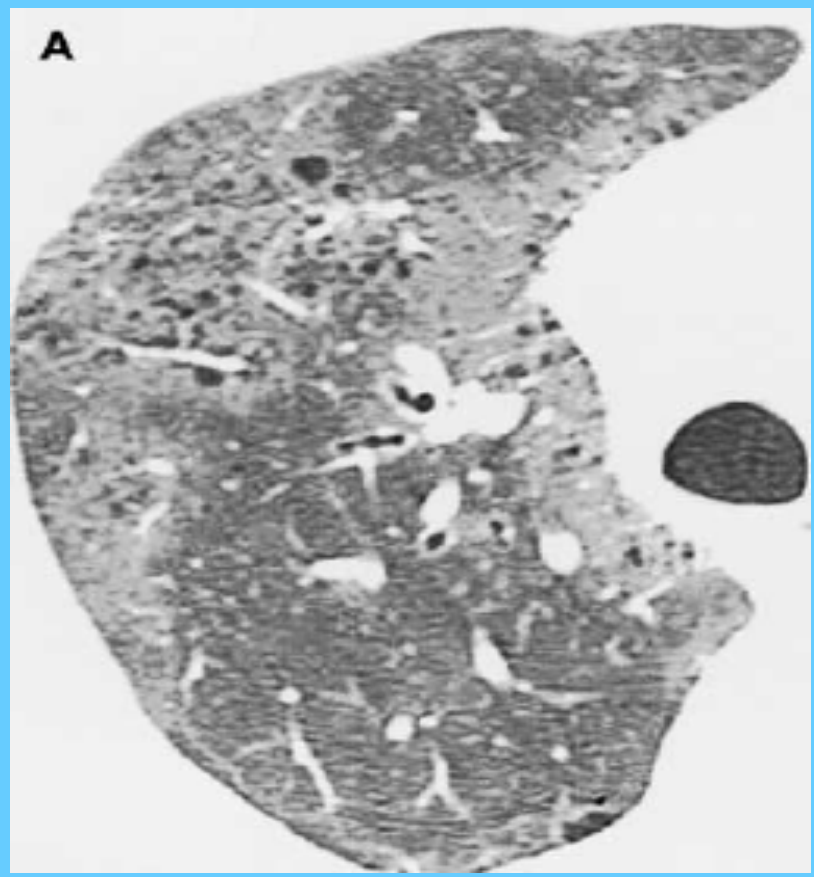


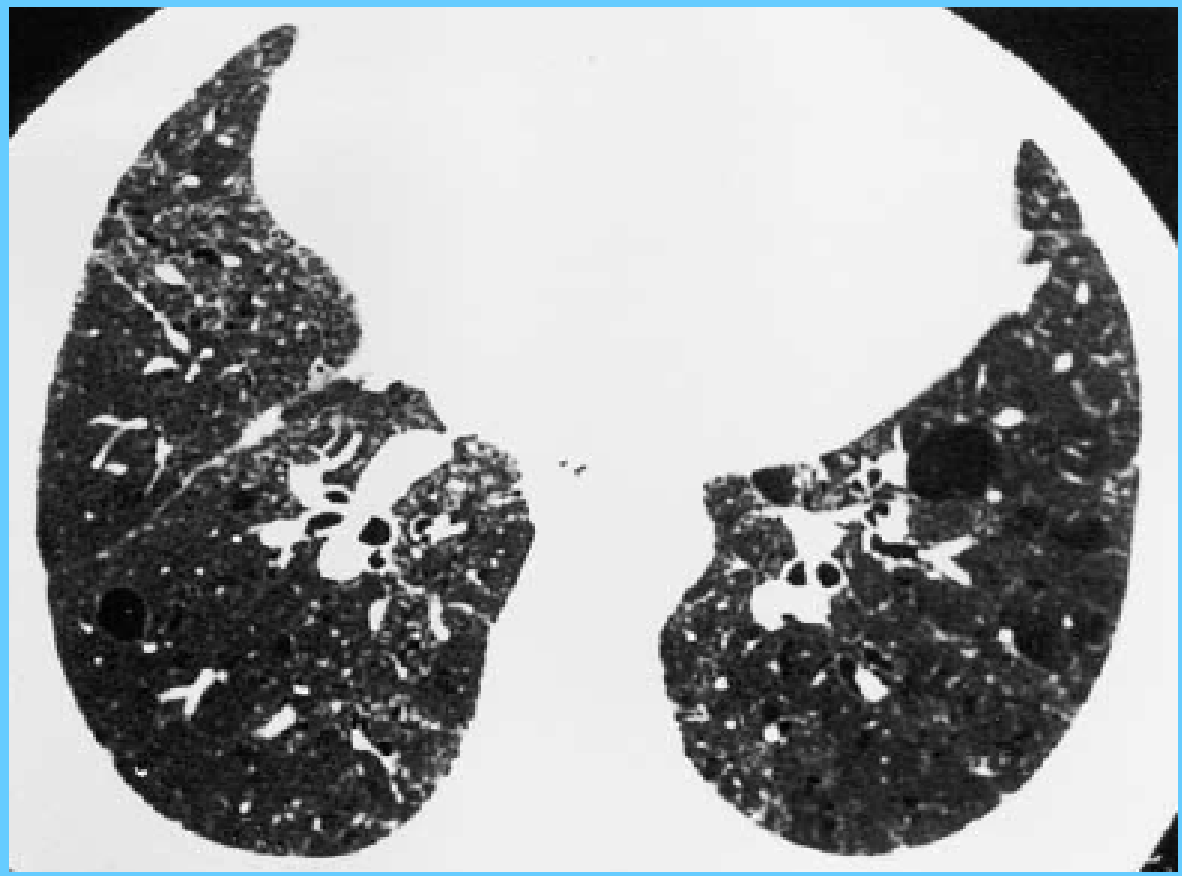


HRCT – RBILD & DIP





HRCT - LIP



COMPARISON IIPs - RADIOLOGICAL

Clinical Diagnosis	Histologic Pattern	Usual Radiographic Features	Typical Distribution on CT	Typical CT Findings	CT Differential Diagnosis
IPF/CFA	UIP	Basal-predominant reticular abnormality with volume loss	Peripheral, subpleural, basal	Reticular, honeycombing Traction bronchiectasis/ bronchiolectasis; architectural distortion. Focal ground glass	Asbestosis Collagen vascular disease Hypersensitivity pneumonitis Sarcoidosis
NSIP, provisional	NSIP	Ground glass and reticular opacity	Peripheral, subpleural, basal, symmetric	Ground glass attenuation Irregular lines Consolidation	UIP, DIP, COP Hypersensitivity pneumonitis
COP	OP	Patchy bilateral consolidation	Subpleural/peribronchial	Patchy consolidation and/or nodules	Infection, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophilic pneumonia, NSIP
AIP	DAD	Progressive diffuse ground glass density/consolidation	Diffuse	Consolidation and ground glass opacity, often with lobular sparing. Traction bronchiectasis later	Hydrostatic edema Pneumonia Acute eosinophilic pneumonia
DIP	DIP	Ground glass opacity	Lower zone, peripheral predominance in most	Ground glass attenuation Reticular lines	RB-ILD Hypersensitivity pneumonitis Sarcoidosis, PCP
RB-ILD	RB	Bronchial wall thickening; ground glass opacity	Diffuse	Bronchial wall thickening Centrilobular nodules Patchy ground glass opacity	DIP NSIP Hypersensitivity pneumonitis
