Interstitial Lung Disease 2007

Paul F. Simonelli, MD, PhD, FCCP

Clinical Director
Center for Interstitial Lung Disease
Columbia University Medical Center

ILD: Definition

1. ILD is not one disorder

2. Strictly speaking, an ILD involves the interstitium
   Anatomic structures other than the interstitium can be involved
   - "alveolitis"
   - "vasculitis"
   - "peri-bronchial disease"

What Conditions Belong to "ILD"?

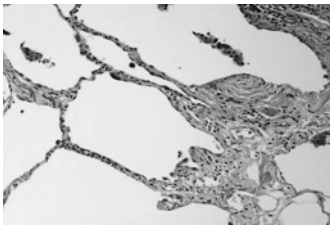
1. Diffuse abnormalities on chest radiology
   "Diffuse Parenchymal Lung Disease" (DPLD) is the more general and preferred term.

2. Similar clinical presentations

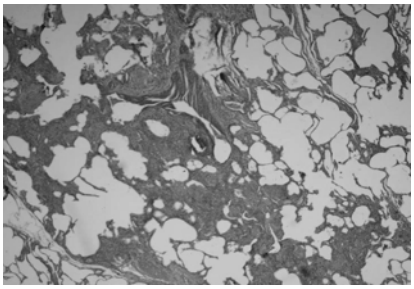
3. Similar physiological consequences

4. Generally, chronic non-infectious, non-neoplastic disease involving the lung parenchyma.

ILD: Thickening of the Interstitium



ILD: Thickening of the Interstitium



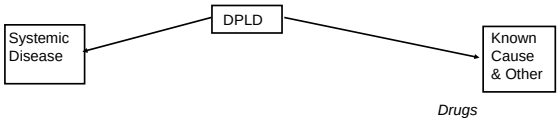
ILD: Cellular and Fibrotic

Slides Courtesy of Alain Borczuk, MD

Classification of Diffuse Parenchymal Lung Disease

Am J Respir Crit Care Med (2002)165:277-304

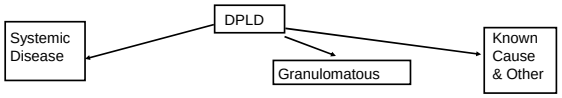
Classification of Diffuse Parenchymal Lung Disease



Drugs
Pneumoconioses
Eosinophilic granuloma

Am J Respir Crit Care Med (2002)165:277-304

Classification of Diffuse Parenchymal Lung Disease

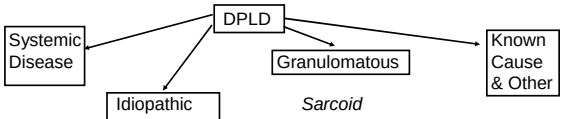


Sarcoid
Chronic hypersensitivity pneumonitis

Drugs
Pneumoconioses
EG

Am J Respir Crit Care Med (2002)165:277-304

Classification of Diffuse Parenchymal Lung Disease



Sarcoid
CHP

Drugs
Pneumoconioses
EG

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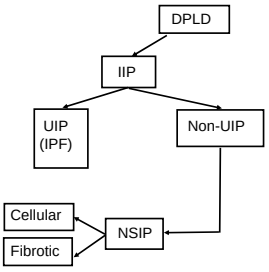
Classification of Diffuse Parenchymal Lung Disease



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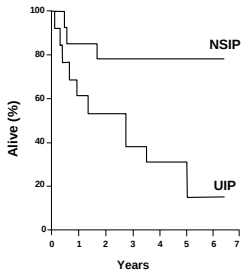
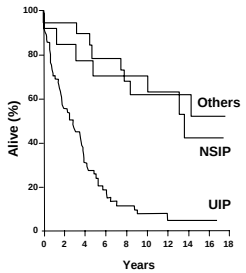
Survival for UIP vs NSIP



Daniil ZD, et al. *Am J Respir Crit Care Med*. 1999;160:899-905.



