A Review of Interstitial Lung Diseases

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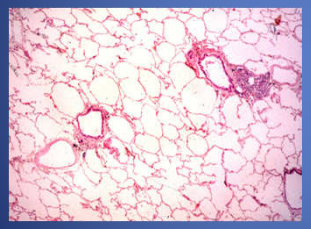
Outline

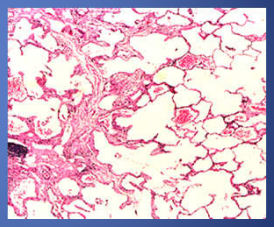
- Overview of diagnosis in ILD
  - Why it is important
  - Definition/Classification
  - High-resolution CT scan
  - Multidisciplinary approach
  - Review of radiology and pathology
  - Treatments
- Questions

The Problem

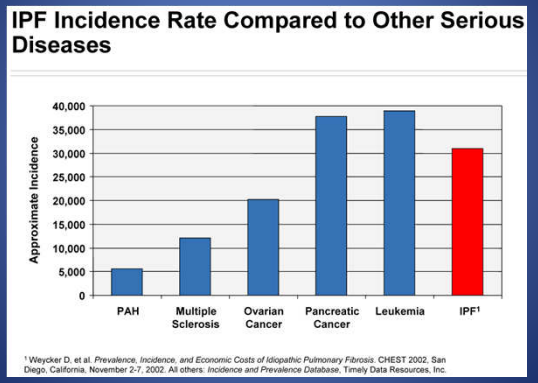
Normal Lung



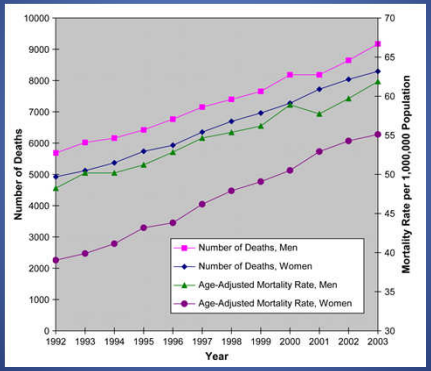
Fibrotic Lung



Why it is Important to be Aware of ILD's



And, the rate of death from pulmonary fibrosis is increasing

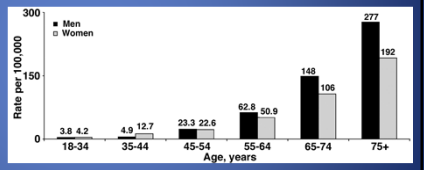


Olson et al, AJRCCM, 2007

IPF is a Disease Associated With Aging

- IPF rarely occurs in patients < 50 yo.
- Prevalence of IPF in general: 15/100,000
- Prevalence of IPF in patients > 75yrs: 227/100,000
- *Incidence is increasing due to aging of the population*

Prevalence of IPF



Raghu et al, AJRCCM, 2006

Don't stop with "pulmonary fibrosis"

- Reasons for a specific diagnosis:
  - Many forms are treatable
  - Treatment depends on the diagnosis
  - Prognosis varies
  - Eligibility for clinical trials

Clinical Classification

Pulmonary Fibrosis

Exposure-related:
- Occupational
- Environmental
- Avocational
- Medication

Idiopathic interstitial pneumonia (IIP)

Idiopathic pulmonary fibrosis (IPF)

Connective tissue disease:
- Scleroderma
- Rheum. arthritis
- Sjogrens
- UCTD

Other:
- Sarcoidosis
- Vasculitis/Diffuse alveolar hemorrhage (DAH)
- Langherhans cell histiocytosis (LCH)
- Lymphagioleiomyomatosis (LAM)
- Pulmonary alveolar proteinosis (PAP)
- Eosinophilic pneumonias
- Neurofibromatosis
- Inherited disorders
- Chronic aspiration
- Inflammatory bowel disease

Desquamative interstitial pneumonia (DIP)

Respiratory bronchiolitis interstitial lung dis. (RBILD)

Acute interstitial pneumonia (AIP)

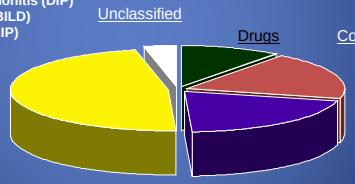
Cryptogenic organizing pneumonia (COP)

