Introduction to Interstitial Lung Disease (ILD)

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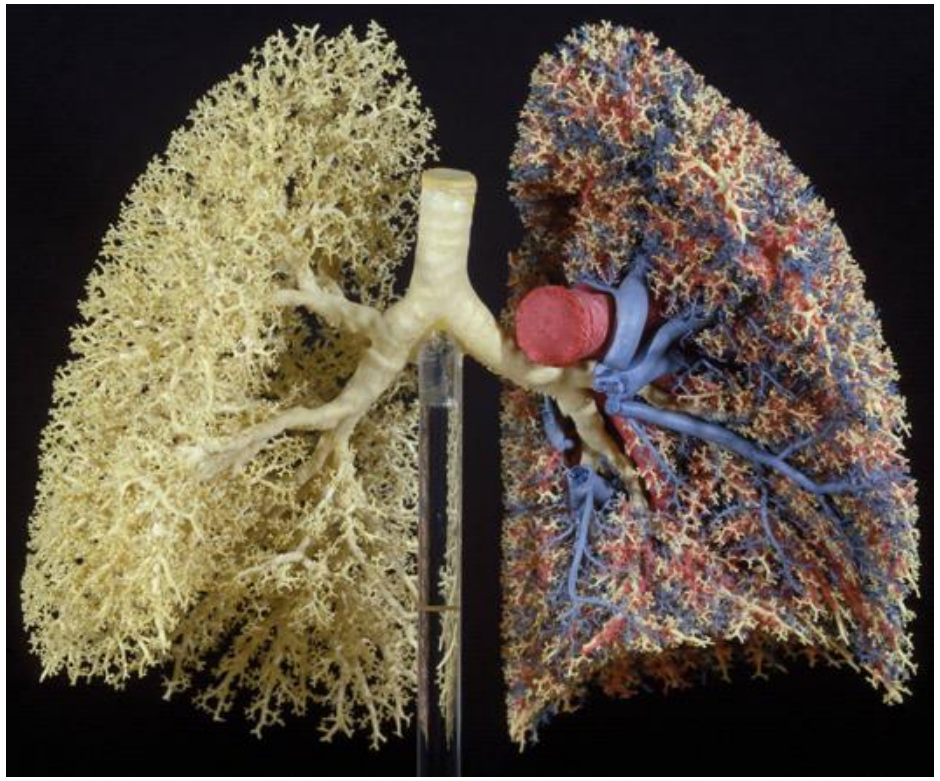


Objectives

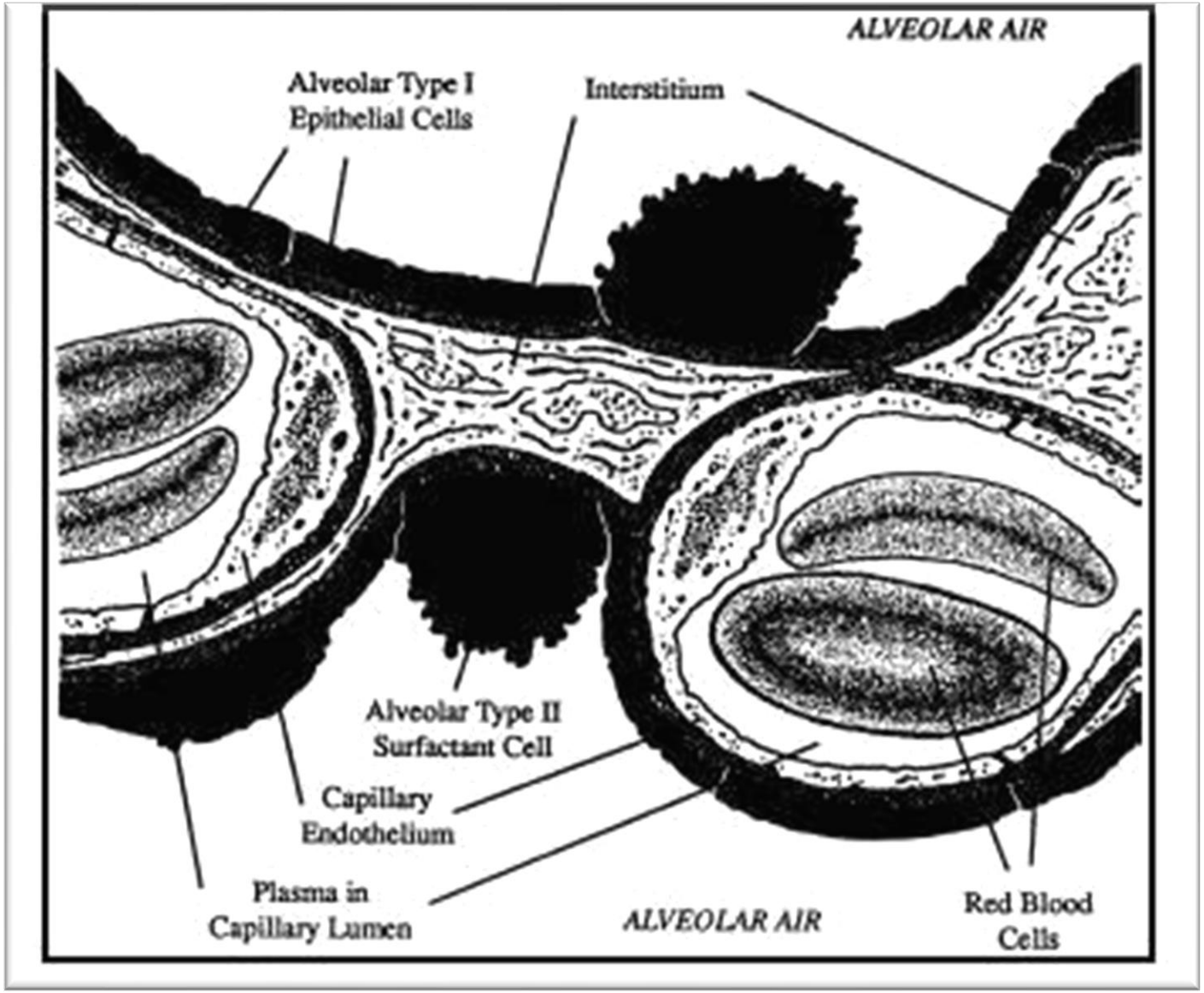
- Introduction and classification of ILDs
- Micro-Anatomy of the lung
- Clinical signs and symptoms of ILDs
- Testing
- IPF/HP Focus

