



MD Seminar

Management of IPF



Idiopathic pulmonary fibrosis

- Also known as CFA
 - Chronic scarring illness limited to lungs & characterized by
 - Progressive dyspnea
 - Restrictive pulmonary physiology
 - Radiographically diffuse lung disease
 - Occurs in adults, manifesting beyond 5th and 6th decade
- Until recently, diagnosis and management was difficult because
 - Vague case definition
 - Clinical features overlapped with other chronic interstitial pneumonias



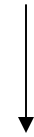
Epidemiology

- IPF is most common diagnosis among all IIPs
- Usually affects older adults and men
- Risk factors
 - Familial IPF- 3% of cases, suggests genetic predisposition may interact with environmental factors
 - Environmental factors
 - Smoking
 - Inhalation of organic and inorganic dust
 - Exposure to dust (pinewood)
 - Use of tricyclic antidepressants
 - Gastroesophageal reflux
 - No connection between IPF and an infective agent

Pathophysiology

- Current hypothesis

Recurrent, unknown injury (extrinsic or intrinsic)
To distal pulmonary parenchyma



Repeated epithelial injury



Abnormal wound healing,
Mediated by fibroblasts and fibroblast-like cells
Or myofibroblasts



Progressive fibrosis

Natural history of IPF

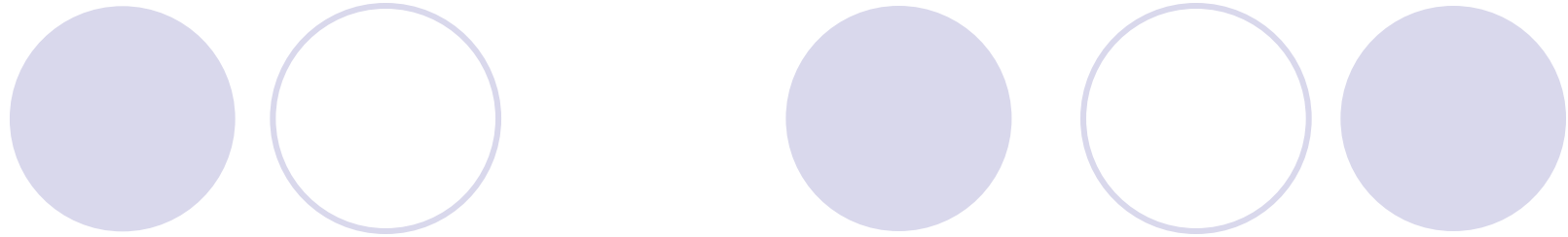


- **Fatal illness** –
 - progressive impairment of lung compliance and gas exchange
 - Inexorable course
 - usually death because of hypoxic respiratory failure, associated with pulmonary hypertension & cor pulmonale
 - Increased risk of bronchogenic carcinoma
- **Median survival** – 80 months from the time of onset of symptoms (King et al.)
- **Acute exacerbations** may occur in absence of infection
 - Fulminant decline in oxygenation
 - Rapidly progressive respiratory failure



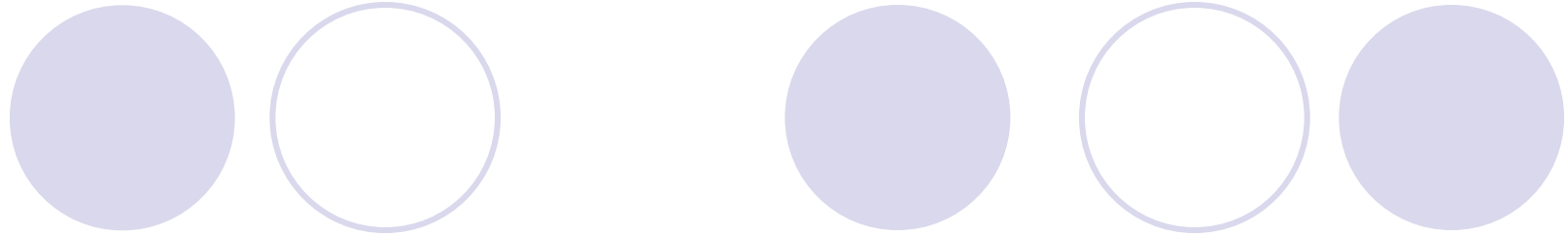
Diagnosis

- Clinical evaluation- based on CRP
 - **History –**
 - subacute course of progressive symptoms (SOB & Cough) over months to years
 - Past, family and environmental history to rule out other types of ILDs (HP, occupational ILD, CT-ILD)
 - **Examination –**
 - Fine end inspiratory crackles at lung bases
 - Pulmonary hypertension & right heart failure late in disease
 - Clubbing in majority



