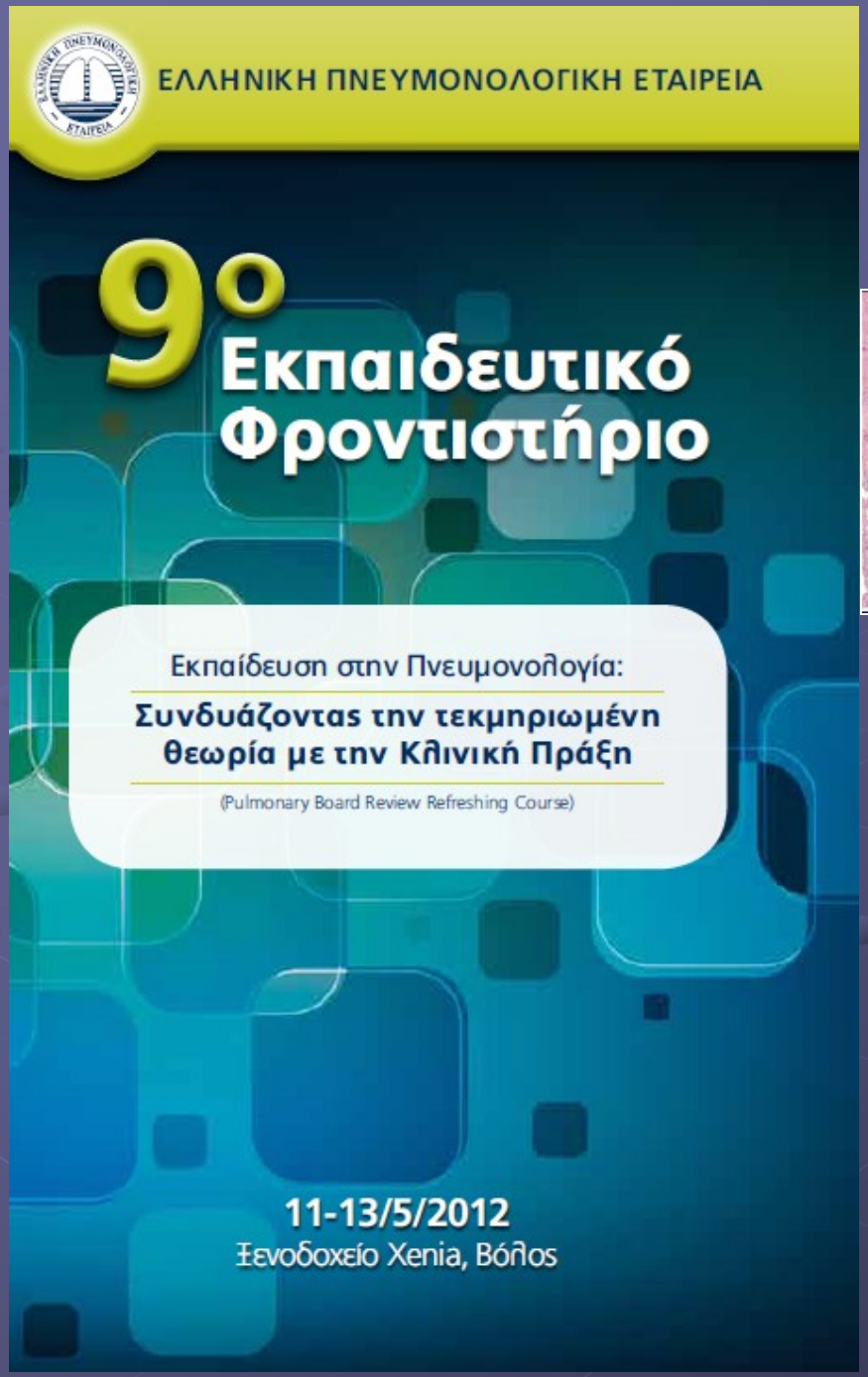
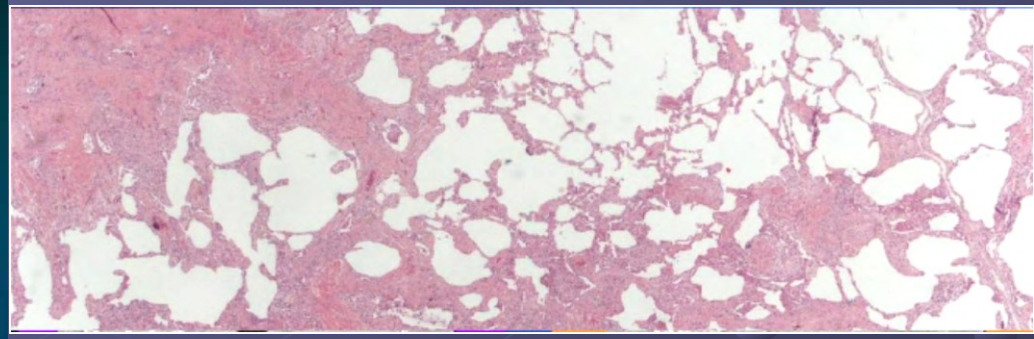


Διάμεσες Πνευμονοπάθειες



Ευφροσύνη Μάναλη
Α΄ Πνευμονολογική Κλινική
ΝΝΘΑ «Η Σωτηρία»
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