Introduction To ILDs

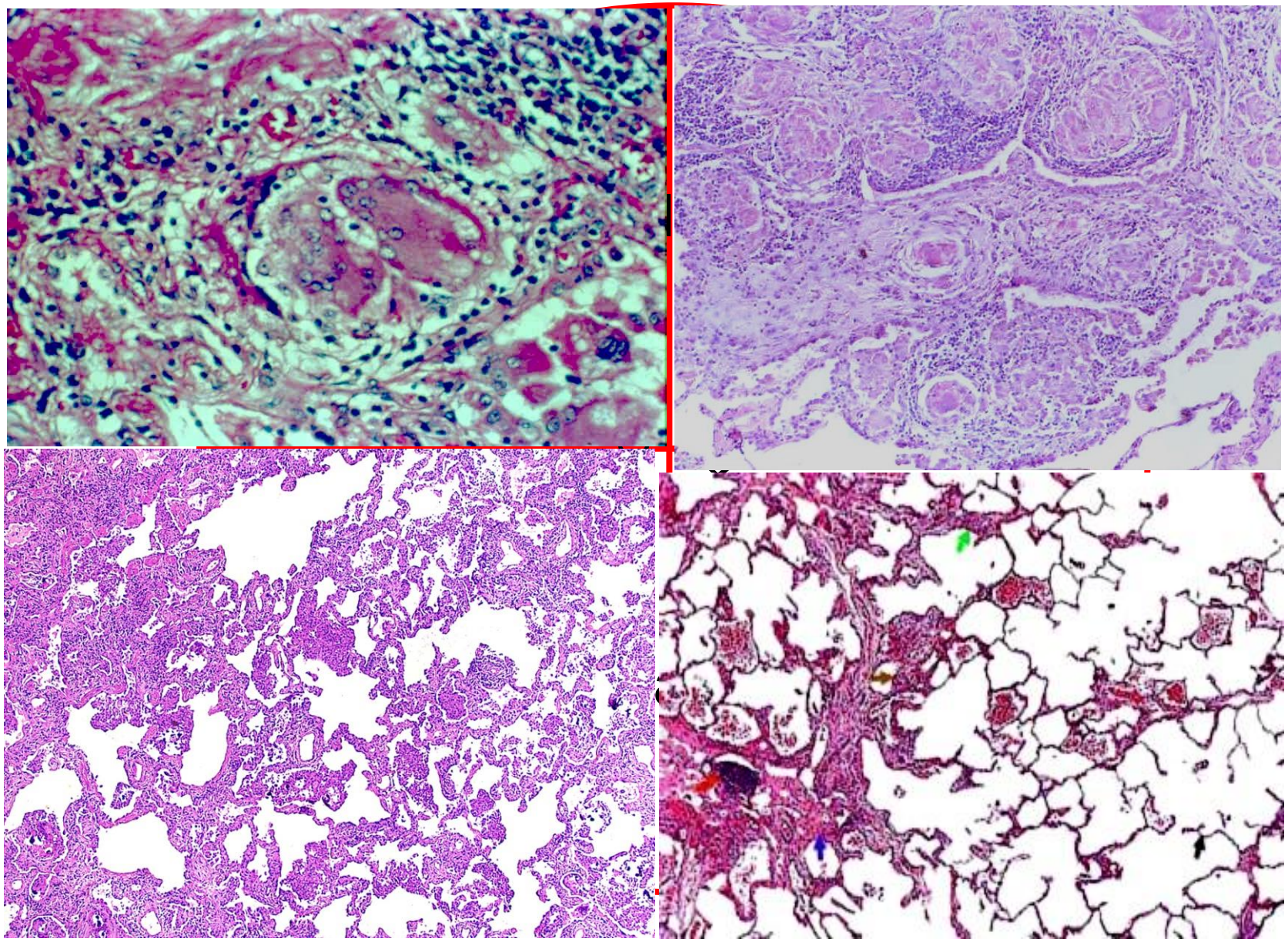
- Diverse group of pulmonary disorders classified based on their similar
  - **Clinical**
  - **Radiographic**
  - **Physiologic**
  - **Pathologic manifestations**
- Can affect airways, blood vessels and pleura
- **Excludes** emphysema, RADs, Pulmonary vascular disease

Micro Anatomy and Structure of the Lungs

- The anatomic space lined by alveolar **epithelial** cells and capillary **endothelial** cells share a common **basement membrane**
- Contains connective tissue elements such as collagen, elastin ECM, fibroblasts



World of ILD



The IIP's

- **Idiopathic Pulmonary Fibrosis (IPF)**
- Acute Interstitial Pneumonia (AIP)
- Non-Specific Interstitial Pneumonitis (NSIP)
- Smoking-related IIP
  - Respiratory Bronchiolitis (RB)
  - Respiratory Bronchiolitis – ILD (RBILD)
  - Desquamative Interstitial Pneumonitis (DIP)
- Cryptogenic Organizing Pneumonia (COP); formerly Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)
- Lymphocytic Interstitial Pneumonia (LIP)

Pathogenesis

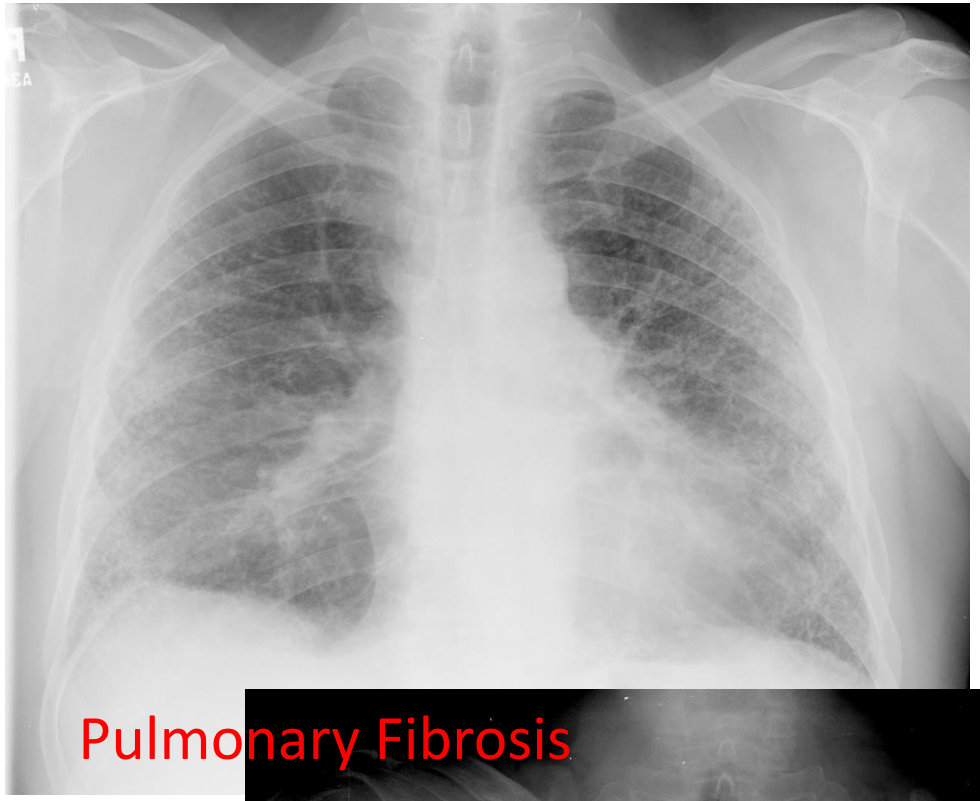
- Pathogenesis of the majority of ILD remains unknown
- Injury to the alveolar epithelial cells- leads to an inflammatory response.
- Dysregulated repair mechanisms leads to scaring and structural changes responsible for clinical findings.
- Injury can be introduced through the airways- via inhalation, or the circulation