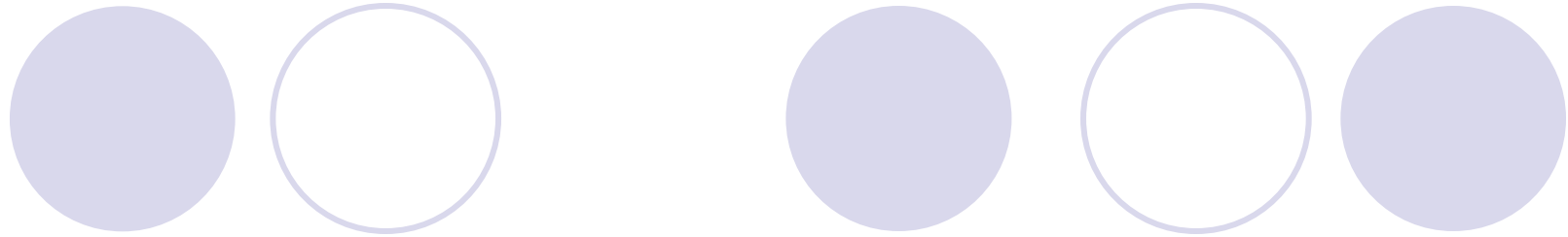
- **Radiological –**

- **CXR-** Useful initial visual perception of overall lung involvement
 - Low lung volumes
 - Bilateral reticular opacities- most severely involving periphery and bases of lungs
 - Features of heart failure
 - Features are not specific but demonstrate disease extent & progression & cardiopulmonary status



○ **HRCT-** necessary step in diagnostic evaluation

- First may illustrate characteristic features of UIP-
 - patchy, predominantly peripheral, sub pleural, bibasal reticular abnormalities
 - Traction bronchiectasis &/or sub pleural honeycombing
 - May enable clinical diagnosis without need for biopsy
- Secondly
 - clinical diagnosis of new onset IPF can be made accurately if classic clinical & HRCT features are present
 - If typical findings not present may identify other disease processes
- Thirdly
 - May assist in decision of whether or not to biopsy & the sample site(s)
 - If extensive fibrosis & honeycombing present, disease likely is end stage



- **Pulmonary function test-** Initial PFT useful for gauging global physiological severity of disease
 - Restrictive impairment (reduced VC & TLC) by body plethysmography
 - DLco corrected for Hb is reduced frequently
 - Resting ABG- normal or hypoxemia & respiratory alkalosis (these abnormalities accentuated by exercise)
- **Bronchoscopy** – can make a definitive diagnosis in few ILDs but not in IPF
 - It is done to detect BAL cellular or histologic patterns atypical for IPF
 - Significant increase in lymphocytes & granulomas is not a feature of IPF



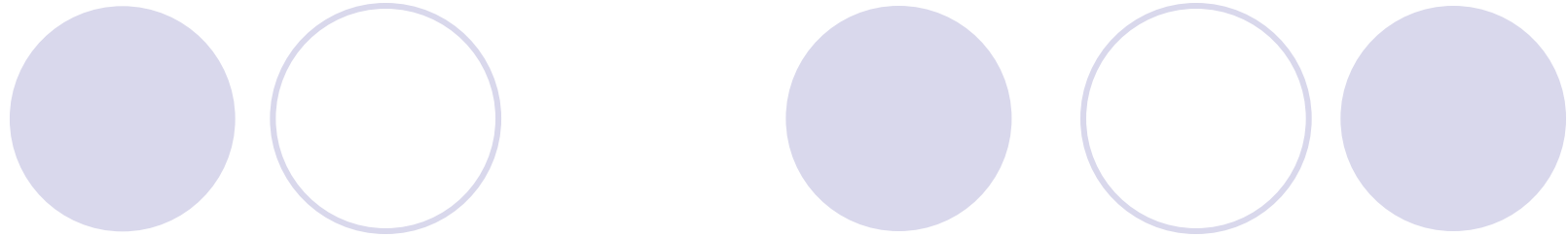
- **Surgical lung biopsy** – open or thoracoscopic
 - Final diagnostic step
 - Decision to proceed must be individualized for each patient
 - Optimal location and number of biopsy sites is important
 - **Location based on radiological appearance on HRCT**
 - Optimal sites- visibly abnormal areas as well as normal appearing lung adjacent to abnormal areas
 - **Biopsy from more than one lobe is helpful**
 - NSIP and UIP may be present in different lobes in same lung
 - **UIP is the pathological abnormality essential to diagnosis of IPF**
 - Heterogenous appearance with alternative areas of normal lung, interstitial inflammation, fibrosis & honeycomb change affecting the peripheral sub pleural parenchyma most severely