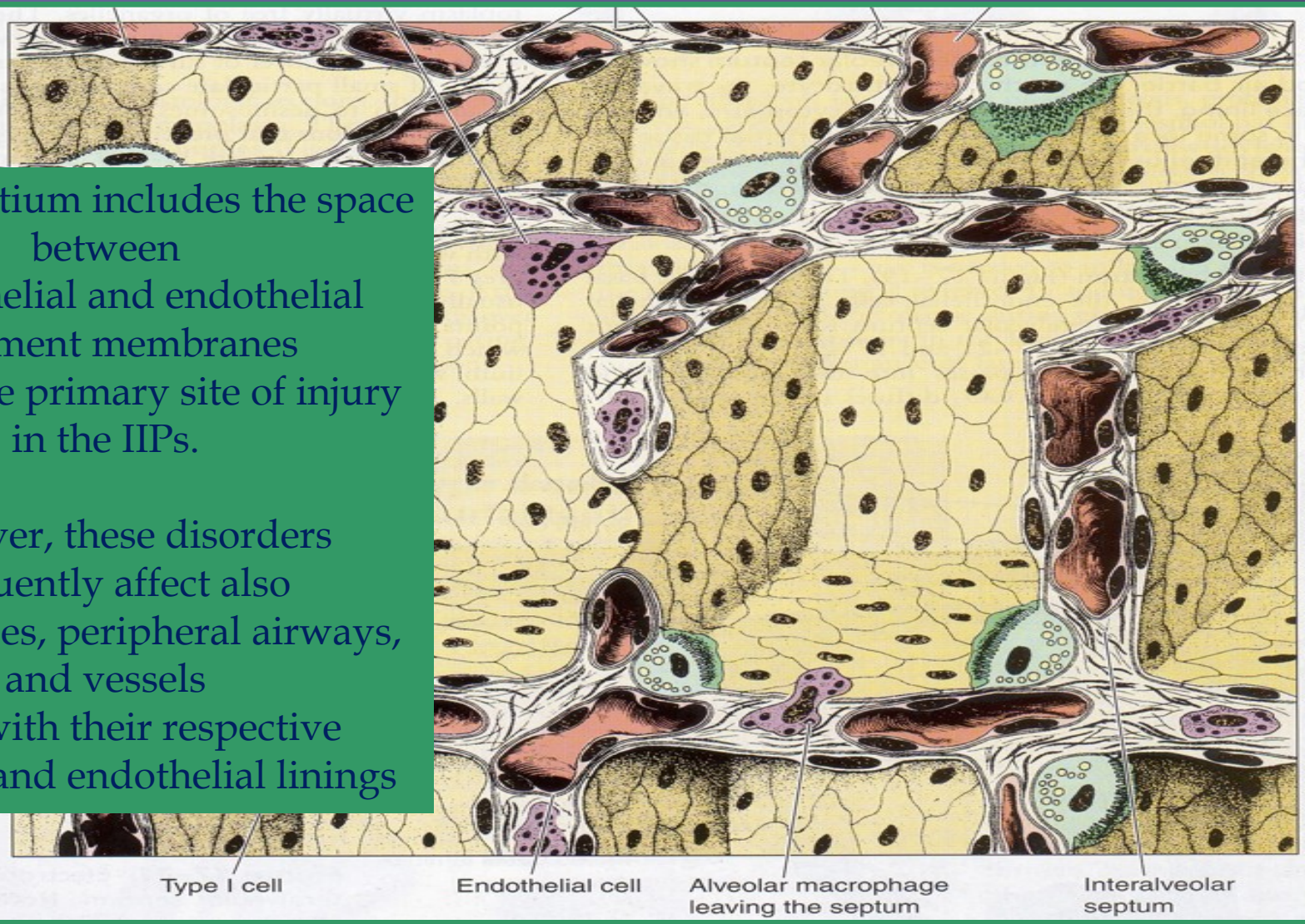
Ορισμός

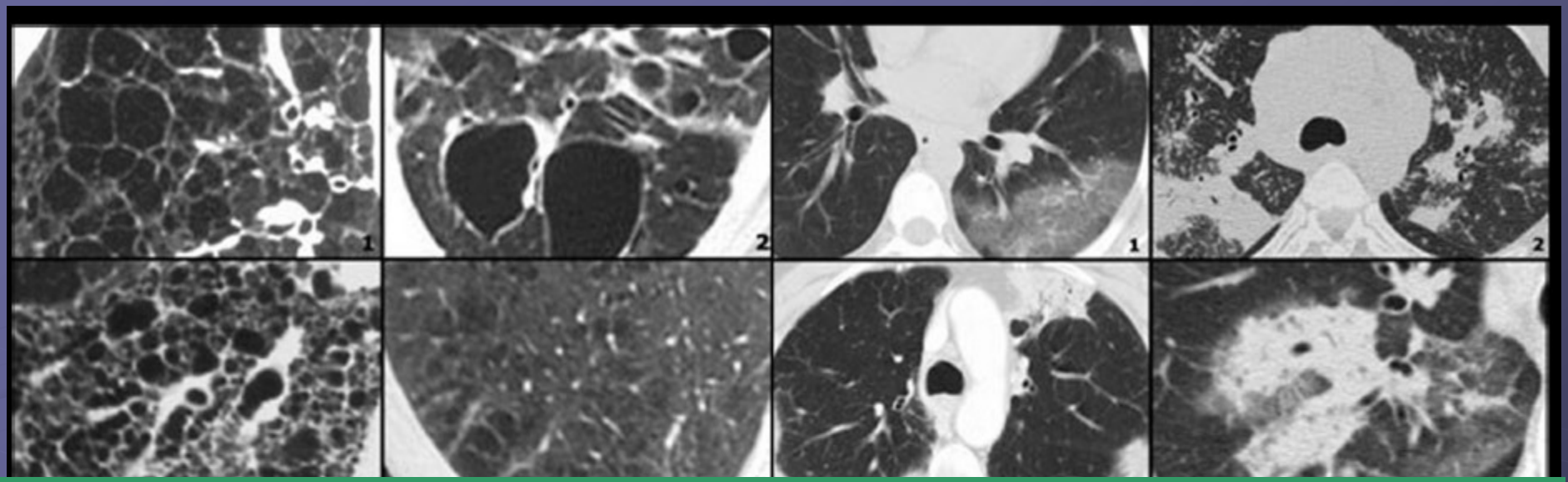
The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases (DPLDs), a group also described as interstitial lung diseases.
The IIPs are a heterogeneous group of non neoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis.

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

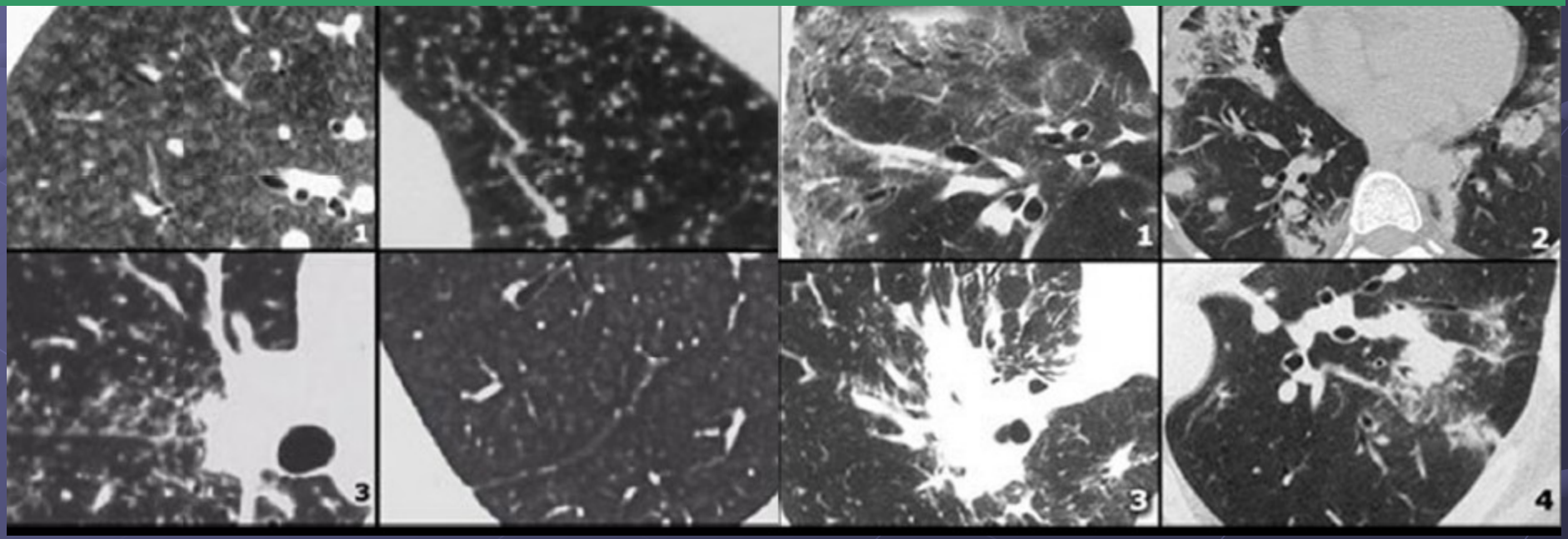
The interstitium includes the space between
the epithelial and endothelial basement membranes
and it is the primary site of injury in the IIPs.

However, these disorders frequently affect also
the airspaces, peripheral airways, and vessels
along with their respective epithelial and endothelial linings





However, these disorders frequently affect also
the airspaces, peripheral airways, and vessels
along with their respective epithelial and endothelial linings



In Remembrance of Averill A. Liebow

March 31, 1911–May 31, 1978

- «Ἤ τοι μεν πρώτιστα χάος γένετο»
  Ησίοδος Θεογονία
  - "In the beginning there was chaos"
- "Disease is an orderly process that continues forward and requires persistent effort to be understood"
- "Seek lux et veritas…"

Am J Pathol 1978; 92:577

Ιστορία

FULMINATING DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS.

By LOUIS HAMMAN, M.D., and ARNOLD R. RICH, M.D.,
BALTIMORE, MD.