Clinical features

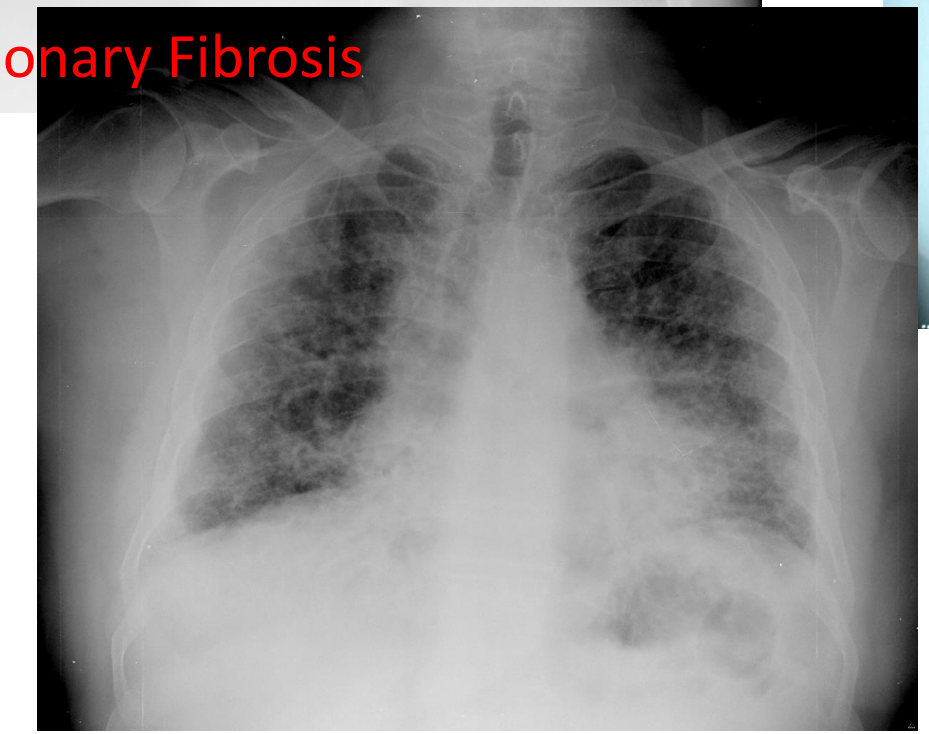
- Shortness of Breath
  - Dyspnea on exertion
  - SOA
  - Tachypnea
- Cough - Typically nonproductive
- Crackles or “dry rales” with inspiration
- Symptoms and signs of right heart failure
- Restriction on PFTs, Decreased DLCO
- **Chest pain is uncommon**
- **Fever is not a primary finding in ILD**

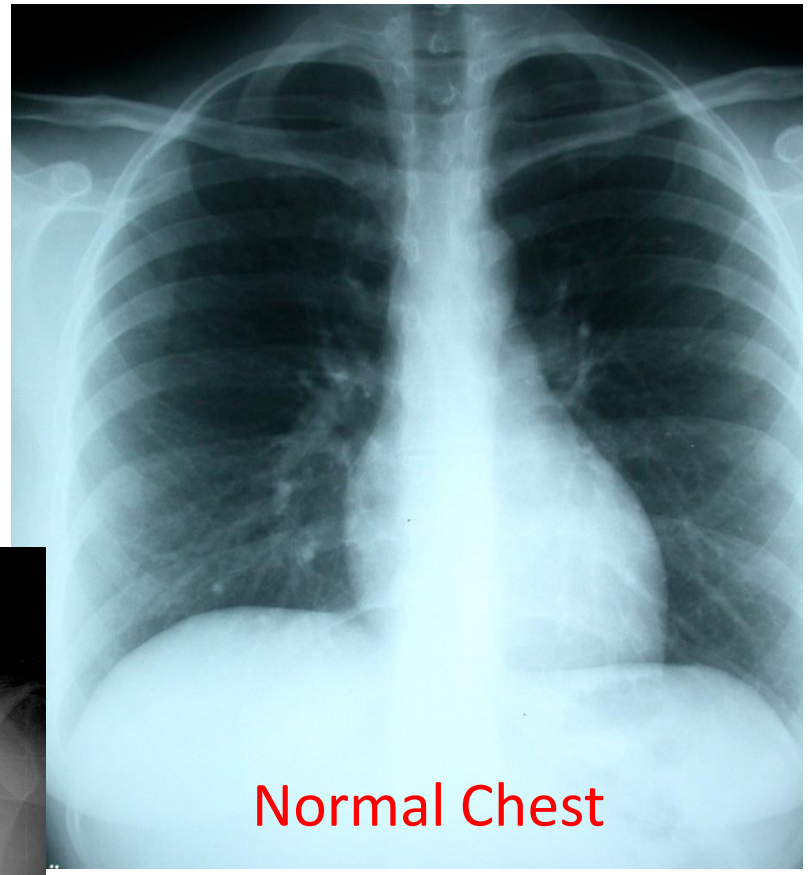
Initial Evaluation

- History and Physical!!!!!!!
- Imaging
- PFTs
- 6MWT
- +/- Tissue sampling



Pulmonary Fibrosis





Normal Chest

HRCT

- Diagnostic imaging of choice since greater resolution permits better definition of pathology
- Usually performed at full inspiration, allowing maximal contrast between inflated lung and diseased areas.
- Full expiration to detect air trapping
- Prone and supine scans to unmask interstitial abnormalities in dependent lung.
- Accuracy increases for end stage disease
- Useful in selecting site of possible biopsy

PFT Findings

- Typically characterized by **restrictive** ventilatory deficit
- Diminished VC and TLC
- Reduction in compliance
  - Due to loss of lung volumes
  - Reduced alveola distensibility
  - Changes in elastic properties of the lung - increase alveolar surface tension
- Airway function is well preserved in ILD
- Decreased DLCO