LIP	LIP	Reticular opacities, nodules	Diffuse	Centrilobular nodules, ground glass attenuation, septal and bronchovascular thickening, thin-walled cysts	Sarcoidosis, lymphangitic carcinoma, Langerhans' cell histiocytosis

HISTOPATHOLOGY

IPF/UIP - Histopathology

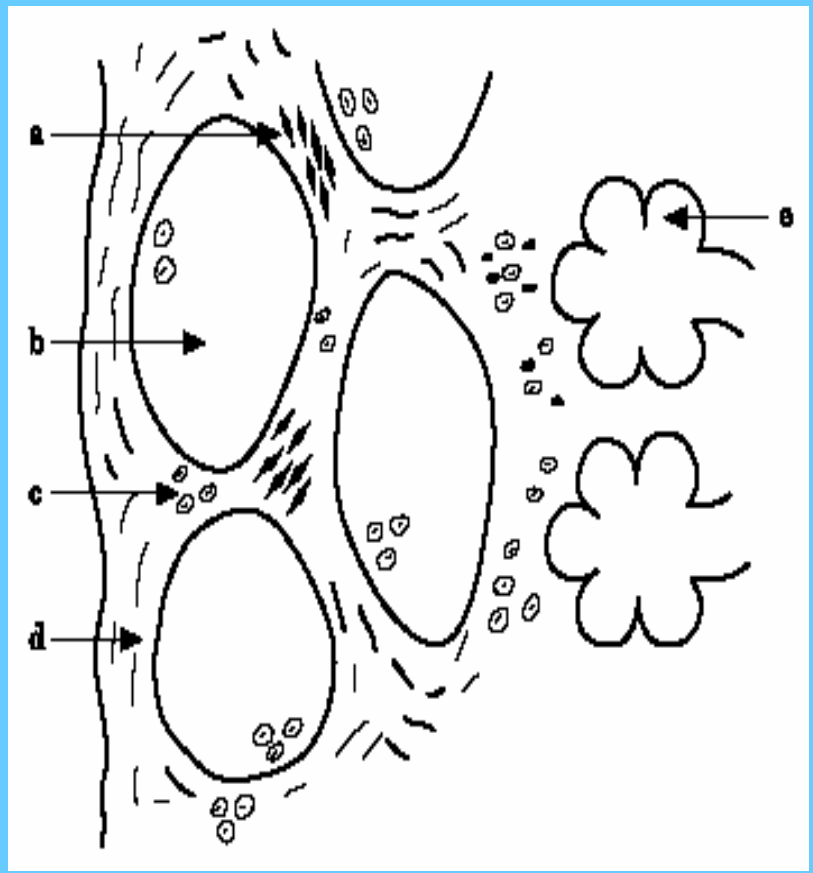
Key Histologic Features

Dense fibrosis causing remodeling of lung architecture with frequent "honeycomb" fibrosis
Fibroblastic foci typically scattered at the edges of dense scars
Patchy lung involvement
Frequent subpleural and paraseptal distribution

Pertinent Negative Findings

Lack of active lesions of other interstitial diseases (i.e., sarcoidosis or Langerhans' cell histiocytosis)
Lack of marked interstitial chronic inflammation
Granulomas: inconspicuous or absent
Lack of substantial inorganic dust deposits, i.e., asbestos bodies (except for carbon black pigment)
Lack of marked eosinophilia

IPF/UIP - Histopathology



(a) = Fibroblast focus

(b) = Cystic air space lined by bronchiolar epithelium & containing scattered infl cells

(c) = Infl cell infiltrate in interstitium

(d) = Area of established fibrosis

(e) = Area of preserved lung parenchyma.

NSIP - Histopathology

Key Histologic Features

Cellular pattern†
- Mild to moderate interstitial chronic inflammation
- Type II pneumocyte hyperplasia in areas of inflammation

Fibrosing pattern†
- Dense or loose interstitial fibrosis lacking the temporal heterogeneity pattern and/or patchy features of UIP
- Lung architecture may appear lost on examination of H&E-stained sections, but relatively preserved with elastic stains
- Interstitial chronic inflammation—mild or moderate