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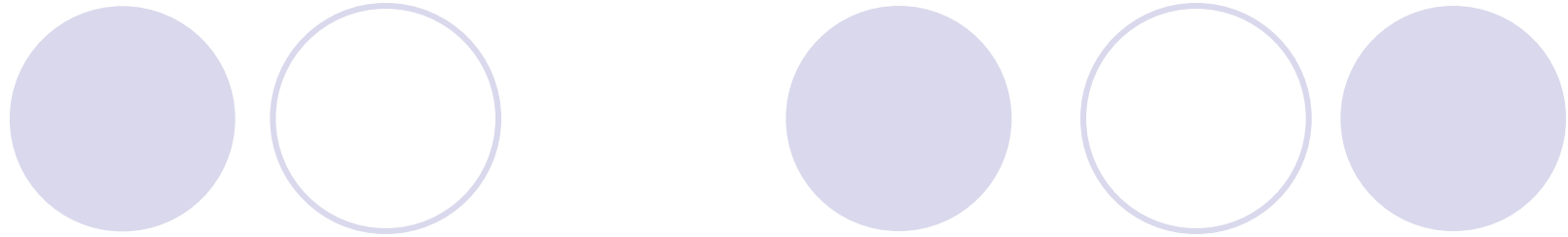
Treatment

- **Conventional therapy**

- **Corticosteroids alone**- ineffective and associated with significant side effects
- **Corticosteroids + immunosuppressives**
 - Limited efficacy in slowing the progressive deterioration in lung function
 - Slightly superior to corticosteroids alone, when initiated for new onset IPF
 - Low dose prednisone + azathioprine- frequently used initial treatment in IPF
 - Alternative -Prednisone + cyclophosphamide



- **Newer therapies-** required because of ineffectiveness and side effects of conventional therapy
 - **Immuno modulators**
 - Interferon γ - inhibitory effect on fibroblasts
 - **Antifibrotic agents**
 - Colchicine
 - D-penicillamine
 - Pirfenidone
 - ACE inhibitors
 - Statins
 - **Anti-oxidants**
 - N-acetylcysteine



- Endothelial receptor-1 antagonist
 - Bosentan
- Tumor necrosis factor- α blocker
 - Etanercept
- Imatinib mesylate - cAbl tyrosine kinase inhibitor + PDGF receptor antagonist
- CTGF blocker
 - FG-3019
- Rapamycin
- Antileukotriene drugs
 - Zileuton

Prognosis



- Indicators of longer survival
 - Younger age (<50 years)
 - Female
 - Shorter symptomatic period (< 1 year) with less dyspnea, relatively preserved lung function
 - Ground glass and reticular opacities on HRCT
 - Increased lymphocytes (20 – 25%) in BAL
 - Beneficial response or stable disease 3-6 months after initial therapy



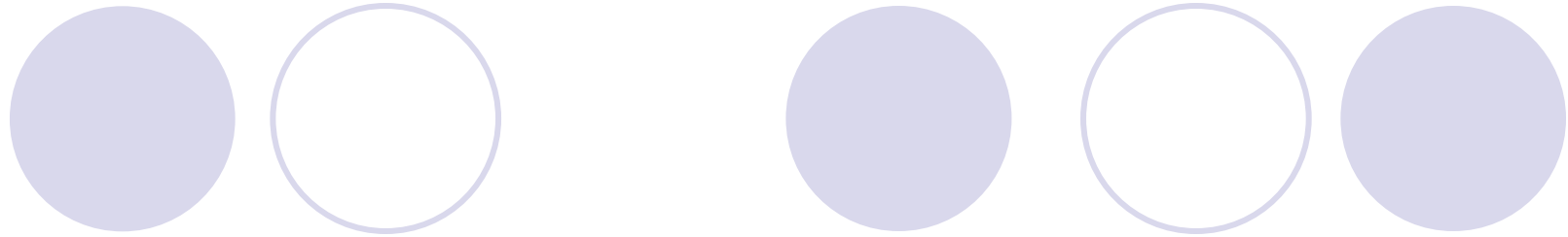
Monitoring clinical course of IPF

- Parameters used are
 - Assessment of dyspnea
 - Physiologic testing
 - Lung volumes
 - **DLco**
 - Resting ABG
 - Cardiopulmonary exercise testing with measurement of gas exchange
 - HRCT