…the diagnosis was made of the peculiar form of universal pulmonary fibrosis we are describing…

…the most conspicuous alteration is an extraordinary and progressive proliferation of fibroblasts *within the walls of the alveoli*.
The walls are greatly thickened by this growth of fibrous tissue…

Trans Am Clin Climatol Assoc 1935; 51: 154-163

Ιστορία

- Sheridan and colleagues 1964: chronic disease with an average survival 2-4 yr
- Gaensler and coworkers 1964: established that open lung biopsy could be performed safely (ante mortem diagnosis) N Engl J Med 1964; 270:1319
- P Gross 1962: Hamman-Rich syndrome "acute diffuse interstitial fibrosis of the lungs" may in some cases be a chronic fibrosis with an acute superimposed exacerbation that is either infectious or non-infectious. Loss of integrity of epithelial basement membrane and failure of successful re-epitheliazation

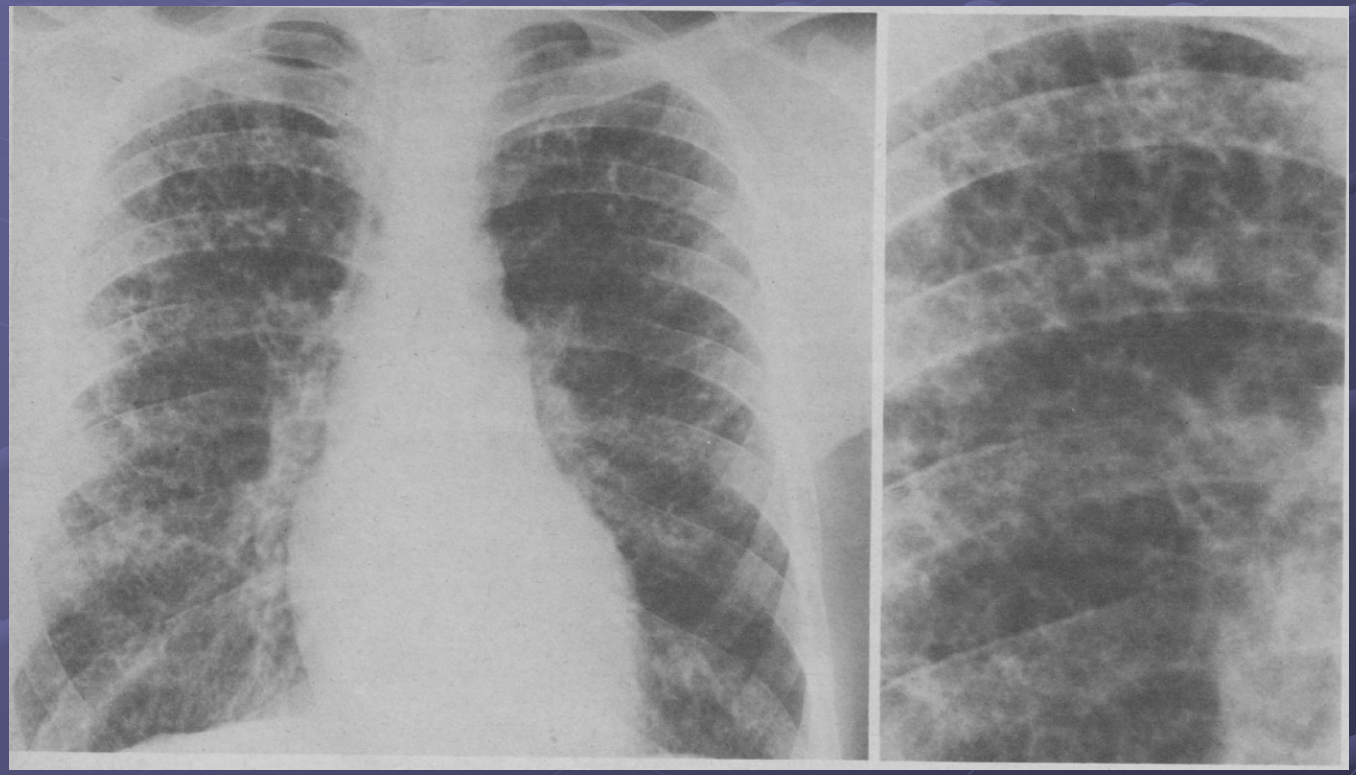
Topics in Radiology / *Gamut of the Month*

Benjamin Felson, MD, *Coordinator*

Honeycomb Lung (Interstitial Fibrosis)

Common

1. [Cystic bronchiectasis]
2. Histiocytosis X (especially eosinophilic granuloma)
3. Idiopathic interstitial fibrosis (Hamman-Rich)



JAMA, Feb 10, 1975 • Vol 231, No 6

Thorax, 1980, **35**, 171–180

Cryptogenic fibrosing alveolitis: clinical features and their influence on survival

M TURNER-WARWICK, B BURROWS, AND A JOHNSON

From the Cardiothoracic Institute, Brompton Hospital, London

A retrospective analysis of 220 cases fulfilling criteria for CFA attending the Brompton Hospital between 1955 and 1973 has been carried out and patients have been followed for between four and 21 years.

DEFINITION OF CRYPTOGENIC FIBROSING ALVEOLITIS (CFA)

The defining criteria are those described by Turner-Warwick and Haslam[6] as follows:

1 All patients in whom an external fibrogenic agent could be implicated were excluded, and to this end a detailed occupational and clinical history was obtained; all patients in whom precipitins to *M faeni* or avian antigens were found have also been excluded.

2 Where a lung biopsy was available, criteria for inclusion included the histological features of fibrosis of the alveolar walls with varying amounts of interstitial and intra-alveolar infiltrate and the absence of granuloma or intra-alveolar organisation, or evidence suggesting a pneumoconiosis.

3 When no biopsy was available, the additional obligatory criteria were widespread persistent bilateral radiographic shadowing and widespread persisting crackles. Supportive but not obligatory criteria were finger clubbing and a restrictive physiological defect.

(mean survival 3.2 years)

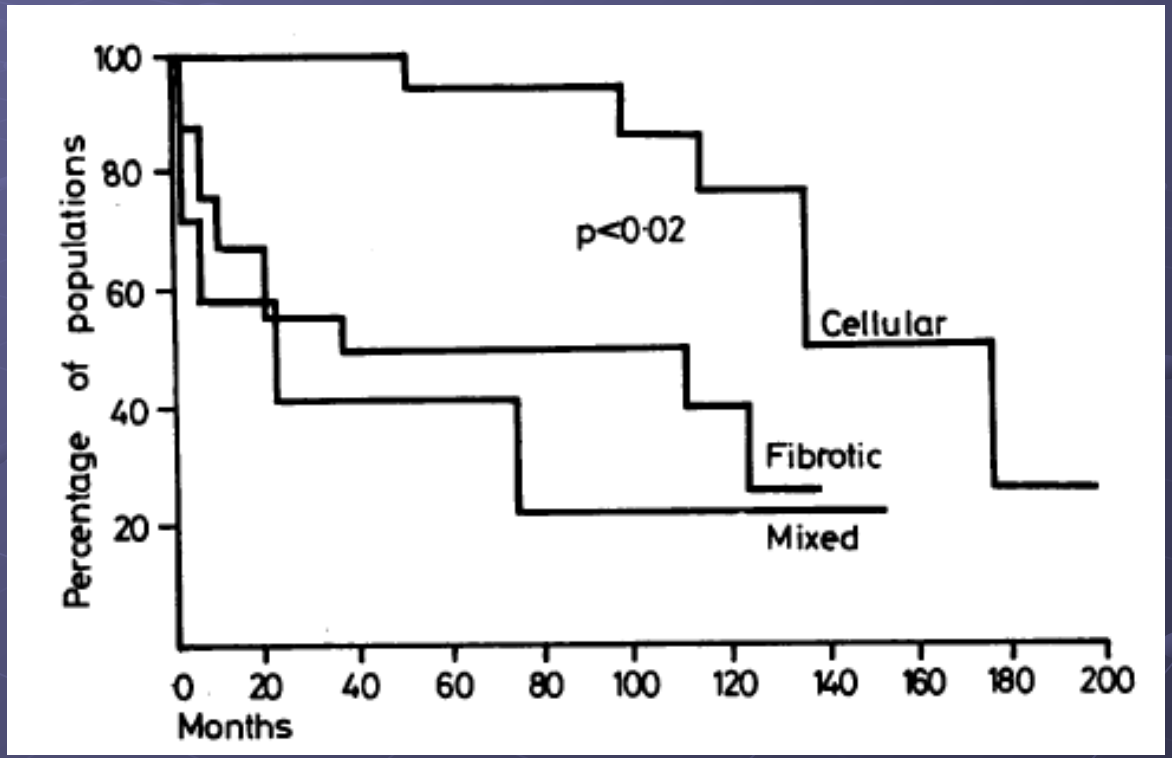


TABLE 1. PREVIOUS CLASSIFICATIONS OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