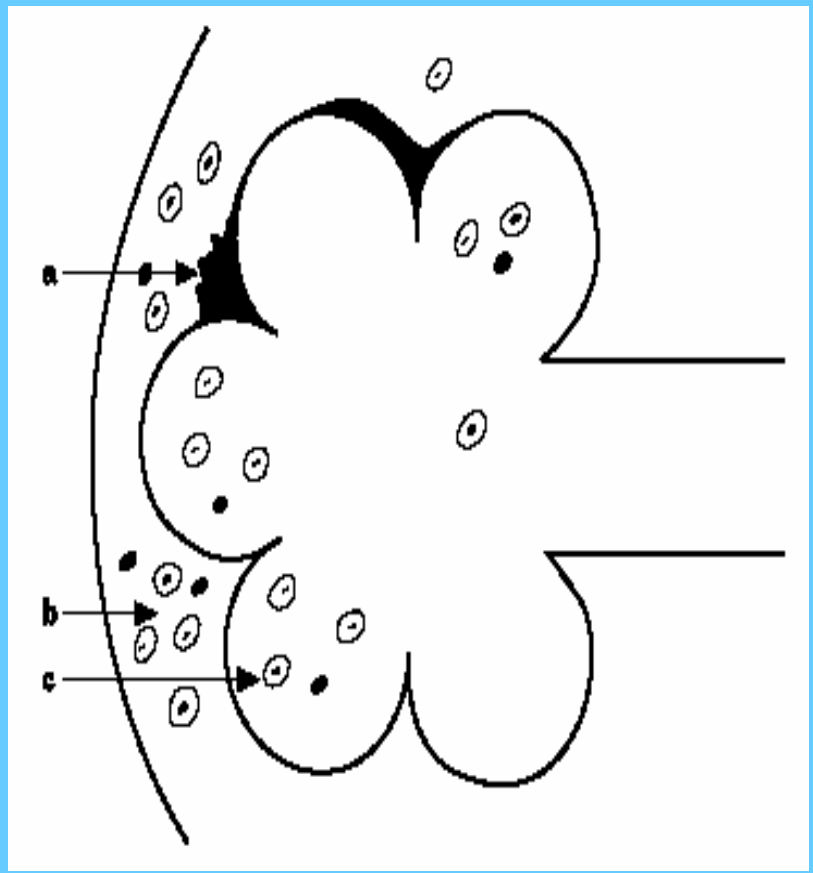
Pertinent Negative Findings

Cellular pattern
- Dense interstitial fibrosis: absent
- Organizing pneumonia is not a prominent feature
- Lack of diffuse severe alveolar septal inflammation

Fibrosing pattern
- Temporal heterogeneity pattern: fibroblastic foci with dense fibrosis are inconspicuous or absent—this is especially important in cases with patchy involvement and subpleural or paraseptal distribution

Both patterns
- Acute lung injury pattern, especially hyaline membranes: absent
- Eosinophils: inconspicuous or absent
- Granulomas: inconspicuous or absent
- Lack of viral inclusions and organisms on special stains for organisms

NSIP - Histopathology



(a) = Variable & patchy fibrosis

(b) = Inflammatory cell infiltration in interstitium

(c) = Alveolar infiltration by infl cells

BOOP/OP - Histopathology

Key Histologic Features

Organizing pneumonia: intralumenal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli)
Patchy distribution
Preservation of lung architecture
Uniform temporal appearance
Mild interstitial chronic inflammation

Pertinent Negative Findings

Lack of interstitial fibrosis (except for incidental scars or apical fibrosis)
Absence of granulomas
Lack of neutrophils or abscesses
Absence of necrosis
Lack of hyaline membranes or prominent airspace fibrin
Lack of prominent infiltration of eosinophils
Absence of vasculitis

AIP/DAD - Histopathology

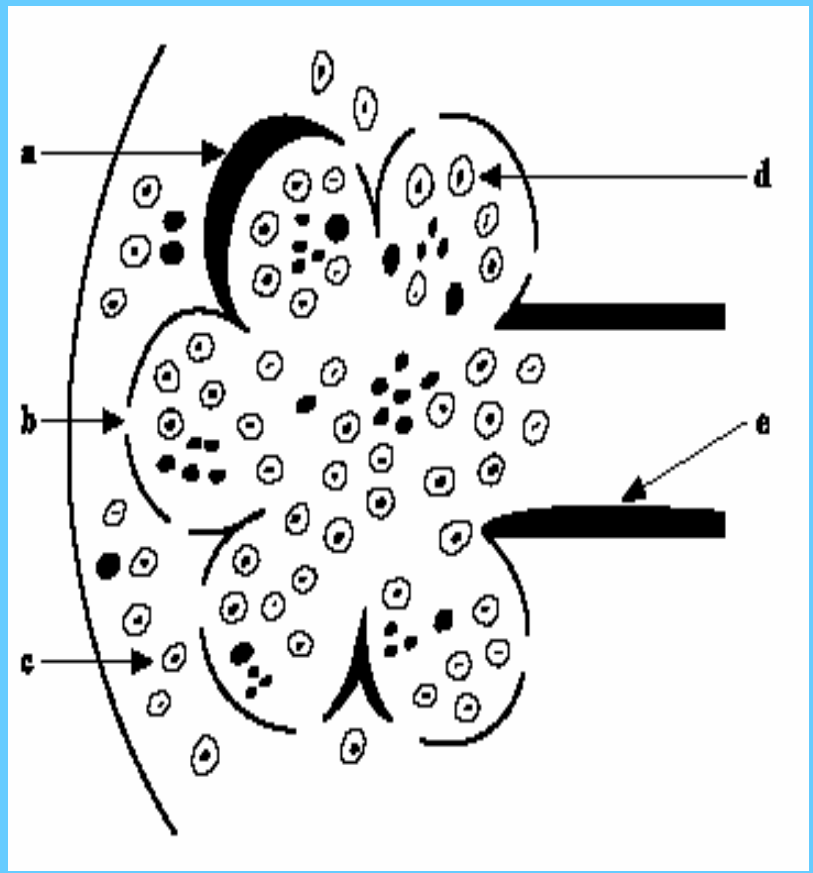
Key Histologic Features

Diffuse distribution
Uniform temporal appearance
Alveolar septal thickening due to organizing fibrosis, usually diffuse
Airspace organization (may be patchy or diffuse)
Hyaline membranes (may be focal or diffuse)

Pertinent Negative Findings

Lack of granulomas, necrosis, or abscesses
Lack of infectious agents (no viral inclusions and negative results with special stains for organisms)
Lack of prominent eosinophils and neutrophils
Negative cultures

AIP/DAD - Histopathology



(a) = Formation of hyaline membrane in alveoli

(b) = Disruption of alveolar lining

(c) = Infl cell infiltrate in interstitium with edema

(d) = Infl cell infiltrate & h'ge within alveoli

(e) = Alveolar duct lined with hyaline memb

RBILD - Histopathology

Key Histologic Features

Bronchiolocentric alveolar macrophage accumulation

Mild bronchiolar fibrosis and chronic inflammation

Macrophages have dusty brown cytoplasm (may be positive for iron stains)