Bjoraker JA, et al. *Am J Respir Crit Care Med*.1998;157:199-203.

COMPARATIVE MORTALITY RATES

DISEASE	5-YEAR MORTALITY
Lung Cancer	85%
IPF	50-70%
CHF	50%
Colorectal Cancer	38%
Breast Cancer	13%
Prostate Cancer	2%

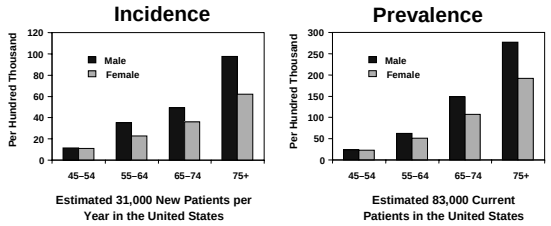
Prevalence of ILD

	MALE	FEMALE
Occupational/ Environmental	20.8	0.6
Drug & Radiation	1.2	2.2
Rheumatologic	7.1	11.6
IPF	20.2	13.2
Pulm Fibrosis (Not IPF)	10.1	14.3
Sarcoidosis	8.3	8.8

(per 100,000/year)

Am J Respir Crit Care Med 1994; 150: 967-972,

Epidemiology of IPF



Weycker D, et al. Prevalence, Incidence, and Economic Costs of Idiopathic Pulmonary Fibrosis. Paper presented at: CHEST 2002, November 2-7, 2002; San Diego, CA.

ILD: CLINICAL HISTORY

- Insidious onset
- Preceding URI
- Occupational Exposure and Cigarette Smoking
- Progressive Dyspnea with Exertion (DOE)
- Paroxysmal cough

ILD: PHYSICAL FINDINGS

- Tachypnea
- Basilar crackles
- May have digital clubbing
- Low lung volume, cyanosis, tachycardia

ILD: PHYSIOLOGIC FINDINGS

- Pulmonary function
  - Restrictive ventilatory defect
    - Reduced total lung capacity (TLC) & FVC
    - Normal or increased FEV_1/FVC ratio
  - Impaired gas exchange
    - Decreased DL_{CO}
    - Desaturation with exercise (pulse oxymetry)
    - Decreased Pa_{O2}
    - Increased A-a gradient

Adapted from ATS/ERS. *Am J Respir Crit Care Med.* 2000;161:646-664.

Pulmonary Function Testing

Examples:

	Obstructive	Restrictive	Normal
FVC	100%	50%	>70%
FEV1	50%	50%	>80%
FEV1/FVC	43%	90%	>70%
TLC	100%	65%	>80%
RV	105%	60%	
FRC	95%	55%	
DlCO	50%	50%	>80%

Six Minute Walk Testing in ILD

Patient encouraged to walk at a maximal pace with as many stops as necessary

Oxygenation (desaturation) and symptom scores are measured

Desaturation may occur in other conditions
- Pulmonary hypertension
- Severe COPD
- Heart failure

Six Minute Walk Testing in ILD

Primary end-point is distance walked

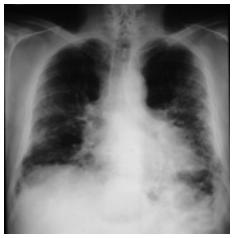
6MWT distance is used as a primary endpoint in clinical trials for ILD therapy

Degree of desaturation may have prognostic significance

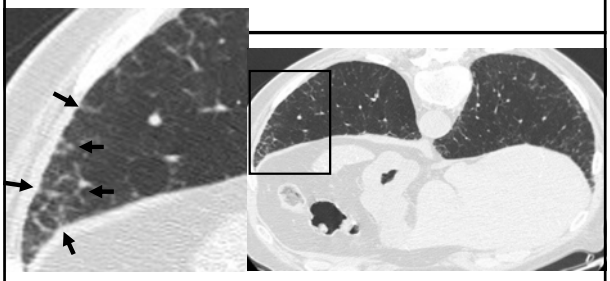
Desaturation during initial 6MWT predicts decreased survival:

Disease	Desaturation	4-Year Survival	
UIP (IPF)	Yes	35%	
	No	69%	n=83, p=0.0018
NSIP	Yes	66%	
	No	100%	n=22, p=0.0089

ILD: PLAIN CHEST X-RAY

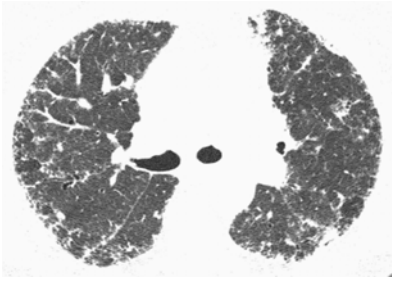


ILD: Early HRCT Findings



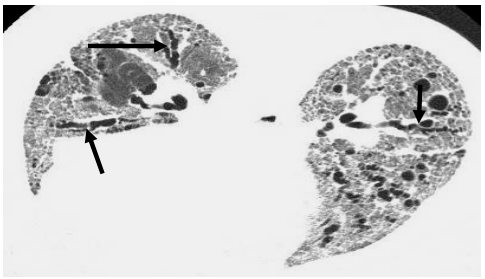
Courtesy of David A. Lynch, MD.

ILD: Early HRCT Findings



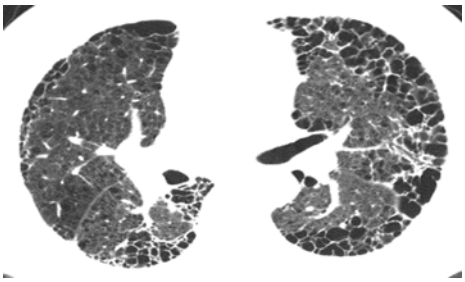
Courtesy of David A. Lynch, MD.

ILD: Traction Bronchiectasis



Courtesy of W. Richard Webb, MD.

ILD: HONEYCOMBING



Courtesy of W. Richard Webb, MD.

ILD: Case Presentation

50 year old man with “rapidly progressive IPF” transferred to CUMC 1/03

Pulm Hx: Cigarette smoking @ 1.5 ppd, teens - 45
Pneumonia 2/02, with full recovery

PMH: Gout
OA

Occupation: Mason

Case Presentation: HPI

7/97-12/00: Subtle bibasilar infiltrates

9/02: Persistent cough
Mild DOE

11/02: Extensive infiltrates, Restrictive PFT's

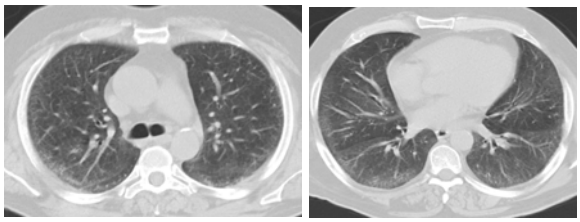
Case Presentation: HPI

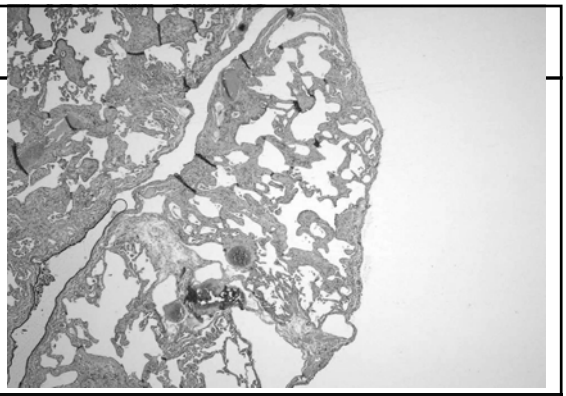
12/02: Surgical Lung Biopsy
(Lingula & SS-LLL)