Liebow and Carrington (1969)*: Chronic Forms	Katzenstein (1997)†	Müller and Colby (1997)‡
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/ respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage		Bronchiolitis obliterans organizing pneumonia
	Acute interstitial pneumonia	Acute interstitial pneumonia
	Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia		
Giant cell interstitial pneumonia		

American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JUNE 2001 AND BY THE ERS EXECUTIVE COMMITTEE, JUNE 2001

Am J Respir Crit Care Med Vol 165. pp 277–304, 2002
Internet address: www.atsjournals.org

Interstitial lung disease guideline

A U Wells, N Hirani and on behalf of the BTS Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society

Thorax 2008;63;v1-v58
doi:10.1136/thx.2008.101691

American Thoracic Society Documents

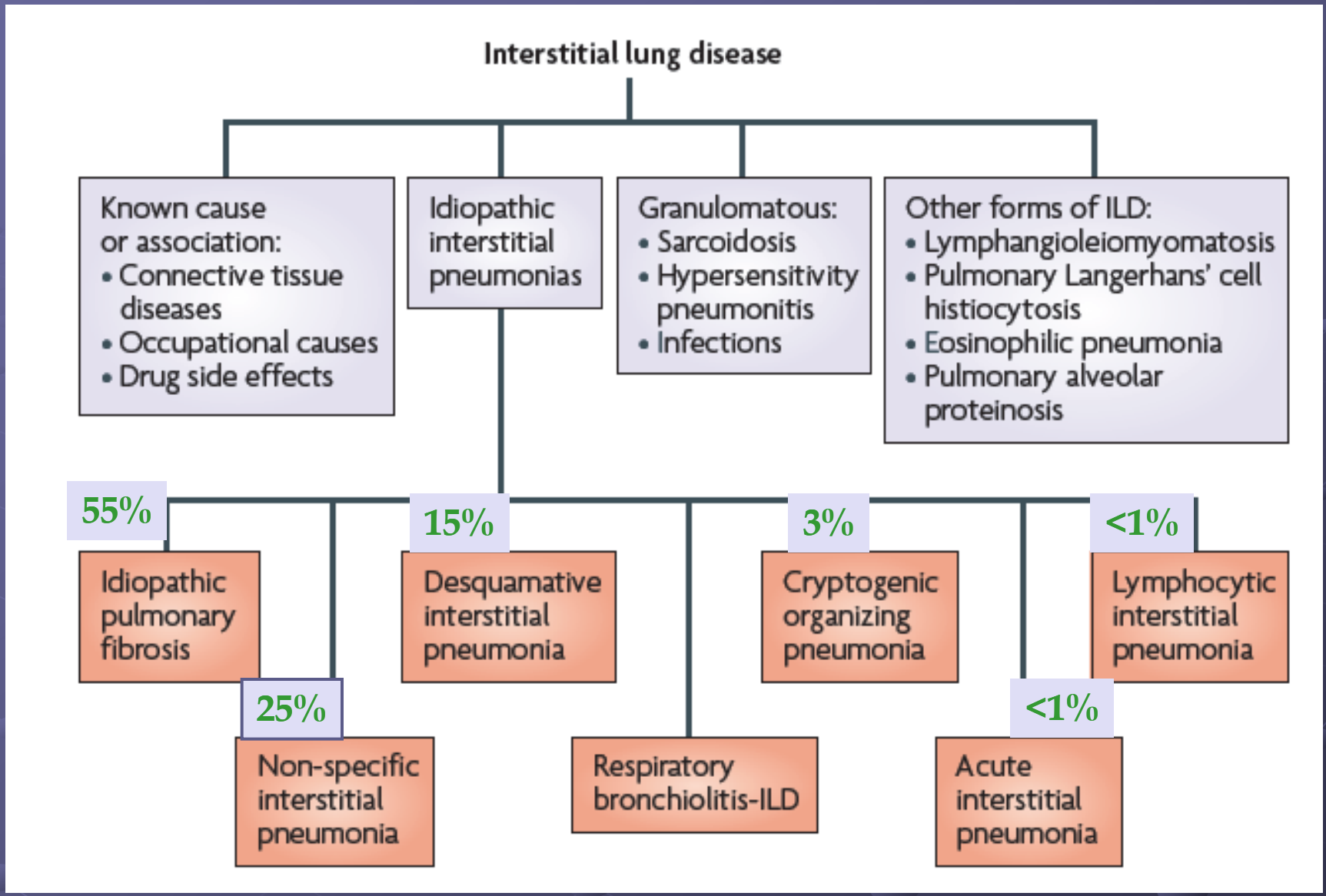
An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), THE EUROPEAN RESPIRATORY SOCIETY (ERS), THE JAPANESE RESPIRATORY SOCIETY (JRS), AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 2010, THE ERS EXECUTIVE COMMITTEE, SEPTEMBER 2010, THE JRS BOARD OF DIRECTORS, DECEMBER 2010, AND THE ALAT EXECUTIVE COMMITTEE, NOVEMBER 2010

THIS STATEMENT HAS BEEN FORMALLY ENDORSED BY THE SOCIETY OF THORACIC RADIOLOGY AND BY THE PULMONARY PATHOLOGY SOCIETY

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011
DOI: 10.1164/rccm.2009-040GL
Internet address: www.atsjournals.org



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

In the revision of the IIPs classification, the main entities are preserved, further subdivided in:

1. **major IIPs including, idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (iNSIP), respiratory bronchiolitis interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), and acute interstitial pneumonia (AIP),**

2. **rare IIPs including, idiopathic lymphoid interstitial pneumonia (iLIP), idiopathic pleuropulmonary fibroelastosis**

3. **unclassifiable IIPs**

Papiris SA, Bouros D. Curr Opin Pulm Med 2012 *in press*
Colby T. Curr Opin Pulm Med 2012 *in press*

Reason for a specific diagnosis

- Many forms are treatable
- Treatments depend on diagnosis
- Prognosis varies
- Clinical trial eligibility requirements