Pertinent Negative Findings

Lack of diffuse macrophage accumulation

Lack of interstitial fibrosis and/or honeycomb fibrosis

DIP - Histopathology

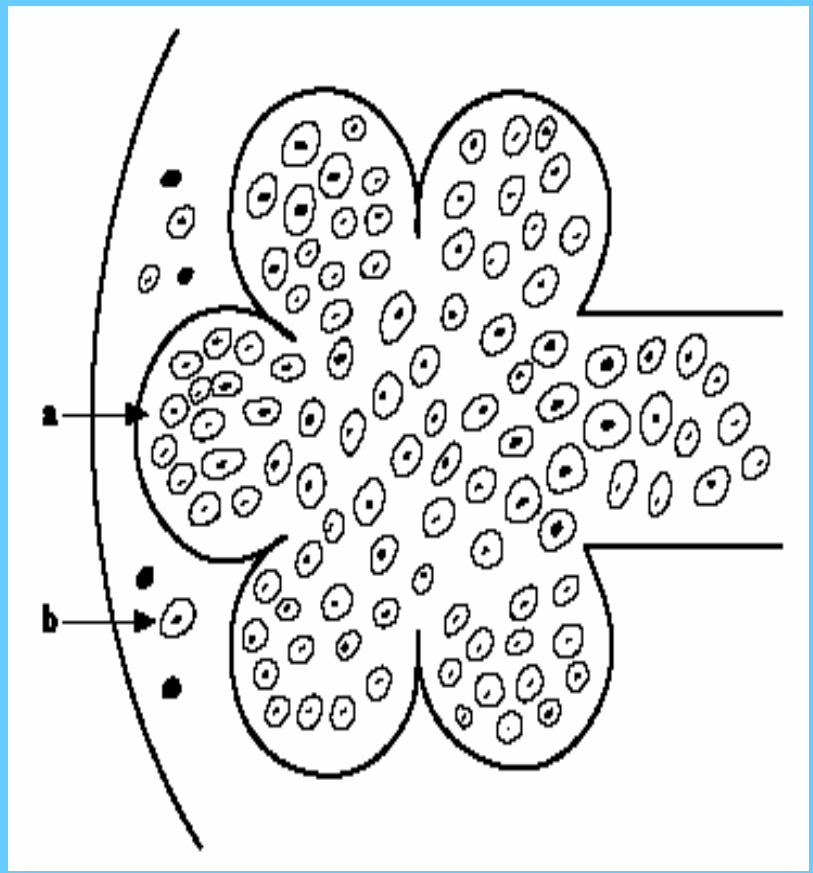
Key Histologic Features

Uniform involvement of lung parenchyma
Prominent accumulation of alveolar macrophages (may show fine granular positivity with iron stains)
Mild to moderate fibrotic thickening of alveolar septa
Mild interstitial chronic inflammation (lymphoid aggregates)

Pertinent Negative Findings

Dense and extensive fibrosis: inconspicuous or absent
Smooth muscle proliferation: inconspicuous or absent
Honeycomb fibrosis absent
Fibroblastic foci and organizing pneumonia: inconspicuous or absent
Eosinophils: inconspicuous, absent, or only focal

DIP - Histopathology



(a) = Moderate to intense macrophage infiltration of alveolar sacs & duct

(b) = Minimal inflammatory cell infiltrate in interstitium

LIP - Histopathology

Key Histologic Features

Diffuse interstitial infiltration of involved areas
Predominantly alveolar septal distribution
Infiltrates comprise mostly T lymphocytes, plasma cells, and macrophages
Lymphoid hyperplasia (MALT hyperplasia)—frequent

Pertinent Negative Findings

Lack of tracking along lymphatic routes (bronchovascular bundles, pleura, and interlobular septa), characteristic of lymphomas
Organizing pneumonia, inconspicuous or absent
Lack of Dutcher bodies
Lack of monoclonal light chain staining pattern of plasma cells (polyclonal pattern present)
Lack of extensive pleural involvement or lymph node involvement
Lack of necrotizing granulomas

COMPARISON IIPs - HISTOLOGICAL

Histologic classification of idiopathic interstitial pneumonias (IIP)

IIP	Site of Injury	D/P	Homo/Hetero	Age of Injury	Special Features
UIP	Subpleural/peripheral lobular	P	Hetero	Cells/fibroblastic foci/scar	–
NSIP	Alveolar septal	D*	Homo	Cells + mild diffuse septal fibrosis	–
DIP	Alveolar septal	D	Homo	Cells + mild diffuse septal fibrosis	Uniform airspace filling by alveolar macrophages
RB/ILD	Bronchiolocentric	P	Homo	Cells + mild bronchiolocentric fibrosis	Centrilobular alveolar macrophages
COP	Bronchiolocentric	P	Homo	Airspace + interstitial granulation tissue	–
LIP	Alveolar septal	D*	Homo	Cells	–

Definition of abbreviations: D, diffuse; Hetero, temporally heterogenous; Homo, temporally homogenous; P, patchy.

TREATMENT

TREATMENT

- Rx of IPF remains at best controversial till date.
- Role of ‘conventional’ therapy – corticosteroids, immunosuppressants and cytotoxic drugs uncertain in IPF/UIP – no documented benefit on survival /quality of life (Bx proven UIP <15% response to any Rx and IPF invariably fatal with mean survival of 2-4 yrs).
- Initial reports of good response to steroids possibly misleading (either without Bx or no histopathological differentiation – IIPs other than IPF/UIP also included).
- Use of high dose steroids not indicated in IPF.

TREATMENT

- Low dose steroids not indicated in presence of ch course, extensive fibrosis or absence of GGO.
- Trial of Azathioprine (OR Cyclophosphamide?) + Prednisolone usually warranted in most pts:
  1. Young age
  2. GGO on HRCT
  3. Clinical or phsiological impairment
  4. Subacute or deteriorating course
- Prednisolone 0.5 mg/kg/d x 4-8 wks → taper to 20 mg/d x 3-4 m. Beyond 3 m, continue only if objective response to Rx. Individualize dose & duration of steroids (response + adverse effects)

TREATMENT

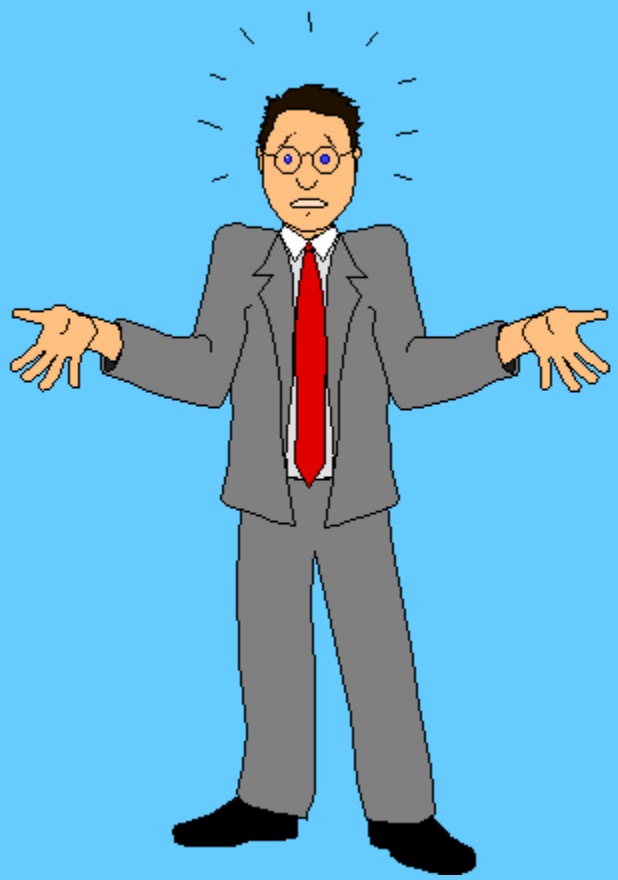
- Response best in young age, female sex, less functional impairment
- Cyclophosphamide alone ineffective. No adv of i/v pulse over oral. Significant adverse effects/toxicity → not routinely recommended
- Azathioprine – Reported response better. Might benefit symptomatic pts with progressive disease by 6m Rx with oral 2 mg/kg/d. DB Prosp RCT (27 pts) - combination with prednisolone ↓ long term mortality (statistically NS) – no objective (DL_{CO} & A-a O_2 grad) or mortality benefit at 1 yr.