12/02: Predisone 60 mg/d (0.7 mg/kg/d)

12/02: URI, oral antibiotics
Acute decompensation
Dexamethasone 30 mg/d

CASE PRESENTATION: HRCT





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Case Presentation: Clinical Course

3/03: Prednisone 25 mg/d
Pulmonary Rehabilitation
Less Dyspneic

4/03: Transplant Evaluation
PA 25/13 (17)
PCW (2)

7/03: Off Prednisone
Full-time work
SpO2 95 - 83% with stair climbing

Case Presentation: PFT's

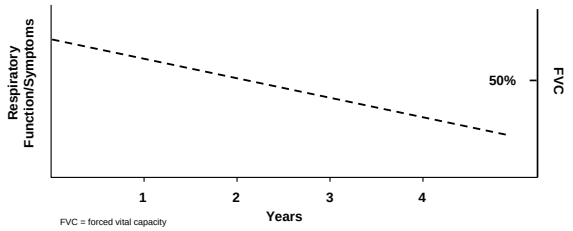
DATE:	1/03	3/03	4/03	7/03	9/03
FVC	2.5L (59%)	2.6	3.0	3.1	2.9
FEV1	2.2L (63%)	2.3	2.7	2.8	2.7
F/V	88%	88%	90%	90%	91%
TLC	3.7L (61%)				
FRC	2.0L (65%)				
DLCO	7.8L (24%)				
SpO2 (R)	92%	89%	92%	95%	91%
SpO2 (EX)	81%		79%	83%	
6MWT	1365'				

Case Presentation: Exercise Physiology

CPET	1/8/03	10/7/03
TIME	7 min	8 min
MAX WORK	65 watts	60 watts (32%)
VO2-max	12.2 ml/min/kg (37%)	11.1 (34%)
VE/VCO2	47	51
MVV	86 L/min (58%)	124 (85%)

Progression of IPF: Acute Exacerbation vs Slow Decline

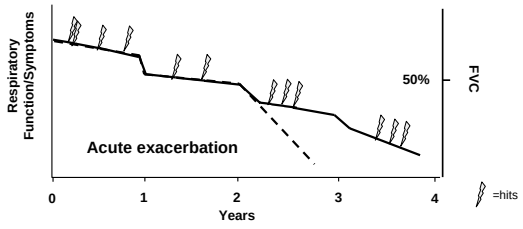
Traditional View of UIP/IPF Progression



FVC = forced vital capacity

Progression of IPF: Acute Exacerbation vs Slow Decline

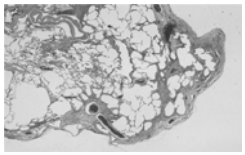
Step Theory of UIP/IPF Progression



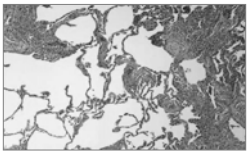
Am J Respir Cell Mol Biol. 2003;29(3 suppl):S1-S105.

Pathological Sections Demonstrating UIP

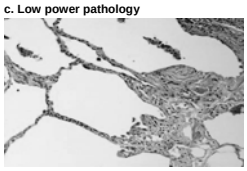
a. Peripheral accentuation of the disease



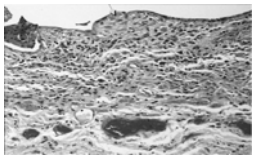
b. Transition into uninvolved lung



c. Low power pathology

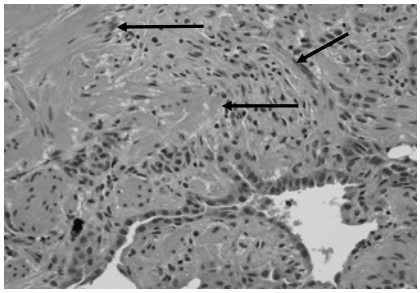


d. High power image of fibroblastic focus



Courtesy of Kevin O. Leslie, MD.