Nonspecific interstitial pneumonia (NSIP)

Lymphocytic interstitial pneumonia (LIP)

Clinical History

Idiopathic
usual interstitial pneumonitis (UIP) = IPF
nonspecific interstitial pneumonitis (NSIP)
desquamative interstitial pneumonitis (DIP)
respiratory bronchiolitis ILD (RBILD)
acute interstitial pneumonitis (AIP)



Joint c/o
Sicca sx
Skin rash
Raynaud's

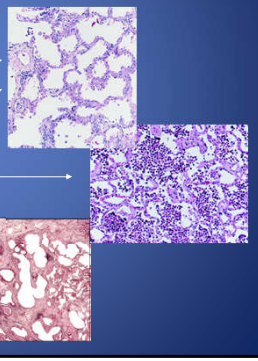
Occupational/Environmental
-Asbestos
-Birds/Molds/Organic Material (HP)

Reevaluation of Pathology of IPF (1990's)

Lumpers

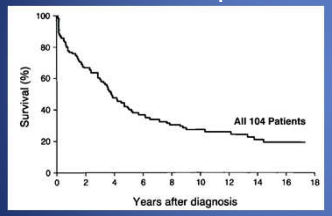
- IPF
  - Nonspecific interstitial pneumonitis (NSIP┼)
  - Lung fibrosis due to arthritis
  - Desquamative interstitial pneumonitis
  - Acute interstitial pneumonitis
  - IPF

Splitters

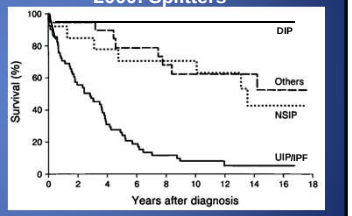


Differentiating diseases predicts prognosis

1950-90's: Lumpers



2000: Splitters

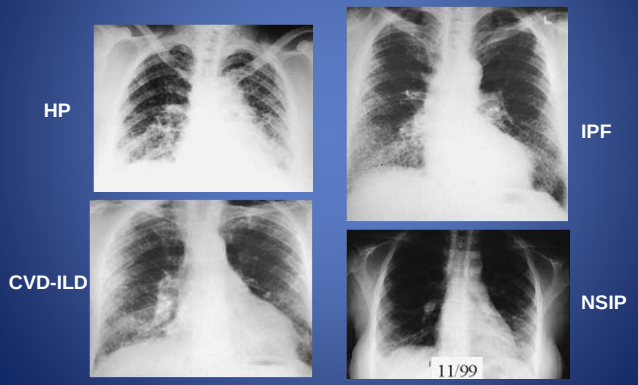


Bjoraker et al, Am J Resp Crit Care Med '98

When to Suspect Pulmonary Fibrosis

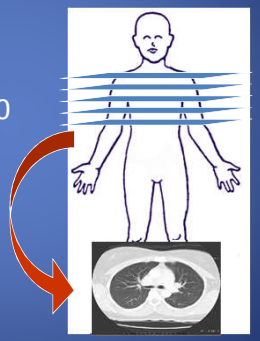
- CC: Shortness of breath, chronic cough
- PEx: Crackles on exam
- Investigate for:
  - Pulmonary fibrosis:
    - Clubbing
    - CTD: synovitis, rash, sclerodactaly
    - Sarcoidosis: uveitis, skin rash, erythema nodosum, hepatomegaly
  - Exclude S/Sx of heart failure and pneumonia

CXR is Not Useful for Differentiating ILD's



High-resolution CT (HRCT)

- 1-1.5 mm collimation
- Images taken every 10 mm
- Supine, prone and expiratory images



HRCT is the Key to Diagnosing ILD's

- Pattern of abnormality on HRCT scan may suggest a specific ILD.
- HRCT findings guide subsequent diagnostic tests.
- HRCT findings may be sufficient for diagnosis.