(*Raghu G et al, Am Rev Respir Dis, 1991*)

TREATMENT

- Cyclosporin – Use in IPF rare – data on efficacy in humans limited to few case reports (?favourable)
- Mycophenolate mofetil – Not evaluated in humans with IPF/UIP

TREATMENT

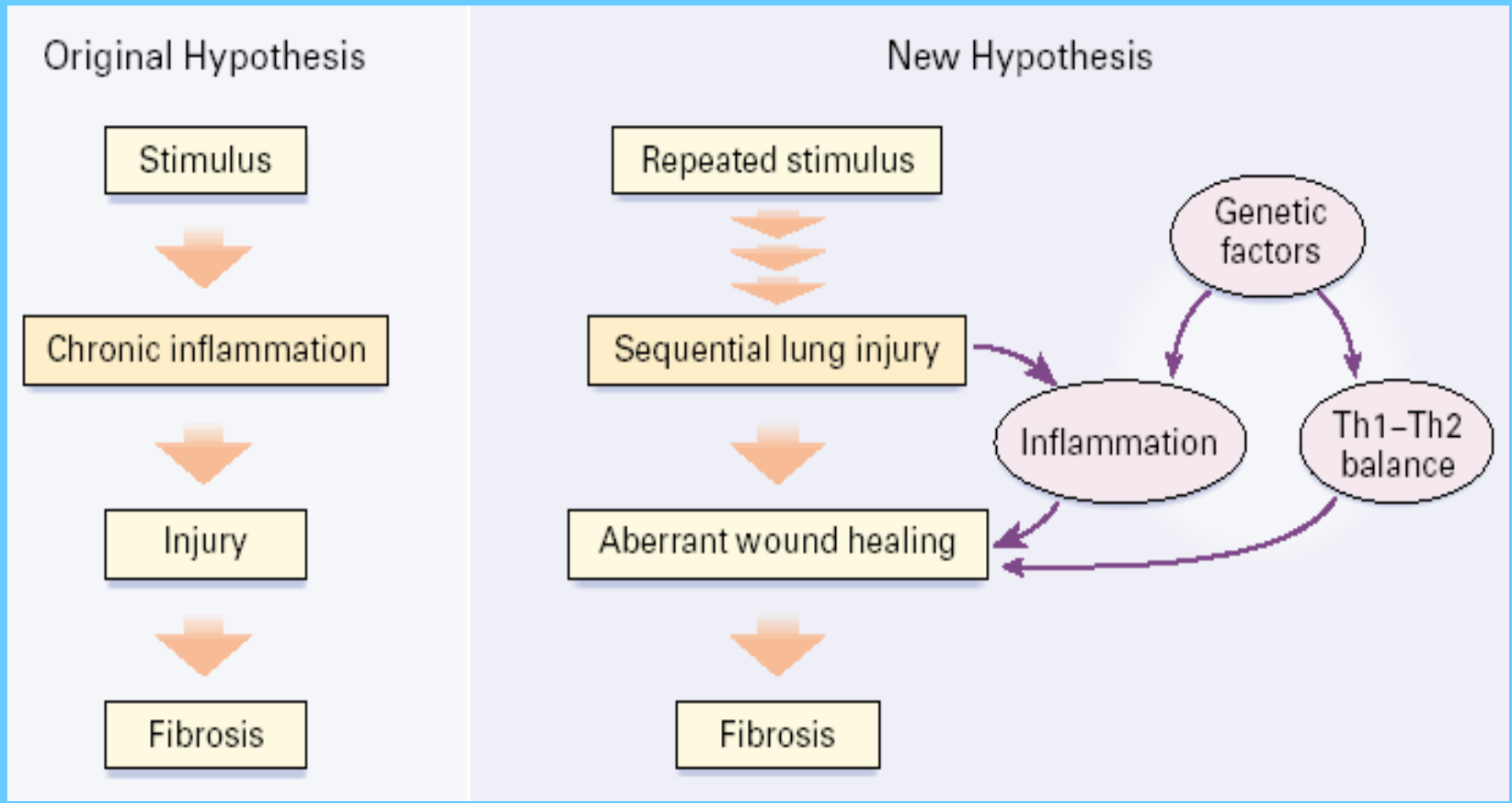


These don't seem to work!