Pulmonary Function Testing in IPF

	Measure	% predicted
FVC	2.34 L	57
FEV_1	1.87 L	56
FEV_1/FVC	80	
TLC	3.43 L	53
DLCO	12.3 ml/Hg/min	43

Idiopathic Pulmonary Fibrosis

IPF

- Most common form of the IIPs
- Chronic progressive fibrosis of unknown etiology
- Insidious onset of unexplained cough, DOE, inspiratory crackles
- Occurs in older adults > 50 yrs of age
- Males > Females
- Pts have a history of smoking, GERD or chronic viral infections
- Can be familial- genetic predisposition in up to 30% of pts

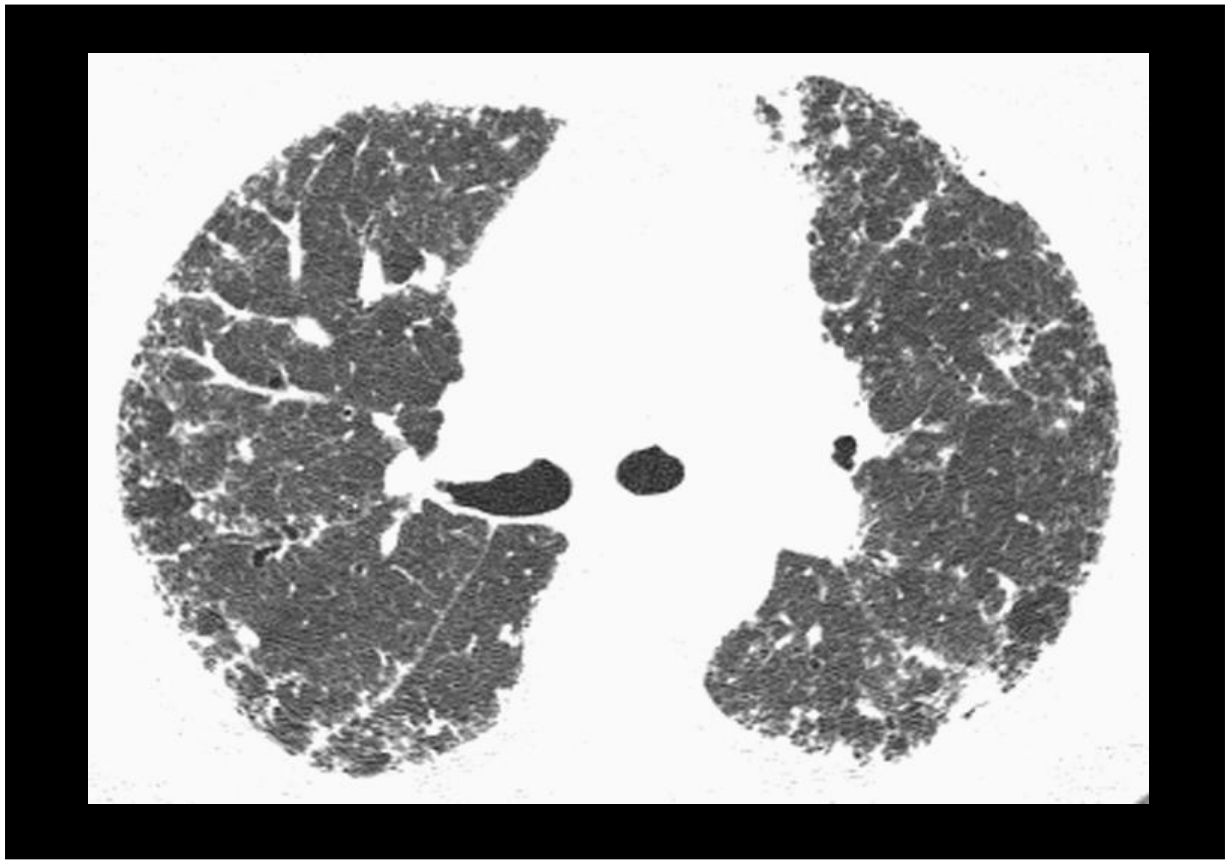
Clinical Features

- Dry crackles of varying intensity
- Clubbing is a late frequent finding
- Histopathological findings are Usual Interstitial Pneumonia (UIP)