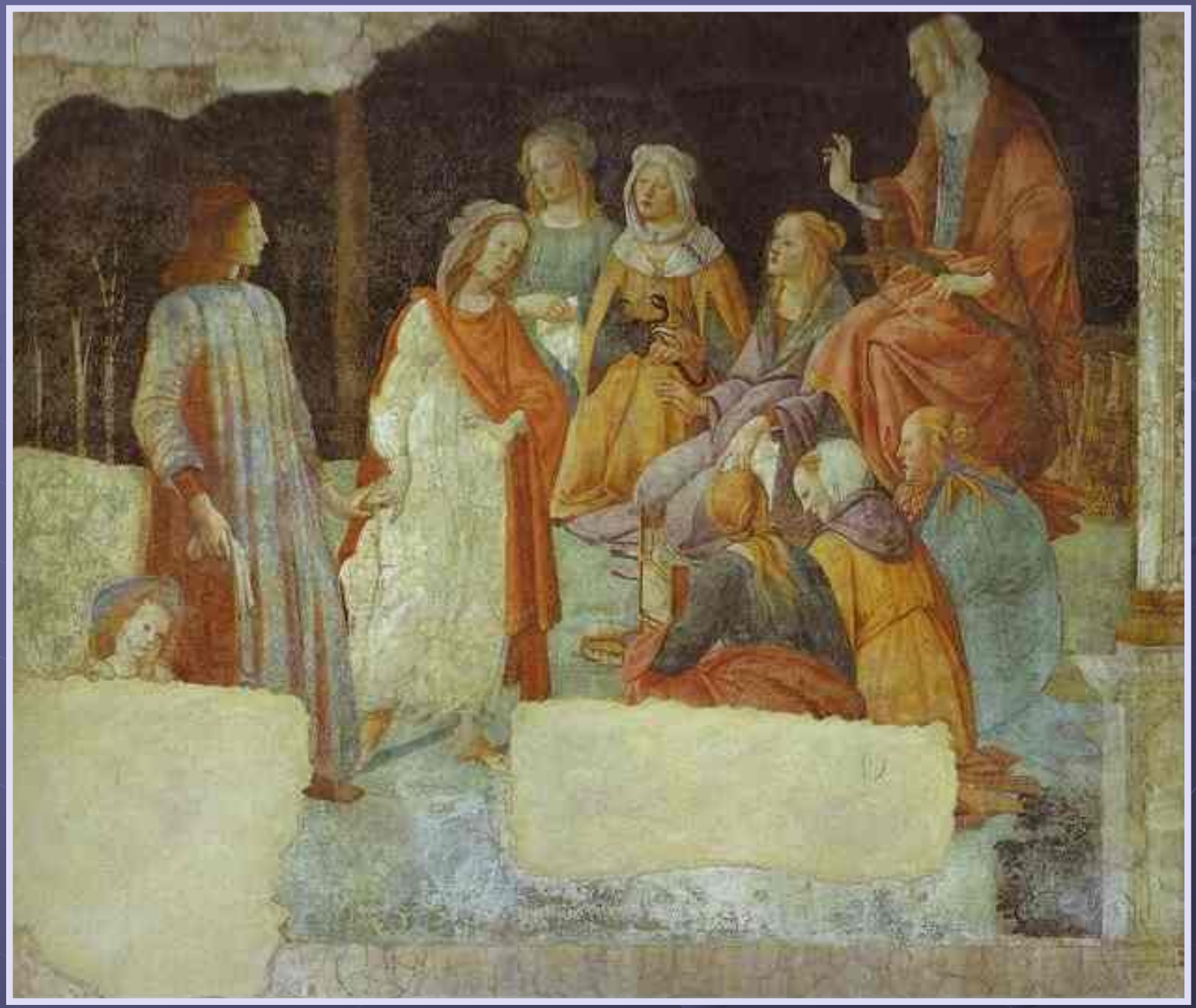
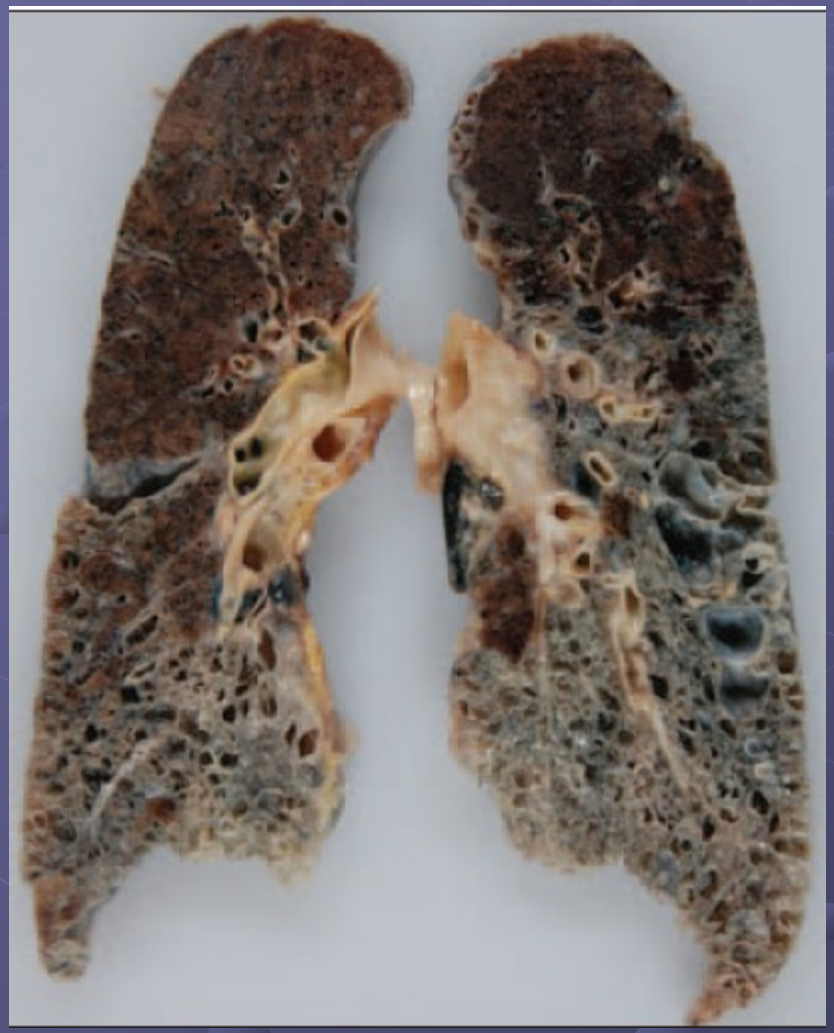


TABLE 2. HISTOLOGIC AND CLINICAL CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS*

Histologic Patterns	Clinical–Radiologic–Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia (provisional)†
Organizing pneumonia	Cryptogenic organizing pneumonia‡
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

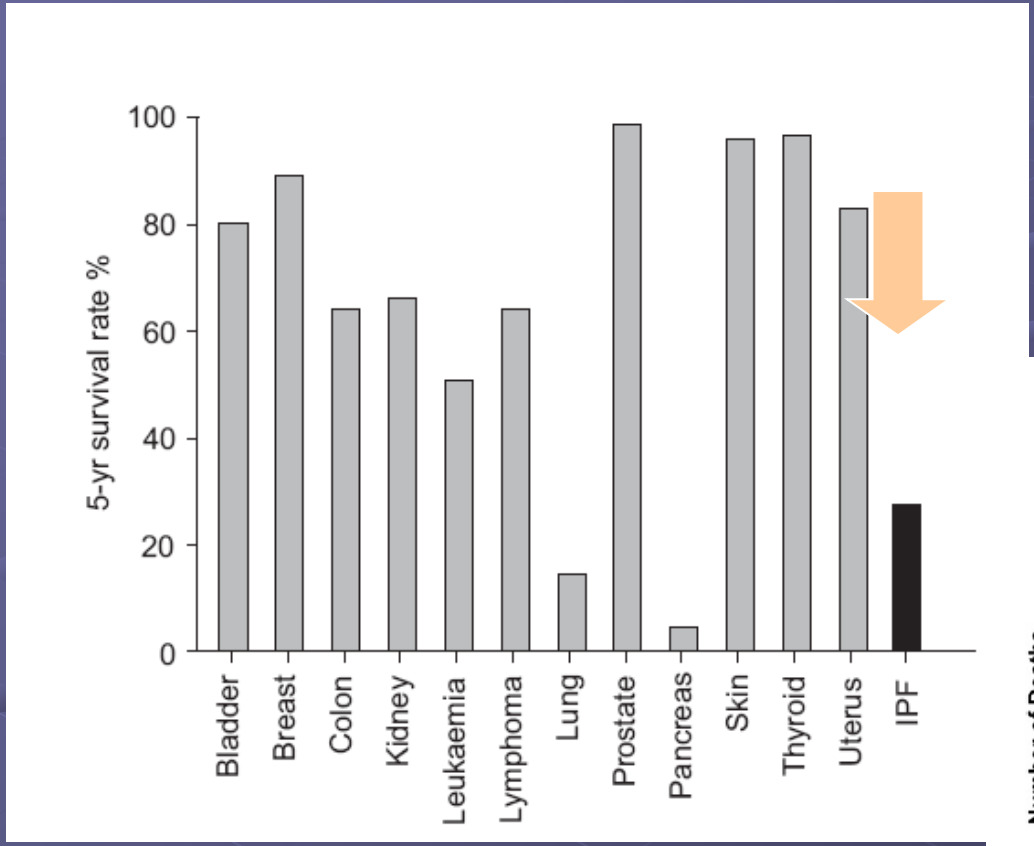
Idiopathic pulmonary fibrosis
Definition