HRCT: Radiation Dose

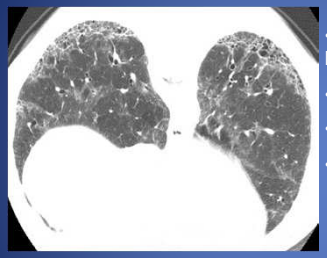
TABLE 4
Comparison of Effective Doses

Procedure	Effective Dose (mSv)
Posteroanterior chest radiograph	0.05*
Conventional CT	7.0†
Spiral CT pitch 1	7.0†
Spiral CT pitch 2	3.5†
High-resolution CT with 10-mm intersection gap	0.7†
High-resolution CT with 20-mm intersection gap	0.35†
Thin-section low-dose high-resolution CT	0.02‡
Conventional pulmonary angiography	9.0§
Digital pulmonary angiography	6.0§
Conventional bronchography	3.0‖
Annual natural background radiation	2.5*

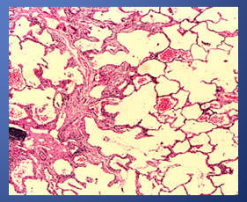
Note.—Reprinted, with permission, from reference 69.
* Source.—Reference 70.
† Source.—Reference 71.
‡ Source.—Reference 49.
§ Calculated with data from reference 72, assuming pulmonary angiography with 5 minutes of fluoroscopy and the equivalent of 30 posteroanterior and 30 lateral views.
‖ Bronchography performed with the assumption of 2 minutes of fluoroscopy and six posteroanterior and six lateral views.

Mayo et al, Radiology 2003

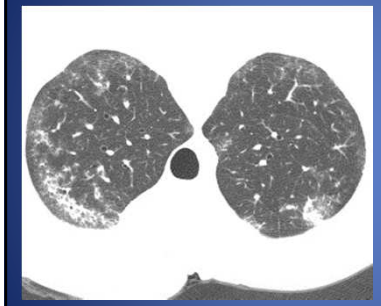
Usual Interstitial Pneumonia (UIP)



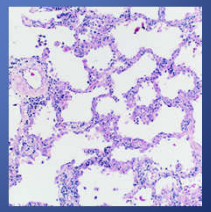
- Irregular lines in a patchy, basilar, subpleural distribution
- Traction bronchiectasis
- minimal Ground glass opacities.
- Honeycomb lung



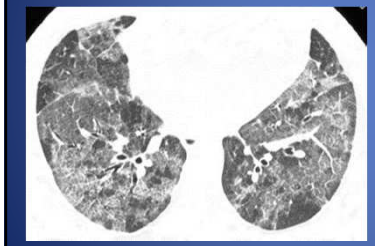
Nonspecific Interstitial Pneumonitis (NSIP)



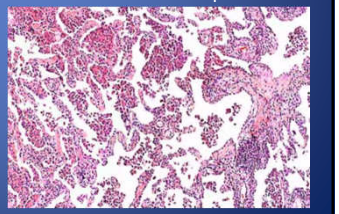
- Ground glass opacities (100%)
- Consolidation (98%)
- Nodules (96%)
- Traction bronchiectasis (95%)
- Intralobular reticulation (87%)
- Lower lobe predominance



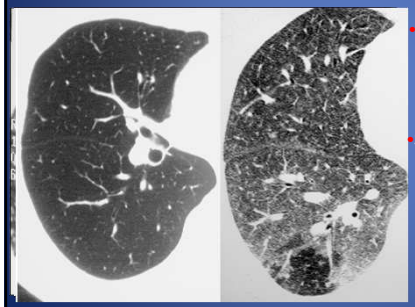
Desquamative Interstitial Pneumonia (DIP)



- Ground glass opacity with a basilar, subpleural, and lower lobe distribution
- Lower lobe reticular opacities

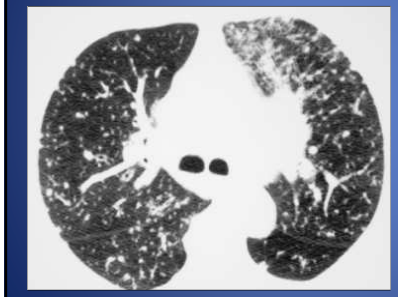


Hypersensitivity Pneumonitis

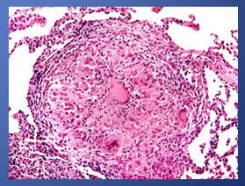


- Subacute phase :
  - multifocal or diffuse GGO
  - poorly defined centrilobular nodules
- Subacute and chronic phases :
  - mosaic perfusion
  - air trapping on expiratory images
- CT may be normal in some cases