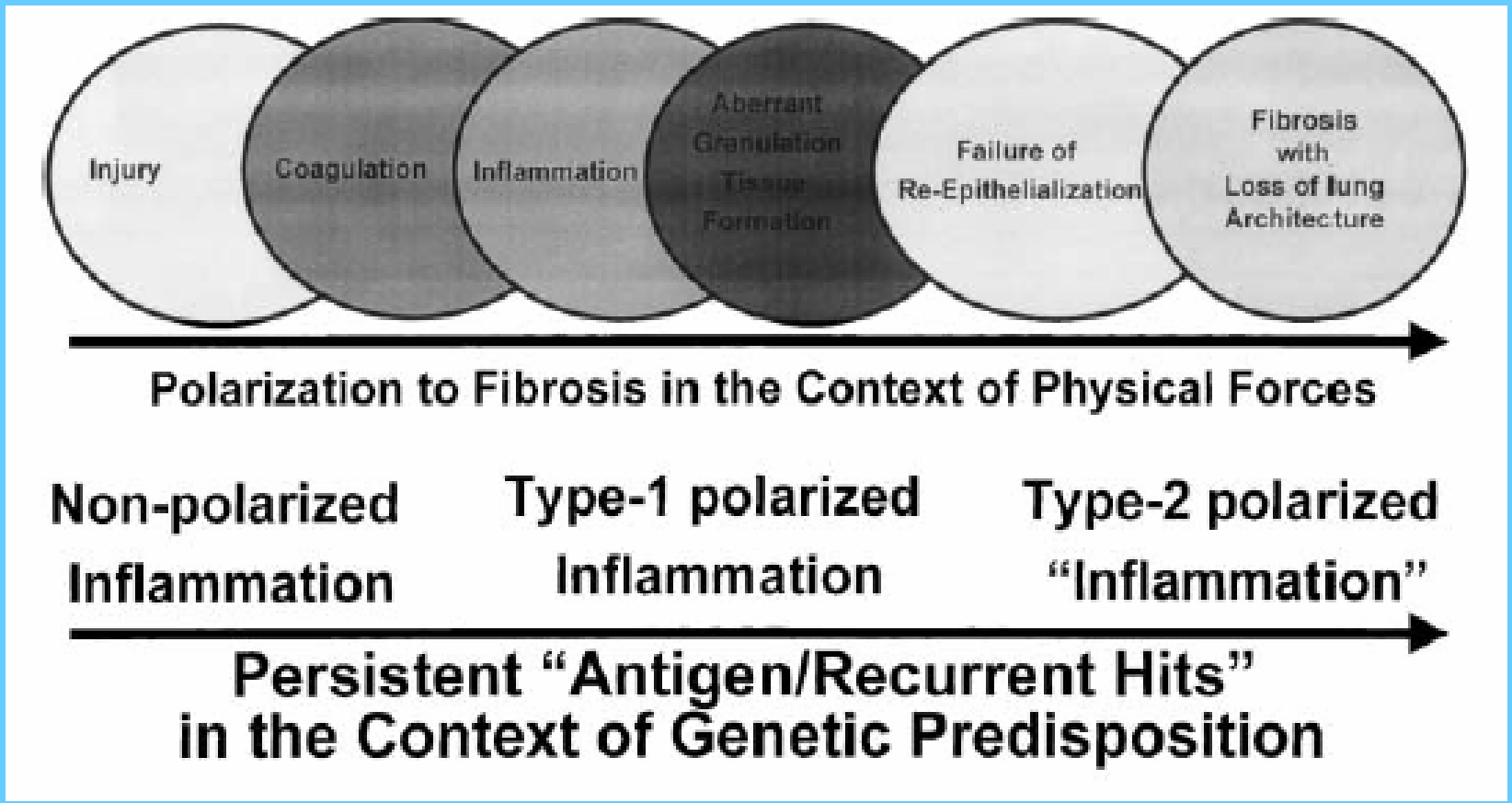
WHERE DO WE GO FROM HERE?

Try Something New!

TREATMENT


Original Hypothesis
Stimulus
Chronic inflammation
Injury
Fibrosis
New Hypothesis
Repeated stimulus
Sequential lung injury
Aberrant wound healing
Fibrosis
Genetic factors
Inflammation
Th1–Th2 balance

TREATMENT


Injury
Coagulation
Inflammation
Aberrant Granulation Tissue Formation
Failure of Re-Epithelialization
Fibrosis with Loss of lung Architecture
Polarization to Fibrosis in the Context of Physical Forces
Non-polarized Inflammation
Type-1 polarized Inflammation
Type-2 polarized "Inflammation"
Persistent "Antigen/Recurrent Hits" in the Context of Genetic Predisposition

TREATMENT

- Novel Approaches (based on targetting fibroproliferative phase rather than controlling inflammation – the 'conventional' approach)

1. IFN-γ1b :

- Antifibrotic effects via multiple mechanisms (incl #- of fibroblast proliferation & collagen synthesis)
- Pts with IPF found deficient in IFN-γ1b on immunohistochemical studies
- Largest study so far had 330 pts randomized to low dose prednisolone + IFN-γ1b OR placebo.

(*Raghu G et al, NEJM, 2004*)

TREATMENT

- Lower mortality seen in study group (10% vs 17%) (statistically NS).
- ↑ incidence of pneumonias & constitutional symptoms.
- Can lead to fibrogenesis under certain conditions (pro-fibrotic effect)

2. PIRFENIDONE:

- Retards pul fibrosis in exp animals
- Multiple mechanisms proposed (incl #- of TGF β mediated collagen synthesis)

TREATMENT

- Used in 54 pts → discontinuation of conventional Rx (83%), stabilization /improvement in PFT at 6m and ?improved survival at 1 & 2 yrs follow up.

  (*Raghu G et al, AJRCCM, 1999*)
- Commercially not available

3. ACETYLCYSTEINE –

- Stimulates glutathione synthesis (anti-oxidant)

TREATMENT

- 20 pts with pul fibrosis (IPF/CTD assoc) Rx 600 mg tds x 3 m → ↑ total & reduced glutathione levels in BAL fluid but no significant changes in BAL TC/DC or PFT.

(*Behr J et al, AJRCCM, 1997*)

4. D-PENICILLAMINE

- Blocks collagen synthesis and deposition at multiple levels
- No improvement in PFT or survival
- Not recommended for use in IPF

TREATMENT

5. COLCHICINE

- #- both inflammatory & fibrotic components – effect on latter dominant (esp binding of µ-tubular proteins reqd for cellular mitosis & #- of collagen/GFs reqd for fibroblast proliferation)
- No survival benefit or improvement in PFT
- No recommendations for use in IPF

TREATMENT

FUTURE TARGETS FOR THERAPY

1. ALVEOLAR EPITHELIAL CELL

   – Injury to alveolar epithelial cells consistent and early feature of IPF.

   – Delay in/inability of alveolar epithelial cells to regenerate→ delay in re-epithelialisation and promotion of fibrosis

   –Promoting regeneration of alveolar epithelial cells.