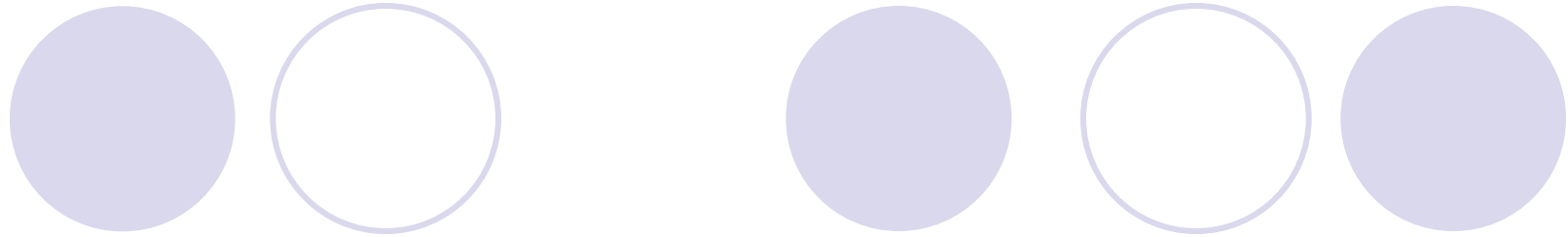
Approach to treatment



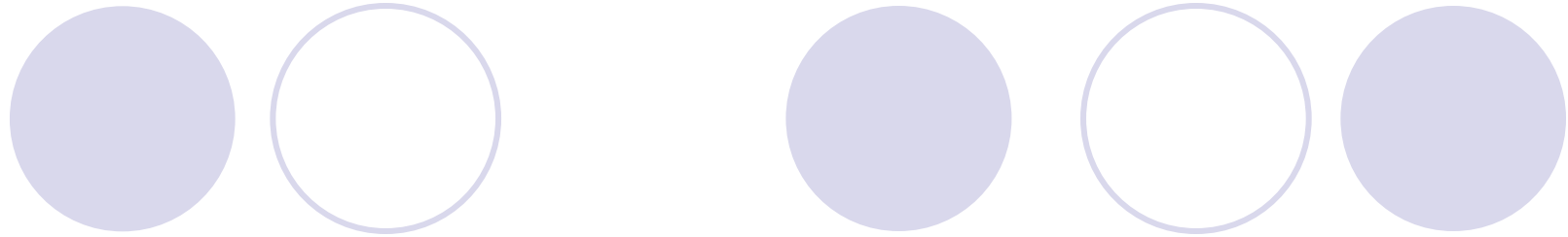
- Therapy is not indicated for all patients
 - Age >70 years
 - Extreme obesity
 - Concomitant major illness
 - Severe impairment in pulmonary function
 - End stage honeycomb on radiology
- Treatment should be started
 - At the first identification of clinical or physiological evidence of impairment of lung function
 - Early in the course of the disease before irreversible fibrosis has developed



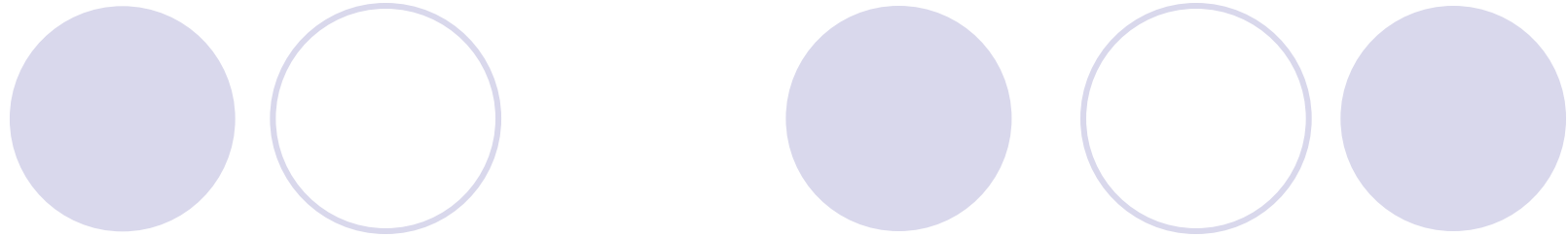
- Combination therapy is a reasonable approach
 - Corticosteroid (prednisone or equivalent)
 - 0.5mg/kg/day orally X 4 weeks
 - 0.25 mg/kg/day X 8 weeks
 - 0.125 mg/kg/day as initial therapy
 - Azathioprine at
 - 2-3 mg/kg/day to maximum dose of 150mg/day orally
 - Begin at 25-50 mg/day
 - Increase by 25 mg increments every 7-14 days
- Or
 - Cyclophosphamide