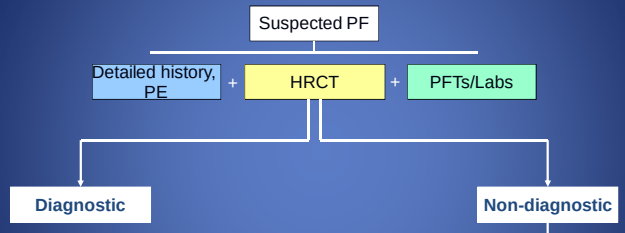
Sarcoidosis



- Perilymphatic nodules
- Peribronchial nodules
- GGO
- Upper lobe predominant, +/- fibrosis



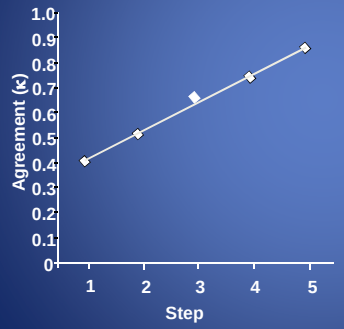
Diagnostic Algorithm



1. IPF
2. Sarcoidosis
3. CV-ILD
4. Hypersensitivity pneumonitis
5. Rare disease (LAM, PAP)

Multidisciplinary approach

- Agreement increased with multidisciplinary approach

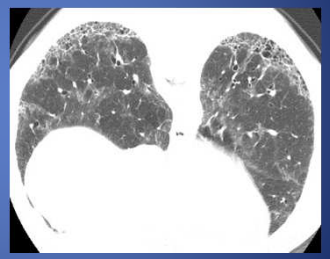


Step	Assessment Method	Information Provided
1	Individual	HRCT
2	Individual	HRCT, clinical data
3	Discussion (clinician and radiologist)	HRCT, clinical data
4	Individual (clinician, radiologist and pathologist)	HRCT, clinical data, SLB
5	Discussion	HRCT, clinical data, SLB

Modified from: Flaherty KR, et al. *Am J Respir Crit Care Med*. 2004;170:904-910.

Idiopathic Pulmonary Fibrosis (IPF)

- One of the most common causes of lung fibrosis
- Average survival from diagnosis: 2.5-3 years
- Afflicts men more than women
- No apparent race or ethnic predilection

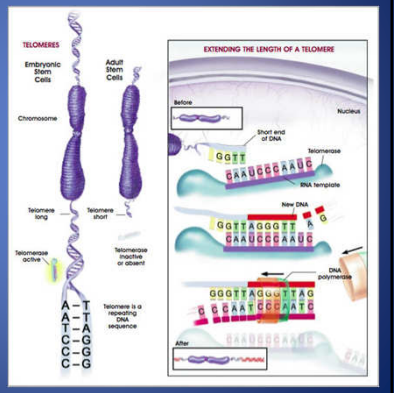


What causes IPF?

Telomere: A DNA sequence at the end of chromosomes, which protects the end of the chromosome from deterioration.

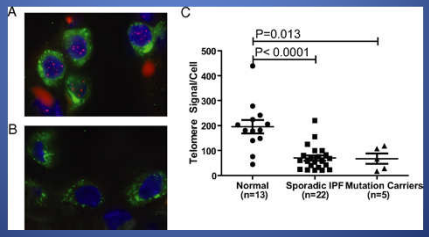
Telomeres shorten with each cell division.

Cells with short telomeres either senesce or die.



Telomeres are Shortened in IPF Type II Cells

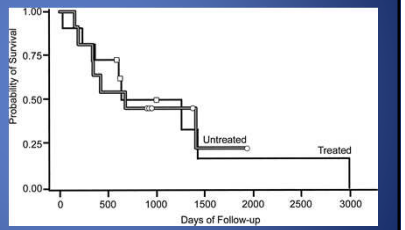
- 8-15% of patients with IPF have telomerase mutations and short telomeres
- Lung fibrosis is found in 40% of patients with telomere mutations.