TREATMENT

FUTURE TARGETS FOR THERAPY

2. FIBROBLAST/MYOFIBROBLAST

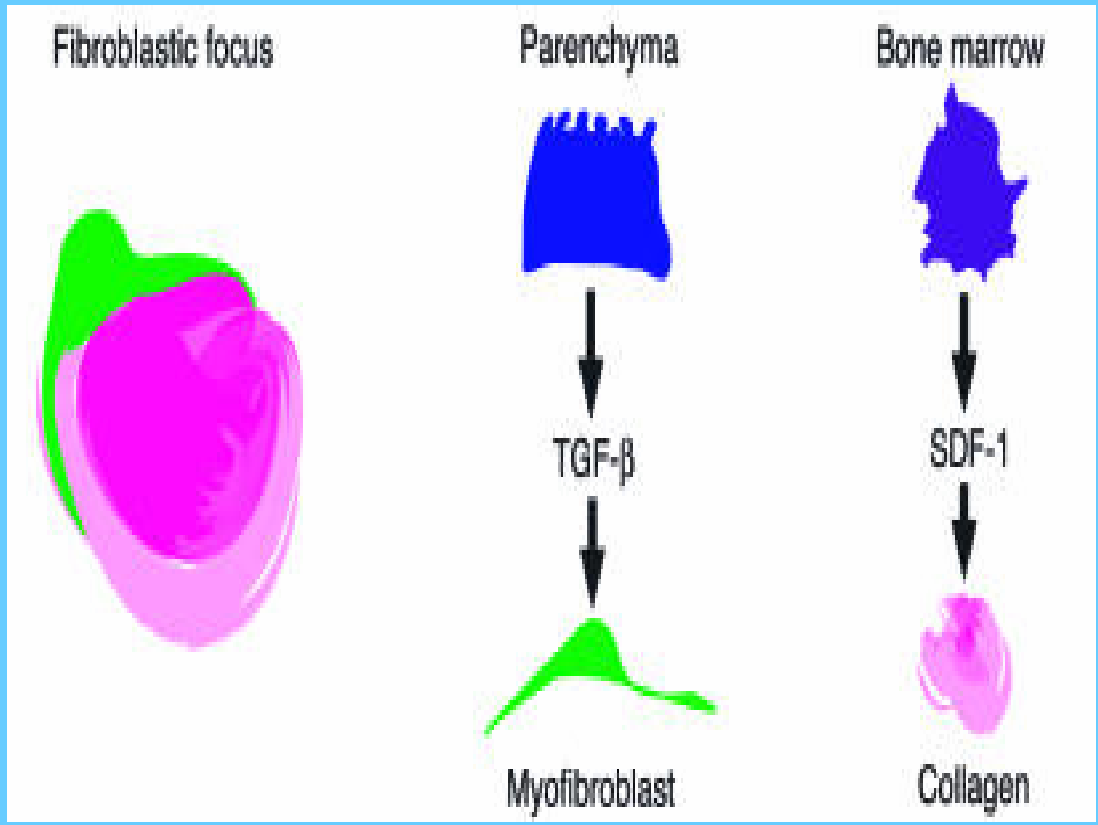
– Fibroblastic foci → sites of active collagen synthesis & pathologic hallmark of pul fibrosis.

– Cytokine secretion by epithelial and infl cells induces parenchymal lung fibroblasts to overproduce collagen and to differentiate into myofibroblasts.

– Recent studies on origin of fibroblastic foci suggest that bone marrow derived cells can engraft into lung tissue & produce collagen. These cells can be recruited to the lung by chemokines released by macrophages

TREATMENT

FUTURE TARGETS FOR THERAPY



SDF –1 = Stromal Cell–derived Factor-1

TREATMENT

ALVEOLAR EPITHELIAL CELL

1. Mitogens for Alveolar Epithelial Cells

- Keratinocyte Growth Factor (KGF)
  - – potent stimulus for growth of type II alv epithelial cells *in vitro* as well as *in vivo*.
- Hepatocyte Growth Factor (HGF)
  - – acts as ligand for tyrosine kinase receptor
  - – antiapoptotic action + promotion of epithelial growth

TREATMENT

ALVEOLAR EPITHELIAL CELL

2. Stem Cell Progenitors of Alveolar Epithelium

Multipotent stem cells seen to differentiate into resp epithelium in exp animals esp:

- Bone marrow derived progenitor cells
- Mesenchymal stem cells

TREATMENT

FIBROBLAST/MYOFIBROBLAST

1. Inhibition of Fibroblast Migration/proliferation

- Phosphodiesterase #$^{-}$ (Rolipram & Cilomilast)
  - #$^{-}$ chemotaxis of fibroblasts towards fibronectin
- PGE_2
  - Reduced synthesis in fibroblasts from pts with IPF
  - #$^{-}$ proliferation & chemotaxis of fibroblasts (and collagen production)

TREATMENT

FIBROBLAST/MYOFIBROBLAST

- 5-Lipoxygenase #$^{-}$ (Zileuton)
  - LT ↑ in lungs of pts with IPF (LT B_4 ↑ in BAL fluid) → profibrotic effect
- Prostacyclin (PGI_2) (Epoprostenol)
  - Antifibrotic + antihypertensive effects (pts with 2º pul HTN)

2. Inducers of Fibroblast/myofibroblast apoptosis

- HMG CoA Reductase #$^{-}$ (statins esp lovastatin)
  - Induce apoptosis of several cell types incl fibroblasts/myofibroblasts and s.m.cells

TREATMENT

FIBROBLAST/MYOFIBROBLAST

3. Inhibitors of ECM Production

- Relaxin
  - – Pregnancy associated peptide hormone
  - – ↓ synthesis & expression of collagens in interstitium and fibronectin
  - – ↑ collagenase-1 → ↑ breakdown of collagen

4. Deactivating Myofibroblasts

- Prolyl 4-hydoxylase #- (Lufironil & Safironil)
- Trans-reversatrol

TREATMENT

OTHER MODALITIES

- Transforming Growth Factor β
  - Profibrotic cytokine
  - Soluble TGF β Receptor and anti-TGF β Ab used in exp models.
  - No data on efficacy in humans
- Tumour Necrosis Factor α

  Overexpression of TNF α → increased inflammation → stimulation of fibroblast proliferation & collagen gene upregulation

TREATMENT

OTHER MODALITIES

- Endothelin-1 Antagonists (Bosentan)

  Endothelin is a mitogenic peptide → proliferation of fibroblasts, ↑ production of collagen, ↓ production of collagenase
- Gene Therapy (HGF & TGF β)

  Gene modification, gene transfer
- Antisense Oligonucleotides

  #- transcription → #- expression of genes → ↓/#- protein synthesis

TREATMENT

- Many drugs that have antifibrotic effects *in vitro* are ineffective *in vivo*.
- Most drugs tested *in vitro* have been in models of bleomycin induced lung fibrosis – effects may be diff in IIPs (incl IPF)
- Most drugs tested before or simultaneously with induction of lung injury – most pts with IPF present after fibrosis well established.
- Many drugs (targetted at cytokines/GF) effective in retarding fibrosis but may exert significant adverse effects (e.g. promotion of neoplastic transformation/growth by TGF-β)

TREATMENT - NSIP

- Corticosteroids mainstay of Rx
- Overall prognosis > IPF
- Type 1 (cellular) > Type 2 (fibrotic pattern)
- Pred GGO with min fibrosis (pred infl cell infiltrate) → ~ complete resolution to Rx with steroids
- Fibrotic type → 5 yr survival ~ 45%

TREATMENT - BOOP

- Corticosteroids mainstay of Rx (>6m)
- Good response
- Symptomatic benefit seen in 48 hrs
- Complete resolution may take several weeks
- Relapses common within 1-3 m of tapering/stopping steroids
- 1/3 have persistent symptoms
- Few cases progress to end stage pul fibrosis

TREATMENT - AIP

- Poor prognosis
- Mortality rate of 60-100% irrespective of nature of Rx used. Most deaths 1-2 m of onset of illness
- Rx incl steroids/immunosupressants + O_2/ventilatory support.
- Pts who recover, may have only mild residual abn of pul f_x or ch progressive ILD or recurrences

TREATMENT – RBILD/DIP

- RBILD – Spontaneous resolutions known. Good response to cessation of smoking and Rx with steroids. Does not progress to end stage fibrosis.