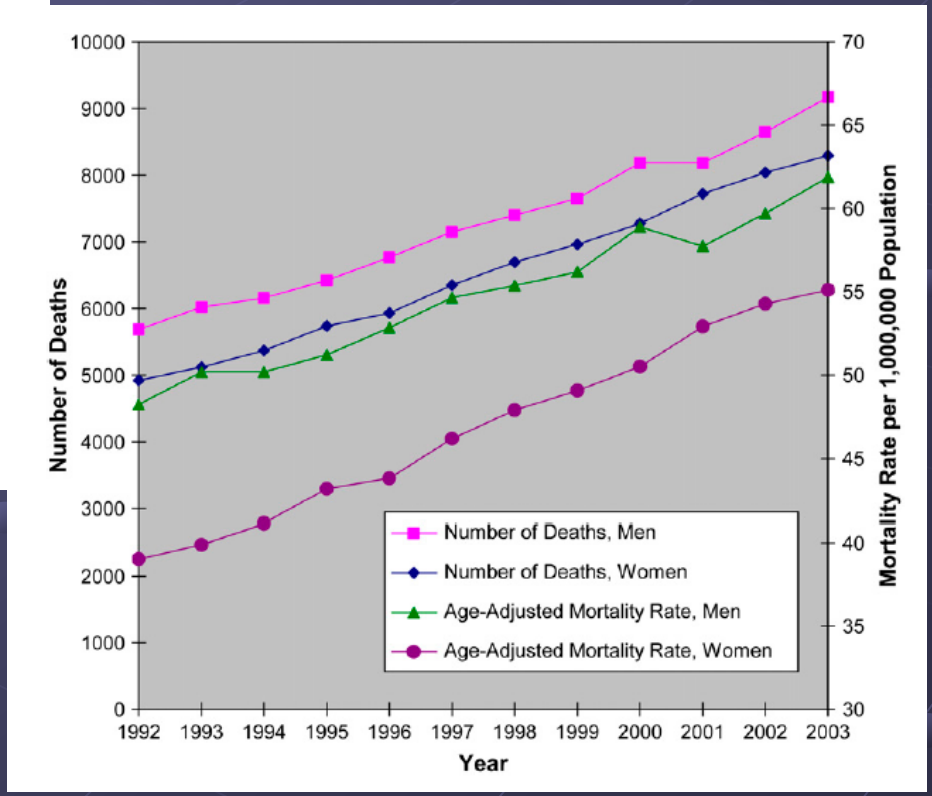
IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP.

The definition of IPF requires the exclusion of other ILDs associated with environmental exposure, medication, or systemic disease

Idiopathic pulmonary fibrosis
the most common and life threatening ILD

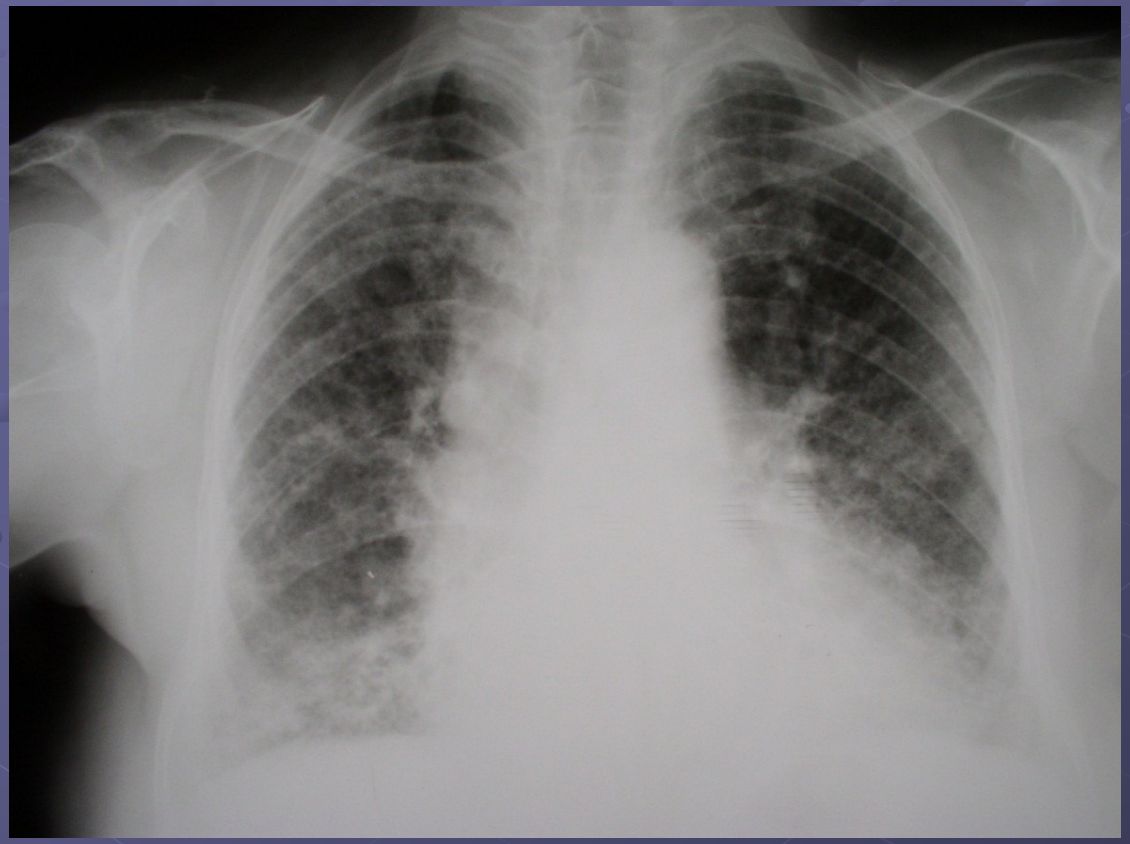


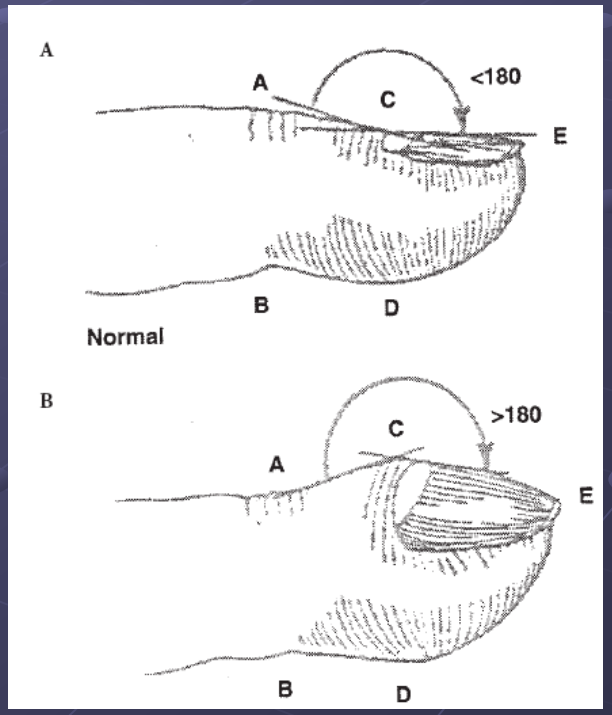
IPF is a dreadful, chronic and irreversibly progressive fibrosing interstitial pneumonia leading to death in all patients affected



Vancheri C, et al. Eur Respir J 2010; 35:496
Papiris SA, et al. Crit Care 2010; 14: 246