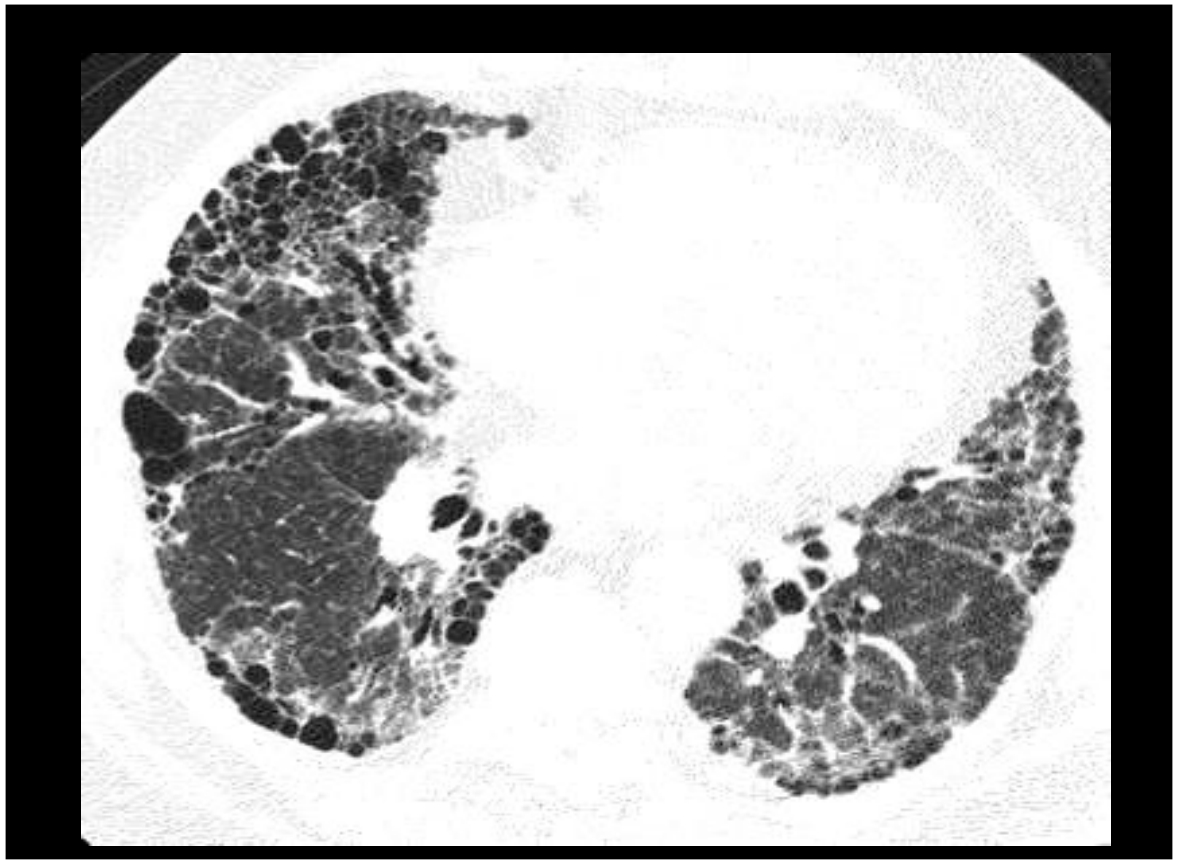
HRCT Pattern- UIP

- Peripheral, basal reticular opacities
- **Honeycombing** in lower lobes- correlates with mortality
- Traction bronchiectasis in advanced disease
- Lower lobe volume loss
- Bilateral but asymmetric
- Lacks consolidation, micronodules, mosaic attenuation, minimal GGO
- CT diagnosis of UIP on 96% cases based on these findings

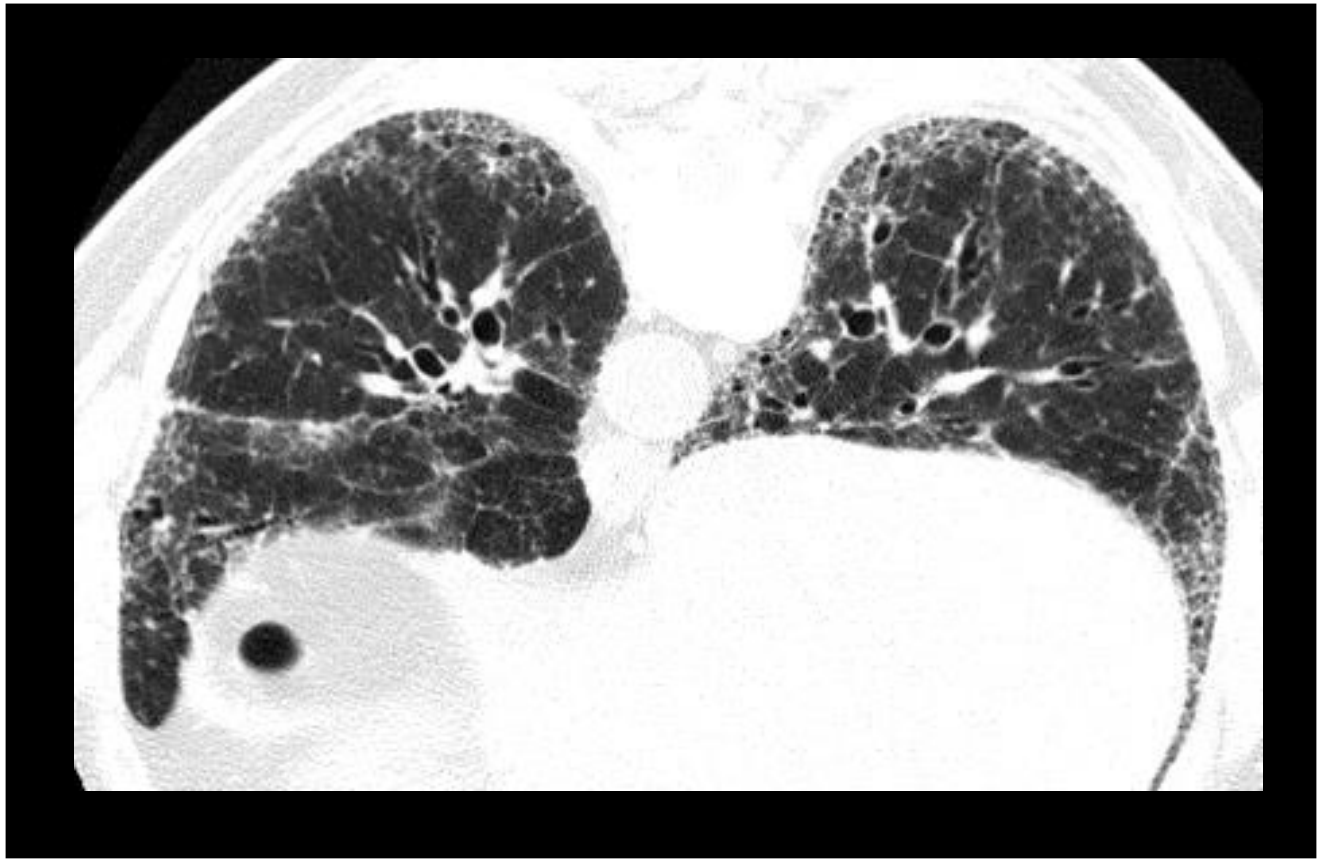
Irregular Reticular Opacities



Honeycombing



Traction Bronchiectasis



Differential Diagnosis for UIP

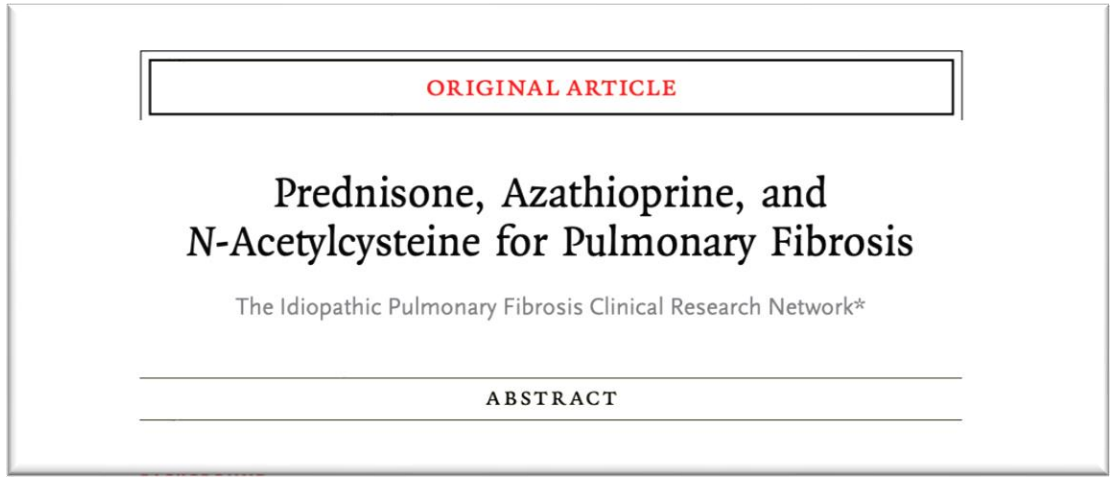
- Connective tissue related ILD (particularly RA)
- Fibrotic HP
- Asbestosis
- End stage Fibrosis

Additional Testing

- All patients should undergo serological work up including:
  - CBC- with differential
  - BMP- renal disease
  - ESR/CRP
  - ANA/ Scleroderma, myositis work up, RF, CCP, Sjogren's.