  DIP – Good response to cessation of smoking and Rx with steroids but relapses on withdrawal common → req for maintenance doses and/or high dose regimens. Rarely progresses to end stage fibrosis. Better prognosis than IPF (~ 1/3 recover completely while ~ 1/4 die. 10 yr survival ~ 70%).

TREATMENT - LIP

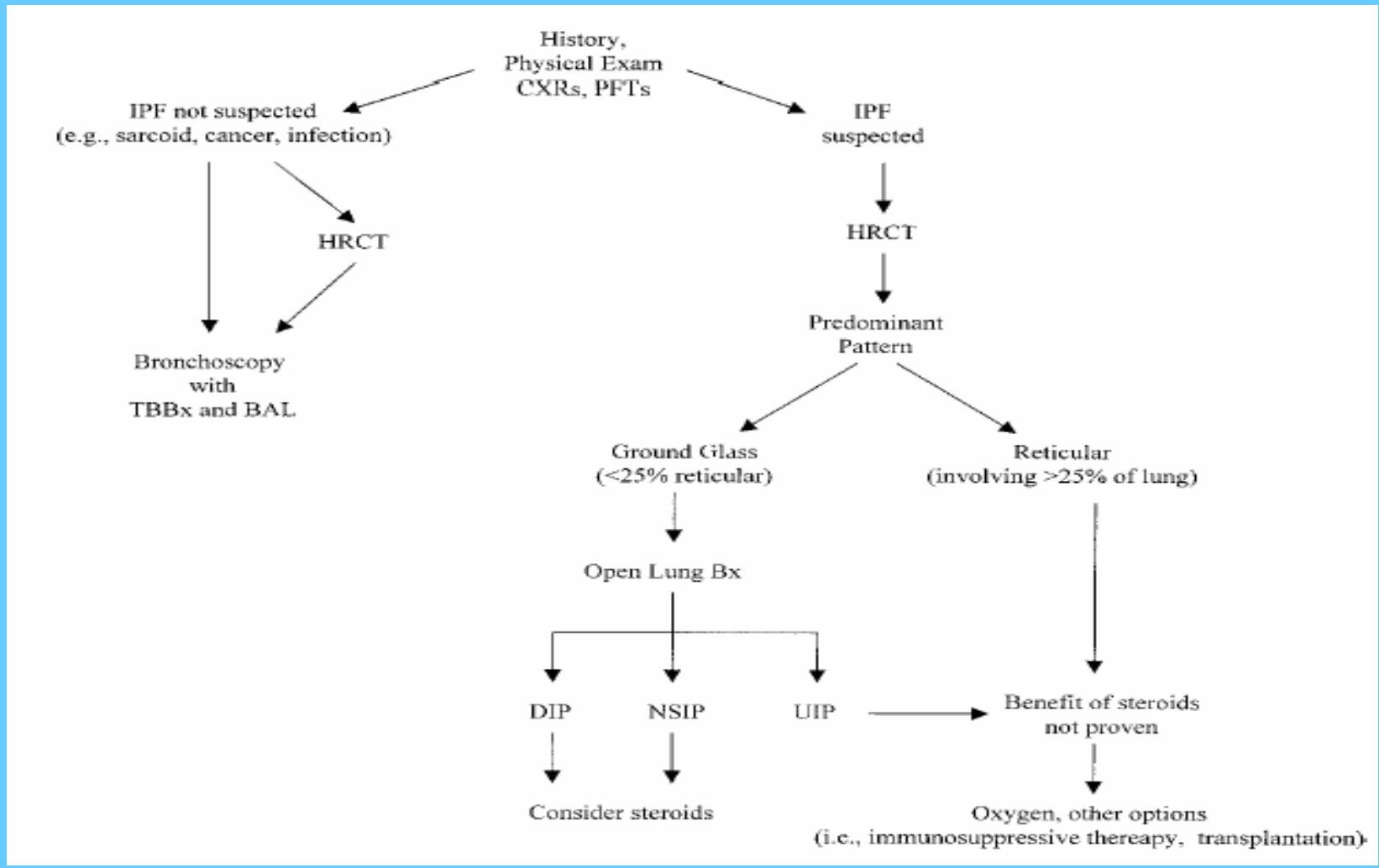
- Rx with corticosteroids
- Immunosuppressants may be tried
- Maj show improvement
- 1/3 progress despite Rx

CONCLUSION

COMPARISON IIPs - OVERALL

Feature	Usual interstitial pneumonitis (UIP)	Non-specific interstitial pneumonitis (NSIP)	Desquamative interstitial pneumonitis (DIP)	Respiratory bronchiolitis–interstitial lung disease (RB–ILD)	Acute interstitial pneumonitis (AIP)
Main pathological features	Honeycombing fibrosis with prominent fibroblast foci	Variable interstitial fibrosis and inflammation	Intra-alveolar macrophage accumulation	Peri-bronchiolar macrophage accumulation	Diffuse alveolar damage with hyaline membrane formation
Onset	Insidious	Sub-acute or insidious	Insidious or sub-acute	Insidious	Acute
Average mortality (and survival from diagnosis)	68% (6 years)	11%	27% (12 years)	0%	62% (2 months)
Main imaging features	Peripheral basal reticular pattern with honeycombing on CXR and HRCT	Variable pattern with ground glass opacity dominating on HRCT	Diffuse ground glass pattern on HRCT	Patchy peripheral ground glass opacity with nodularity on HRCT	Bilateral air space consolidation and ground glass background
Response to steroids	Poor	Good	Good	Good	Poor
Complete recovery possible?	No	Yes	Yes	Yes	Yes

IIPs- OVERVIEW



Thank you