Idiopathic pulmonary fibrosis
Clinical presentation

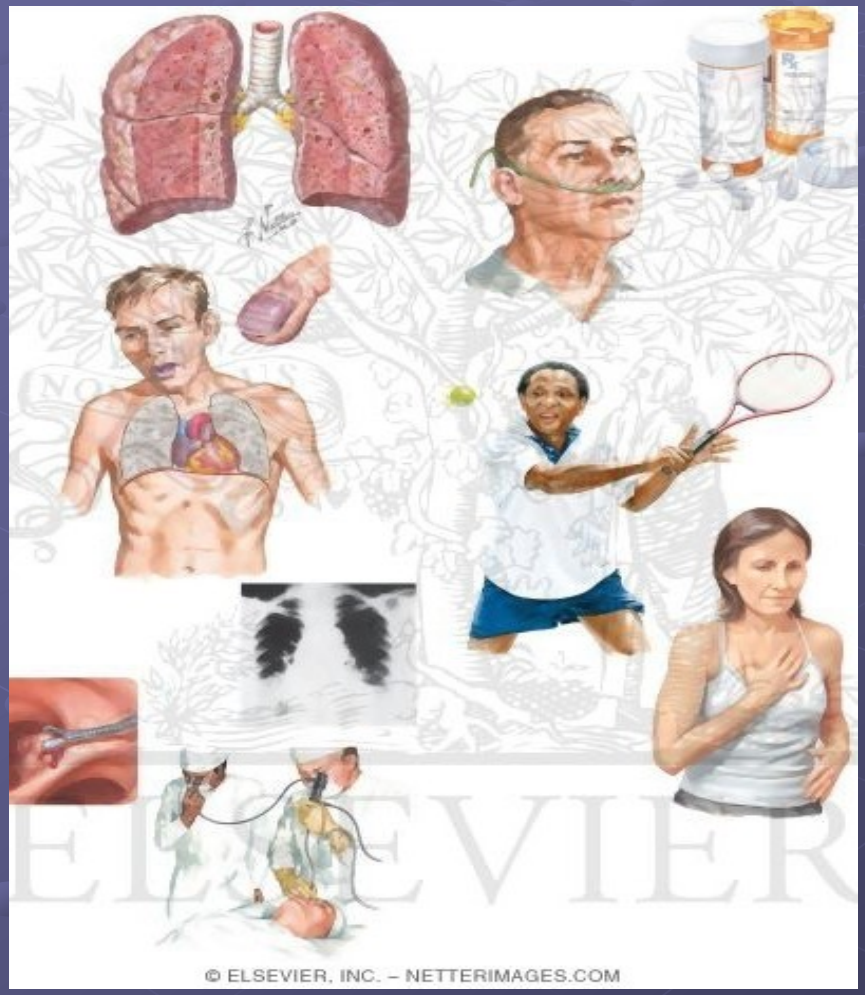




Idiopathic pulmonary fibrosis

Clinical presentation

Symptoms may precede diagnosis by a median of 1-2 years

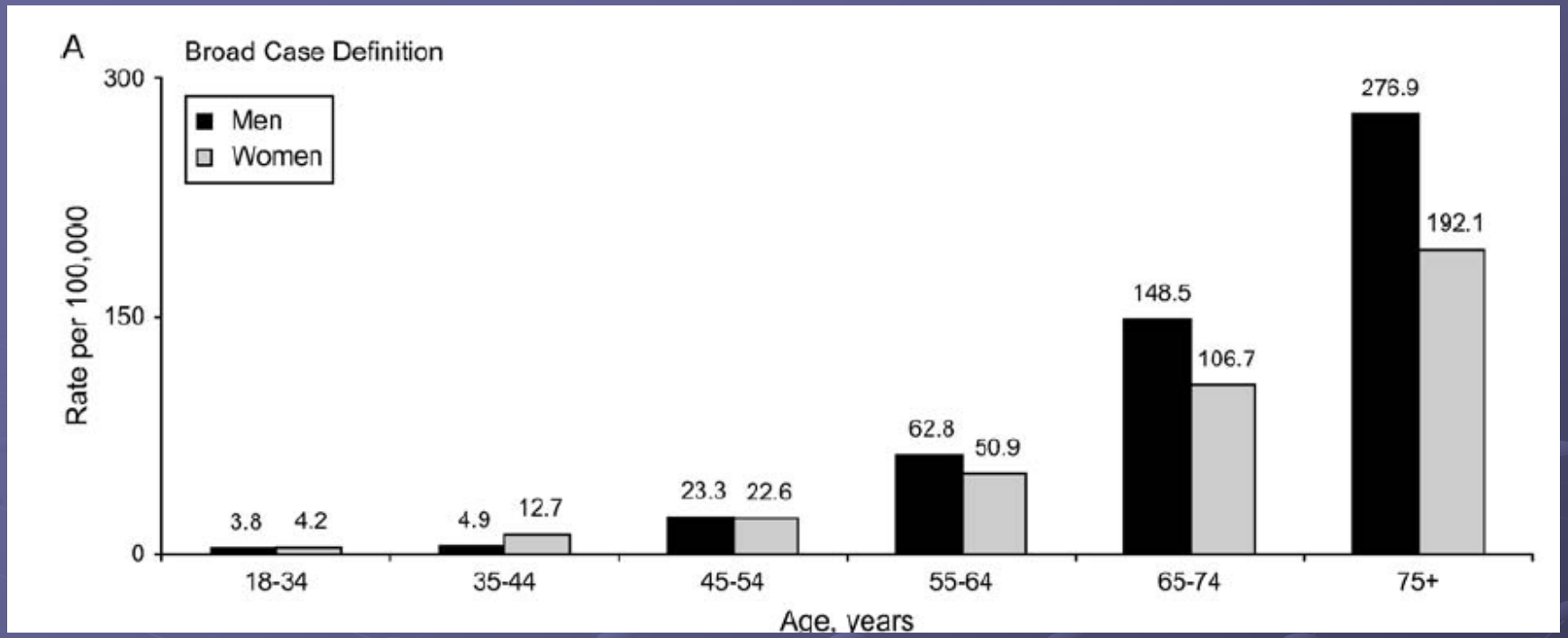


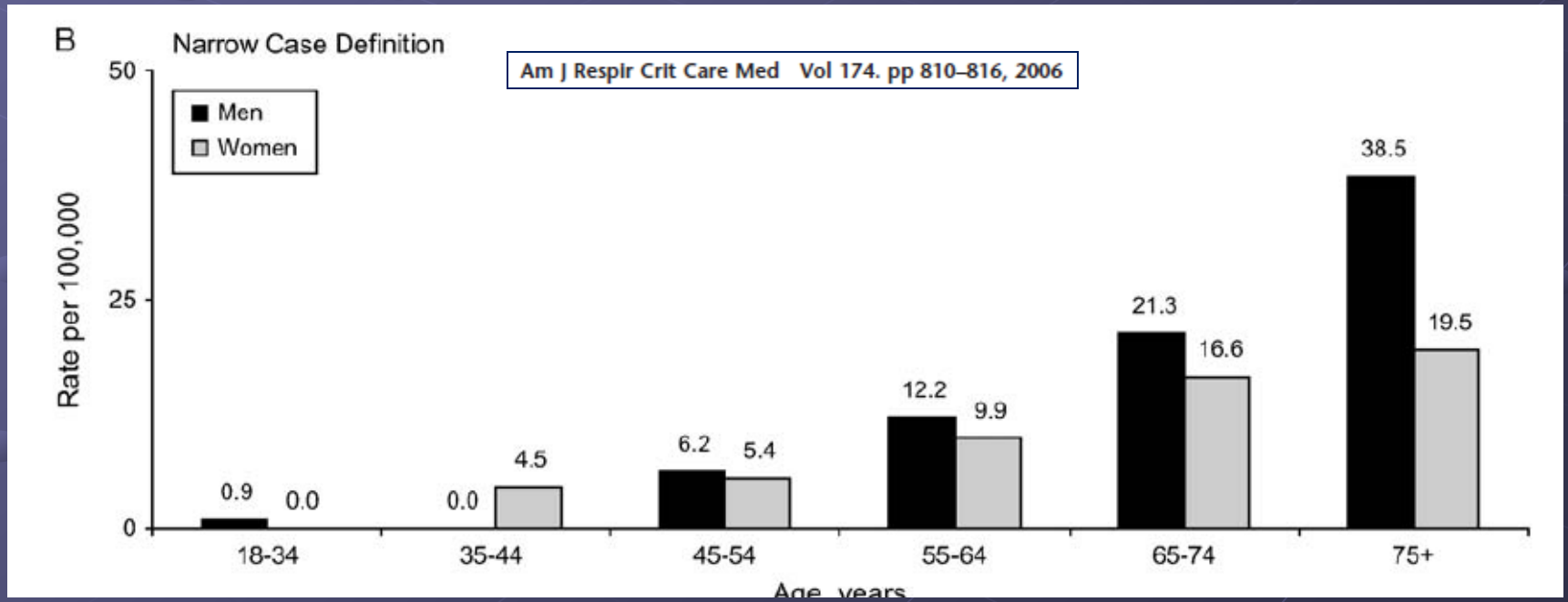
- In IPF a combination of inflammatory and fibrotic lung parenchymal damage leads to the defects in gas mechanics and gas exchange