Treatment Options For IPF

Panther Trial



ORIGINAL ARTICLE

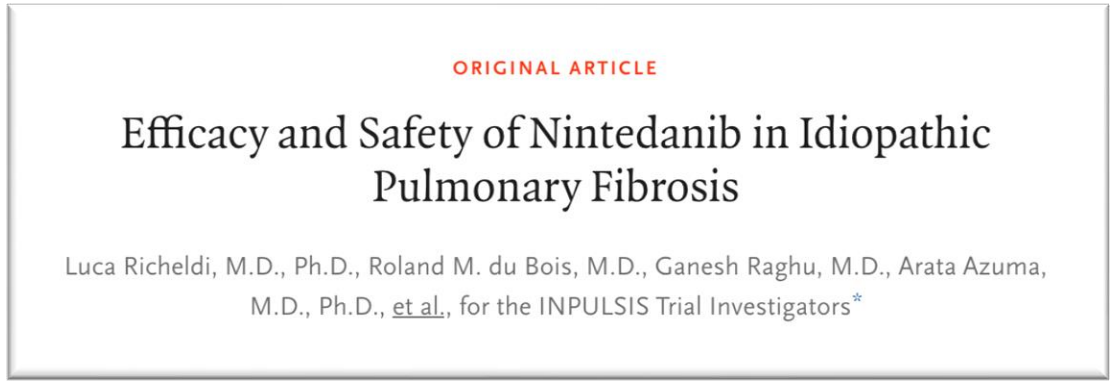
Prednisone, Azathioprine, and
N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

ABSTRACT

- Published in 2012
- RCT double-blinded placebo control
- **Pred/AZA and NAC vs NAC vs placebo**
- Evaluate FVC
- **Increased rate of death and hospitalizations in treatment group**
- **Trial terminated early**

INPULSIS-1/ INPULSIS-2



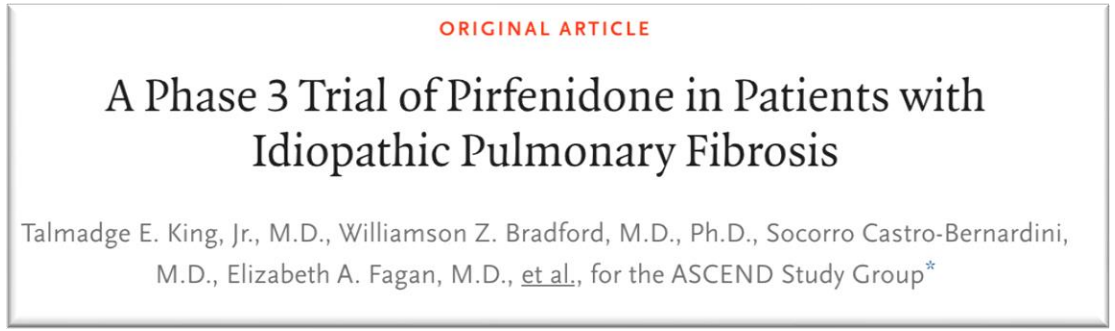
ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., et al., for the INPULSIS Trial Investigators*

- Published 2014 MAY
- 52 week RCT double blinded phase 3 trail
- 150mg BID treatment
- End point was rate of decline annually in FVC
- Time to exacerbation and St Georges questionnaire
- 1066 pts
- Loss of 115mls vs 240mls placebo
- difference to exacerbation
- **INHIBITS TYROSINE KINASE TARGETS GROWTH FACTORS**

ASCEND Trial- 2014



ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., et al., for the ASCEND Study Group*

- Phase 3 RCT double blinded
- End-point decline in FVC or death
- Reduction in number of pts who had a decline of 10% or more on FVC or those who died
- Increase in no decline of FVC
- Reduced decline in 6MWT
- **Inhibits TGF-BETA AND TNF-ALPHA**
- Shown to reduce respiratory related hospitalizations
- Reduces exacerbation when combined with steroids and Recombinant human thrombomodulin-

Non-Medical Treatments**

- Long-term oxygen therapy
- Pulmonary rehabilitation
- Treatment of chronic debilitating cough
- Treatment of GERD
- Cardiac work up for development PH

Acute exacerbation of IPF

- Unexplained worsening of symptoms and lung function within 30 days + new infiltrates in HRCT
- Occurs in 5-10% of pts
- More common in advanced disease, smokers, LTOT, GERD, post intervention and PH
- Post exacerbation survival is 3-4 months

AE-IPF treatments

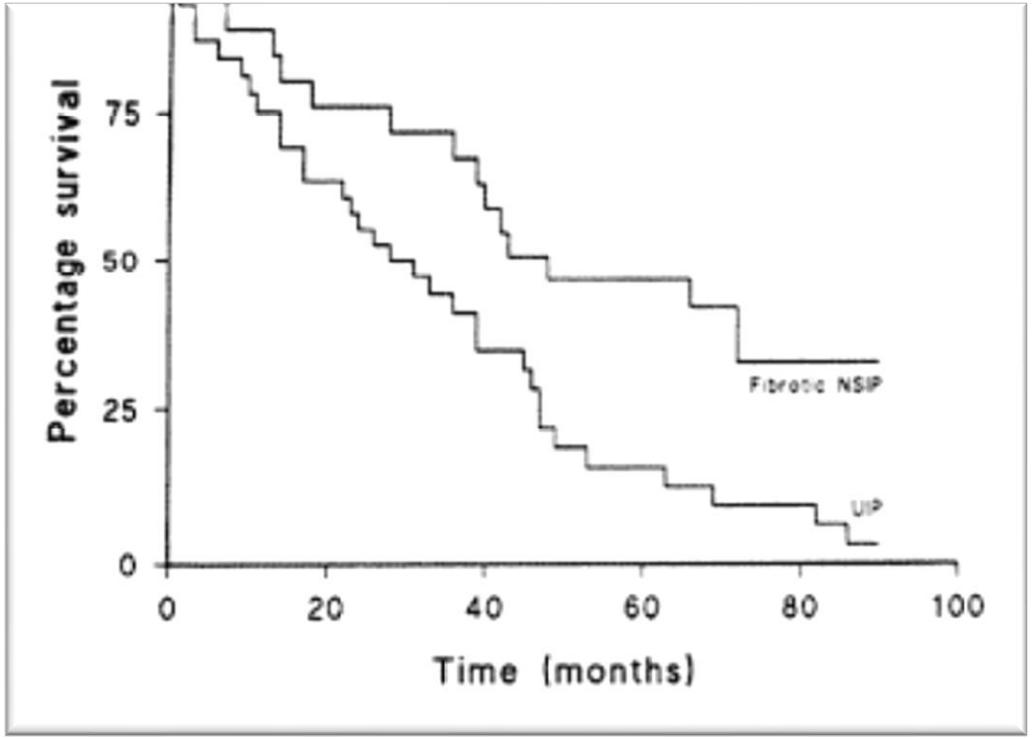
- Treatment is supportive care, high dose steroids/Immunosuppressive therapy and antibiotics- no data
- Recombinant human thrombomodulin- anti-inflammatory and anti-fibrotic- shown to significantly improve 3-month survival small trial
- Polymyxin-d +hemoperfusion: remove pro-inflammatory and profibrotic cytokines
  - Improved 1 year survival rate vs usual care
- NO ROLE FOR BRONCHOSCOPY MOST CASES