Myofibroblast Proliferation in UIP



Slide courtesy of Alain Borczuk, MD.

Multiple Hypotheses for the Pathogenesis of IPF

- *Inflammation causes fibrosis*
- *Noninflammatory (multiple hit) hypothesis: fibrosis results from epithelial injury and abnormal wound healing in the absence of chronic inflammation*
- *Vascular remodeling: aberrant vascular remodeling supports fibrosis, and may contribute to increased shunt and hypoxemia*
- *Abnormalities in host defense.*

Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii.
Raghu G, Chang J. *Clin Chest Med*. 2004;25: 621-636, v.
Strieter R. *Am J Respir Cell Mol Biol*. 2003;29(3 suppl):S67-S69.

Inflammatory Hypothesis

- *Inflammation causes fibrosis*
  - Inflammatory concept was dominant in the 1970s and 1980s
    - IPF resulted from unremitting inflammatory response to injury culminating in progressive fibrosis
  - Role of inflammation remains controversial
    - Lack of efficacy of corticosteroids

Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii.
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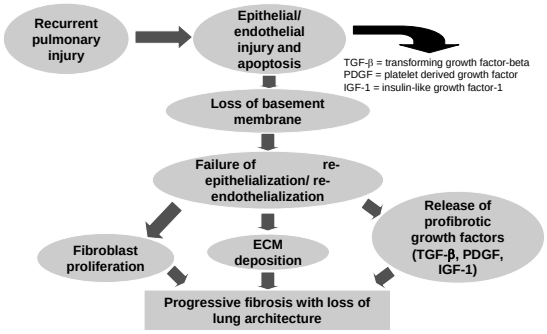
Noninflammatory (multiple hit) Hypothesis



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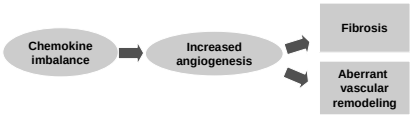
Raghu G, Chang J. *Clin Chest Med*. 2004;25:621-636, v.
Selman M, et al. *Drugs*. 2004;64:405-430.

Vascular Remodeling Hypothesis

- *Aberrant vascular remodeling supports fibrosis and may contribute to increased shunt and hypoxemia*
  - Increased angiogenesis results from imbalance of pro-angiogenic chemokines (IL-8, ENA-78) and anti-angiogenic, IFN-inducible chemokines (IP-10)
  - Vascular remodeling leads to anastomoses between the systemic/pulmonary microvasculature, increasing right-to-left shunt, contributing to hypoxemia



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Strieter RM, et al. *Am J Respir Cell Mol Biol*. 2003;29(3 suppl):S67-S69.

Defects in Host Defense Mechanisms May Contribute to Fibrosis

- Defects in endogenous host defense mechanisms (eg, IFN-γ, PGE2 production) that limit fibrosis after acute lung injury may contribute to progressive fibrosis

Noble PW, Homer RJ. *Clin Chest Med*. 2004;25:749-758, vii.

Center for Interstitial Lung Disease

A multi-disciplinary group at NY-Presbyterian Hospital, based in the Jo-Ann LeBuhn Center for Chest Disease

Goals:
- Diagnosis
- Monitoring disease progression
- Coordination of therapy
- Clinical trials
- Investigative research

Center for Interstitial Lung Disease

Composition of the multi-disciplinary group

Pulmonologists	Clinical coordinators
Lung pathologists	Physical therapists
Chest radiologists	Respiratory techs.
Exercise Physiologists	Outside consultants
Rheumatologists	Cardiologists
Transplant physicians	Thoracic surgeons
Basic researchers	(Medical Informatics)

Center for Interstitial Lung Disease

Potential system-wide goals & projects:

- Data base
  - Diagnosis, natural history, pathogenesis
- Diagnosis
  - Central review of cases, clinical conferences
- Coordination of care
  - Clinical trials, transplant/tertiary care
- Basic research