Alder J K et al. PNAS 2008

IPF: Traditional Therapy

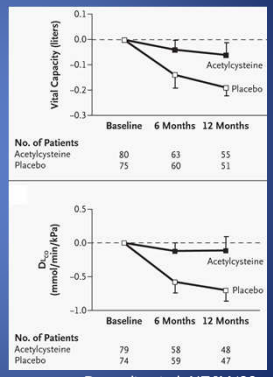
Corticosteroids + Immunomodulator (azathioprine or cyclophosamide @ 2 mg/kg/d)



Collard et al. Chest 2004

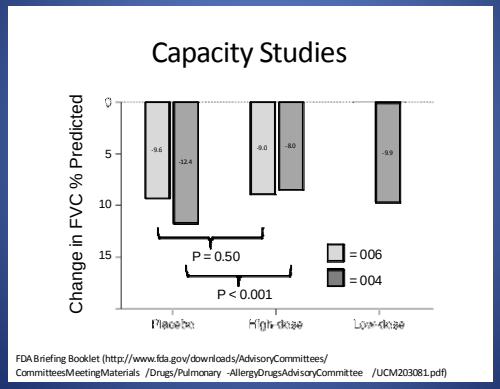
IPF: Traditional Therapy + NAC

- IPF patients taking prednisone (0.5 mg/kg/d ⮙ 10 mg/d) and azathioprine (2 mg/kg/d) were randomized to:
  - N-acetyl cysteine, 600 mg TID (n=80)
  - Placebo (n= 75)



Demedts et al, NEJM '06

IPF: Pirfenidone



FDA Briefing Booklet (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials /Drugs/Pulmonary -AllergyDrugsAdvisoryCommittee /UCM203081.pdf)

IPF: Sildenafil

- Phosphodiesterase-5 inhibitor
- Double-blind, placebo controlled RCT
- Primary outcome (≥ 20% improvement in 6MW distance) was not met
- Small, but significant differences in arterial oxygenation, DLCO, degree of dyspnea, and QOL favoring sildenafil
- No difference in adverse events
- Consider in advanced IPF

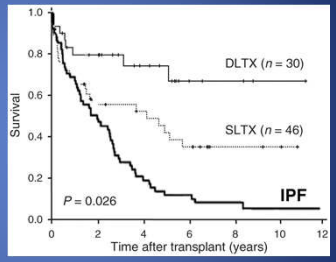
Zisman et al. NEJM 2010

Treatment

- No medical therapy has been proven to be effective for improving survival.
- Possibilities that hold promise.
  - Prednisone/Azathioprine/NAC
  - Pirfenidone
- Clinical Trials
  - Ongoing: Prednisone/Azathioprine/NAC
  - Recently stopped: coumadin, ambrisentan
  - On the horizon: BI Kinase Inhibitor, pirfenidone

Lung Transplant in IPF

- Should be considered in all patients less than age 70.
- 50-60% 5 year survival after transplant
- Patients that do well – younger, minimal co-morbidities, minimal steroids, healthy BMI, pulmonary rehab



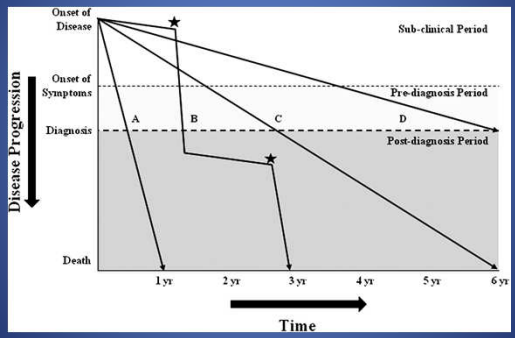
Bjoraker et al, Am J Resp Crit Care Med '98, Neurohr et al, Transplant International, '10

IPF: General Management

- Recently published consensus statement on IPF diagnosis and management (AJRCCM March 2011)

- Pulmonary rehabilitation
- Weight loss (if overweight)
- Consider clinical trial participation
- Lung transplant referral
- Medical management of symptoms

IPF Clinical Course: Individual Patient



Ley et al, AJRCCM 2011

Acute Exacerbation of IPF

TABLE 2. DIAGNOSIS OF ACUTE EXACERBATION

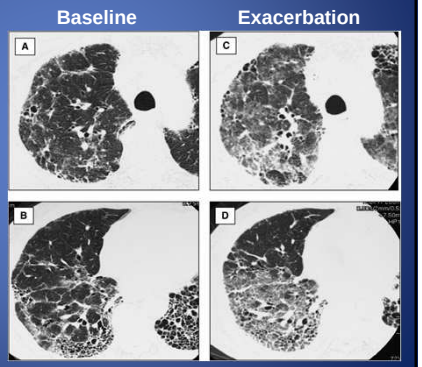
Diagnostic Criteria
Previous or concurrent diagnosis of idiopathic pulmonary fibrosis*
Unexplained worsening or development of dyspnea within 30 days
High-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern†
No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage‡
Exclusion of alternative causes, including the following:
• Left heart failure
• Pulmonary embolism
• Identifiable cause of acute lung injury§