- Length of therapy –
 - objective response may take >3 months of therapy
 - Combined therapy should be continued for at least 6 months in absence of complications
- Monitoring of therapy
 - At 6 month
 - If patient worse – therapy stop or changed
 - If patient improved or stable - therapy continued at same doses
 - At 12 months
 - If patient worse - therapy stop or changed
 - If patient improved or stable - therapy continued at same doses
 - At 18 month or more
 - Therapy continued indefinitely only in individuals with evidence of continued improvement or stabilization



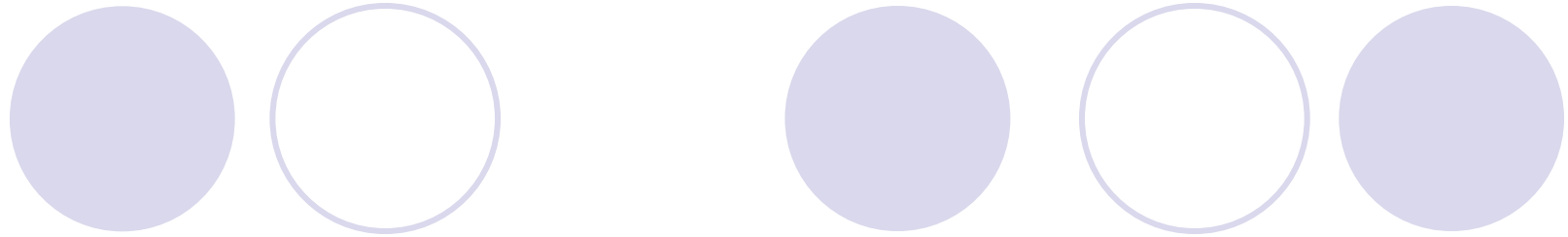
- Favorable (or improved) response to therapy- Decrease in symptoms (SOB, cough)
 - Reduction of CXR/ HRCT findings
 - Physiologic improvement
 - $\geq 10\%$ increase in TLC or VC (or at least ≥ 200 -ml change)
 - $\geq 15\%$ increase in single breath **DLco**
 - Improvement or normalization of O₂ saturation
- 2 or more, on 2 consecutive visits over a 3- to 6- month period



- **Stable response**

- 10% change in TLC or VC (or <200- ml change)
- <15% change in DLC
- No change in O₂ saturation

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



- **Failure to respond to therapy-** (after 6 month of therapy)
 - Increase in symptoms
 - Increase in opacities, honeycombing, PHT
 - Deterioration in lung function
 - $\geq 10\%$ decrease in TLC or VC (or ≥ 200 -ml change)
 - $\geq 15\%$ decrease in single breath **DLco**
 - Worsening of O₂ saturation



Monitoring for adverse effects

- Corticosteroids
- Azathioprine & cyclophosphamide
 - Hematological
 - Hepatic
 - Oncogenic potential
 - Hemorrhagic cystitis
- Also monitor for
 - Opportunistic lung infection
 - Pneumonia
 - Pulmonary emboli
 - Secondary pulmonary hypertension
 - Heart failure
 - Neoplasm

Lung transplantation



- Considered for progressive physiologic deterioration despite therapy and who meet established criteria
 - Severe functional impairment
 - Oxygen dependency
 - Deteriorating course
 - <60 year age
- Early listing important because long waiting period
- 5 year survival- 50-60%



Summary

- IPF has evolved into a well defined clinical pathological syndrome characterized by UIP on HRCT & lung biopsy
- Diagnosis is straight forward in advanced cases, SLB is required if atypical features are present
- Gold standard of diagnosis rests on an interactive discussions among pulmonologists, radiologists and pathologists



Summary

- For treatment, until an efficacious regimen is developed patients should be treated with combined prednisone and azathioprine (as recommended by ATS) for at least 6 months
- Patient should be encouraged to enroll in ongoing clinical trials for development of novel therapies
- Patient should be monitored during therapy for response, adverse effects and other complications