Role of Lung Transplant

- Transplant is definitive treatment
- Progressive disease with poor prognosis
- Frequent exacerbations
- Change in FVC or DLCO > 10% in 6months is indication for transplant referral
- Development of PH

IPF PROGNOSIS

- SURVIVAL OF UIP VS FIBROTIC NSIP
- 70% MORTALITY AT 5 YEARS
- INCREASED RISK OF LUNG CANCER



HYPERSENSITIVITY PNEUMONITIS

Table 1. Common Types of Hypersensitivity Pneumonitis According to Major Classes of Antigens

Class of Antigens	Specific Antigens	Sources	Type of Disease
Bacteria	*Saccharopolyspora rectivirgula*, *Thermoactinomyces vulgaris*	Moldy hay, grain	Farmer's lung
Fungi, yeasts	*Aspergillus* species	Moldy hay, grain	Farmer's lung
	Aspergillus species	Moldy compost and mushrooms	Mushrooms worker's lung
	Trichosporon cutaneum	Contaminated houses	Japanese summer-type HP
	Penicillium species	Moldy cork	Suberosis
	Penicillium casei	Moldy cheese or cheese casings	Cheese washer's lung
	Alternaria species	Contaminated wood pulp or dust	Woodworker's lung
Mycobacteria	*Mycobacterium avium-intracellulare*	Mold on ceiling, tub water	Hot tub lung
	Mycobacterium avium-intracellulare	Mist from pool water, sprays and fountains	Swimming pool lung
Animal proteins	Proteins in avian droppings and serum and on feathers	Parakeets, budgerigars, pigeons, parrots, cockatiels, ducks	Pigeon breeder's lung, bird fancier's lung
	Avian proteins	Feather beds, pillow, duvets	Feather duvet lung
	Silkworm proteins	Dust from silkworm larvae and cocoons	Silk production HP
Chemicals	Diisocyanates, trimellitic anhydride	Polyurethane foams, spray paints, dyes, glues	Chemical worker's lung

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Background

- Known as extrinsic alveolitis
- HP is an interstitial lung disease caused by the sensitization to an inhaled antigen- usually after repeated exposure
- The duration, type of exposure and host factors may affect disease course
- Prevalence varies with regional differences and climates, occupational exposures
- No advances in HP research for > 30 years
- Antigen not identified in 60% of cases

Sings and Symptoms

- Dyspnea
- Cough
- Constitutional symptoms- weight loss, chills, low grade fevers, malaise
- Chest tightness and *wheezing*
- Symptoms may develop over days to months to years
- Timing of onset is not associated with the development of fibrosis
- *Inspiratory squeaks are characteristic*
- Pts may stabilize, or progress to resp failure and death