- Occurs in 5-20% of patients

Akira, et al. Am J Roentgenol, 1997
Collard et al. AJRCCM, 2007

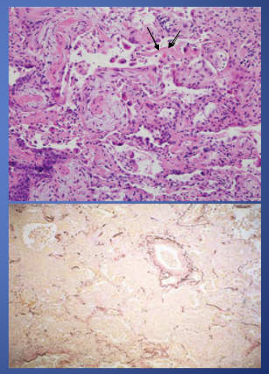
IPF Acute Exacerbation: HRCT

- Background of:
  - Bilateral subpleural reticulation
  - Traction bronchiectasis
  - Honeycombing
- Increased parenchymal opacities
- *Can be initial presentation of IPF.*



IPF Acute Exacerbation: Pathology

- UIP Pathologic changes
  - Fibroblast foci
  - Honeycombing
  - Dense fibrosis
- Diffuse Alveolar Damage
  - Interstitial edema, Type II cell hyperplasia
  - Hyalin membranes
  - Intra-alveolar Organizing Pneumonia/fibrosis

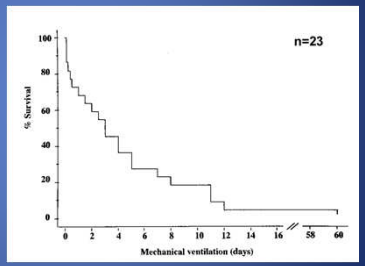


Management

- Supportive care
  - Oxygen
  - Antibiotics
- No medical therapy is proven effective
  - High dose corticosteroids
  - Cytotoxic agents (cytoxan, azathioprine)
  - Cyclosporine

Acute Exacerbation: Mechanical Ventilation

- 23 Patients w/ IPF and acute respiratory failure (14 w/ AE)
- Median survival: 3 d
- Overall Survival: 4%
- Select pts with AE have been transplanted at UCSF



Stern et al, Chest 2001

IPF vs. NSIP

- Why distinguish?
  - Different prognosis
  - We have treatments for NSIP
- Distinguishing NSIP from IPF is a challenge!
  - Patients usually younger, more likely to be women
  - Honeycombing on HRCT is uncommon in NSIP
  - Surgical biopsy shows diffuse thickening of alveolar septae and few if any fibroblast foci

NSIP

- The pathologic diagnosis of NSIP should prompt you to go back to look for an etiology
  - Occult connective tissue disease
  - Drug reaction
  - Exposure that could cause Hypersensitivity pneumonitis

CT-ILD

- CTDs associated with ILD
  - Polymyositis-Dermatomyositis, Rheumatoid Arthritis, Scleroderma, Sjogren's syndrome
- Undefined CTD
  - Don't meet ACR criteria for defined CTD
  - Lung may be primary (or only) manifestation of CTD

Diagnostic Criteria for UCTD-ILD

- ≥ 2 S/Sx of CTD
  - Raynaud's
  - Arthralgias
  - Morning stiffness
  - Dry eyes/mouth
  - Dysphagia
  - Unexplained fever
  - GERD
  - Synovitis
  - Telengiectasia
  - Etc…
- ≥ 1 positive serology
  - ANA ≥ 1:640
  - RF > 60 or CCP
  - Antisynthetase Ab
  - Centromere
  - dsDNA
  - PM-Scl
  - RNP
  - Scl-70
  - Smith
  - SSA or SSB

Management of UCTD

- Prednisone + cytotoxic therapy
  - Cellcept, Azathioprine, Cytoxan
- Pulmonary rehabilitation
- Evaluation by rheumatology

UCSF Interstitial Lung Disease Clinic

Clinical Coordinator: (415) 353-8764
Clinic fax: (415) 353-2568

http://www.ucsfhealth.org/adult/medical_services/pulmonary/ild/index.html

References

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