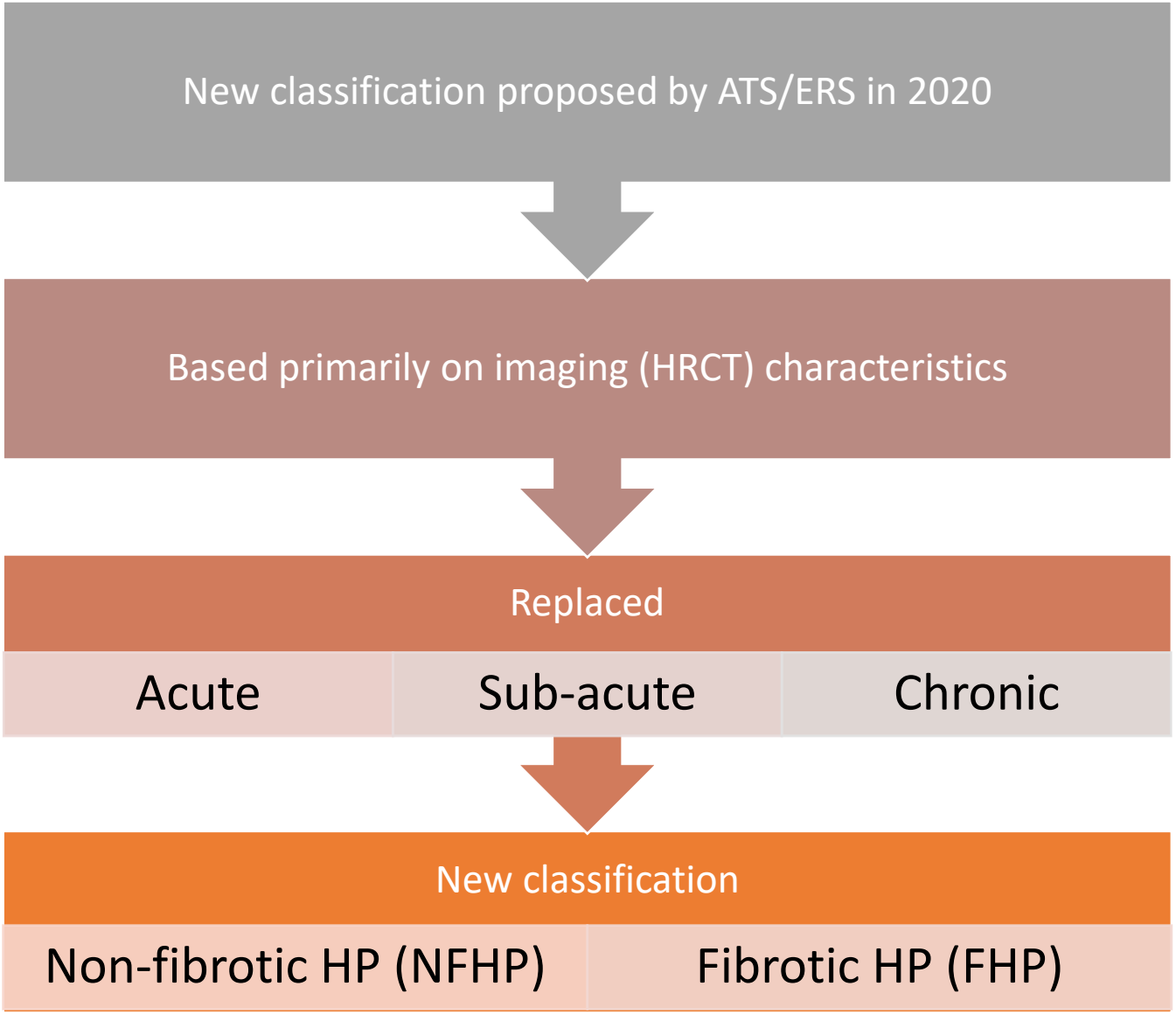
Original HP classification

- Acute:
  - Following limited and recent exposure to an antigen
  - Abrupt onset of flu like symptoms within 4-8 hours
  - Resolves within 24-48 hours- can re-occur with repeated exposure

- Subacute results from continued low exposure to the inhaled antigen
  - Progressive DOE, fatigue and weight loss
  - cough-productive
  - Unrecognized may progress to CHP
  - Often mistaken for other ILD due to insidious onset

- CHP:
  - Presence of fibrosis and permanent architectural distortion
  - May be progressive or stable

Reclassifying HP



Imaging

- HRCT gold standard as with most ILD’s
- Deep inspiration and prolonged expiration
- Prone and supine are not necessary

- Further classification into
- Typical HP
- Compatible with HP
- Indeterminate for HP

NFHP

- Typical pattern:
  - Diffuse infiltrative parenchymal abnormalities with **GGO** or **mosaic** attenuation
  - Plus 1 of the following suggestive of small airway disease
  - **<5mm centrilobular nodules on INSPIRATORY images**
  - **Air trapping on expiratory images**

Typical Fibrotic HP

- Fibrosis- **irregular linear coarse reticulations** with architectural distortion
- +/- Traction BE or honeycombing
- Most severe in **mid lung zones** (not upper) or equally distributed with basal sparing
- Presence of 1 abnormality indicating small airway disease
  - Ill defined centrilobular nodules
  - GGO/Mosaic attenuation
  - Air trapping
  - **3-densitiy pattern - highly specific for FHP**

Role of Bronchoscopy

Biopsy?

- TBBX for:
  - **Suggested** for newly diagnosed ILD with **NFHP** in the differential
  - No recommendation for newly diagnosed ILD with FHP in the differential
- Cryobiopsy
  - Suggested for newly diagnosed ILD with **FHP** in the differential
  - No recommendation for newly NFHP
- SLB
  - **Recommended** for ALL HP AFTER alternative diagnosis ruled out

BAL Fluid

- One of the most sensitive tools to detect alveolitis in HP
- Typical pattern is **marked lymphocytosis often > 20%) in NFHP**
- Lymphocyte count usually > 50% and increased CD8 T cells
- Less marked elevation in **FHP** or following treatment (increased neutrophil) poor prognostic sign

Role of Antigen Testing

- Identifying antigen is crucial for diagnosis and preventing disease progression
- Meticulously collect and exposure history (no validated questionnaire) (CHEST)
- IgG against antigens- highlights exposure and sensitization, not diagnostic of HP
- Recommend performing serum IgG testing that targets potential antigens

Histopathological Features

- **Typical** NFHP requires presence of
  - **Cellular** interstitial changes around the small **airways** (bronchiolocentric)
  - **Granulomatous inflammation- poorly formed**
  - No findings of an alternative diagnosis

  - FHP: UIP*

Overall Diagnosis:

- No individual feature on history, HRCT or histopathology is adequate in isolation to make HP diagnosis
- Should rely on MDD
- Identifying a know antigen is not essential and only possible in up to 40% of cases
- NFHP often have systemic symptoms, BAL lymphocytosis, centrilobular nodules more frequently due to acute exposure history
- FHP less likely to identify known antigen, and has insidious onset of symptoms with fibrosis on CT

PFTs

- PFTs are neither specific or sensitive for diagnosing HP
- Used to determine disease severity
- Classic restrictive pattern (most notably in VC)
- Correlation between PFTs and disease severity is poor

Management

- Treatment guided by PFTs and symptoms and CT improvement.
- Avoid exposure- cornerstone
- Manage comorbidities- DM, GERD, **smoking**, vaccines
- Oxygen therapy, pulm rehab
- Transplant referral- progressive/ relapsing disease

Management and Prognosis

- Prednisone 0.5/1mg/kg/d for up to 8 weeks followed by slow taper
- Immunomodulating agents:
  - AZA, MMF- improve gas exchange (DLCO)and reduces steroid use, not FVC
- INBUILD trial
- Rituximab
- Treat for 1 year and re-evaluate- wean medications
- Approx 25% of pts die within 5 years oof diagnosis

Poor Prognostic Indicators

- Patients with familial HP
- UIP pattern
- Cigarette smoking
- Low VC at presentation
- Lack of BAL lymphocytosis
- Persistent exposure to inciting agent
- Lack of identification of agent
- Female sex

Rapid Fire Round

- Name 3 symptoms/clinical features associated with ILDs
  - DOE
  - Dry cough
  - Inspiratory crackles
  - Restrictive PFTs

Question 2

- What are the 2 types of HP?
- Cellular
- Fibrotic HP

- Bonus question
- What histopathological feature is often seen in HP?
- Poorly formed granuloma

Question 2

- What are the 3 radiographic signs of UIP?
  - Bilateral, peripheral reticulations
  - Traction bronchiectasis
  - Honeycombing

- Bonus points!
- What should not be present in UIP imaging?
  - Lack of GGO
  - Lack of nodules

Question 3

- Name 3 prognostic indicators for HP
  - Patients with familial HP
  - UIP pattern
  - Cigarette smoking
  - Low VC at presentation
  - Lack of BAL lymphocytosis
  - Persistent exposure to inciting agent
  - Lack of identification of agent
  - Female sex

Question 4

- What other diseases can be associated with UIP on HRCT?
  - Connective tissue related ILD (particularly RA)
  - Fibrotic HP
  - Asbestosis
  - End stage Fibrosis

Questions?