  and exertional dyspnea,

  the most prominent and disabling symptom in these patients

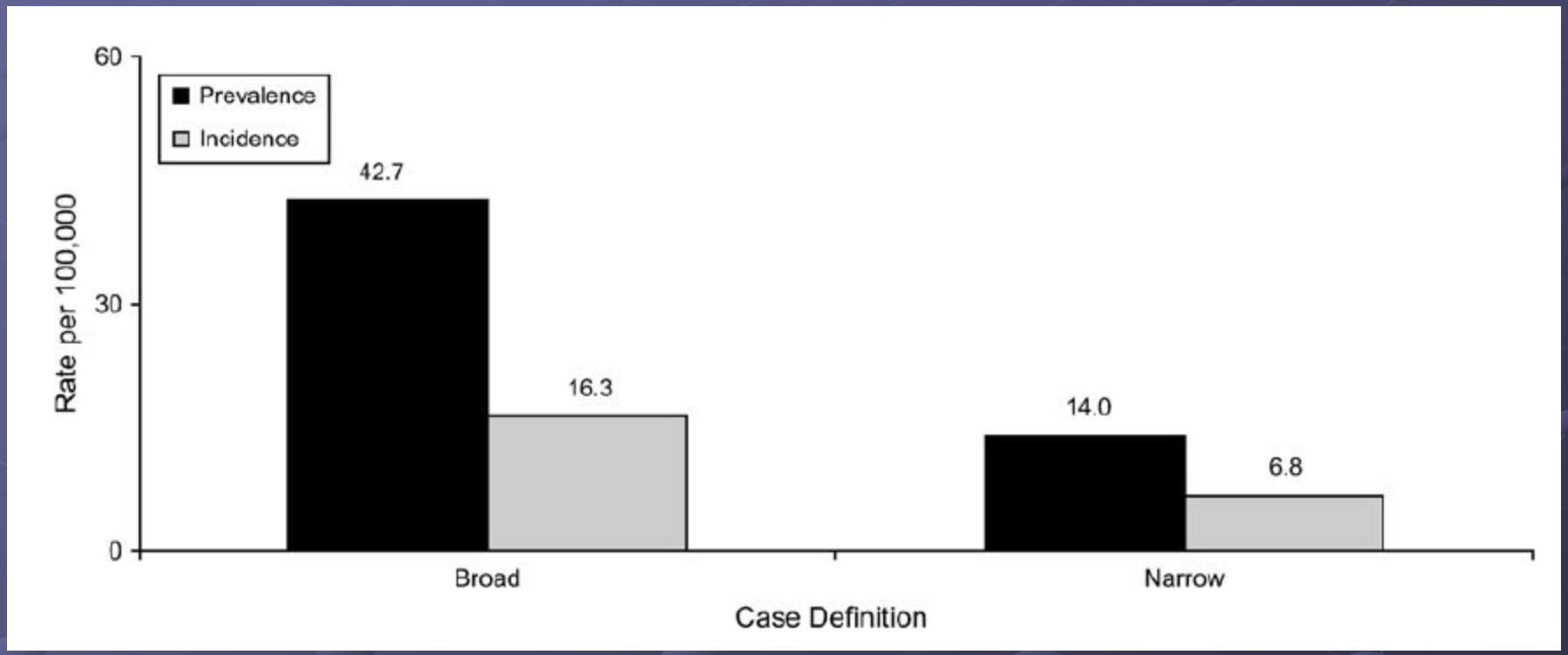
- Cough
- Finger clubbing
- Inspiratory crackles


A
Broad Case Definition
Men
Women
Rate per 100,000
300
150
0
3.8
4.2
4.9
12.7
23.3
22.6
62.8
50.9
148.5
106.7
276.9
192.1
18-34
35-44
45-54
55-64
65-74
75+
Age, years


B
Narrow Case Definition
Am J Respir Crit Care Med Vol 174. pp 810–816, 2006
Men
Women
Rate per 100,000
50
25
0
0.9
0.0
0.0
4.5
6.2
5.4
12.2
9.9
21.3
16.6
38.5
19.5
18-34
35-44
45-54
55-64
65-74
75+
Age, years

Incidence and Prevalence of Idiopathic Pulmonary Fibrosis

Ganesh Raghu, Derek Weycker, John Edelsberg, Williamson Z. Bradford, and Gerry Oster



Am J Respir Crit Care Med Vol 174. pp 810–816, 2006

Epidemiology of interstitial lung diseases in Greece☆

A. Karakatsani [a], D. Papakosta [b], A. Rapti [c], K.M. Antoniou [d], M. Dimadi [c], A. Markopoulou [e], P. Latsi [f,☆], V. Polychronopoulos [g], G. Birba [c], Labrakis Ch [c], D. Bouros [h,*,i]

Table 1 Numbers of prevalent cases of ILDs in the Greek population.

Clinical entity	Prevalent cases (%)	Prevalence (10^{-5})
Sarcoidosis	330 (34.1)	5.89
IIPs	285 (29.5)	5.09
IPF—UIP	189 (19.5)	3.38
NSIP	27 (2.8)	0.48
COP/BOOP	51 (5.3)	0.91
LIP	4 (0.4)	0.07
RBILD	4 (0.4)	0.07
DIP	8 (0.8)	0.14
AIP	2 (0.2)	0.04
Connective tissue diseases	120 (12.4)	2.14
Scleroderma	45 (4.6)	0.80
Rheumatoid arthritis	43 (4.4)	0.77
Dermatomyositis/polymyositis	7 (0.7)	0.13
Systemic lupus erythematosus	7 (0.7)	0.13
Sjögren's syndrome	5 (0.5)	0.09
Mixed connective tissue disease	2 (0.2)	0.04
Not specified	11 (1.1)	0.20
ILD unclassified, not otherwise specified	82 (8.5)	1.46
Histiocytosis	37 (3.8)	0.66
Hypersensitivity pneumonitis	25 (2.6)	0.45
Chronic eosinophilic pneumonia	21 (2.2)	0.38
Drug-induced ILD	17 (1.8)	0.30
Occupational	20 (2.0)	0.36
Vasculitides	14 (1.5)	0.25
Lymphangioleiomyomatosis	6 (0.6)	0.11
Alveolar proteinosis	5 (0.5)	0.09
Hemosiderosis	1 (0.1)	0.02
Bronchiolitis obliterans	4 (0.4)	0.07
Total	967	17.3

Respiratory Medicine (2009) **103**, 1122—1129

Table 2 Numbers of incident cases of ILDs in the Greek population.

Clinical entity	Incident cases (%)	Incidence (10^{-5}/y)
Sarcoidosis	60 (23.2)	1.07
IIPs	84 (32.4)	1.50
IPF—UIP	52 (20.1)	0.93
NSIP	10 (3.9)	0.18
COP/BOOP	18 (7.0)	0.32
RBILD	1 (0.4)	0.02
DIP	2 (0.8)	0.04
AIP	1 (0.4)	0.02
Connective tissue diseases	30 (11.6)	0.54
Scleroderma	12 (4.6)	0.21
Rheumatoid arthritis	9 (3.5)	0.16
Dermatomyositis/polymyositis	2 (0.8)	0.04
Systemic lupus erythematosous	2 (0.8)	0.04
Sjögren's syndrome	2 (0.8)	0.04
Mixed connective tissue disease	1 (0.4)	0.02
Not specified	2 (0.8)	0.04
ILD unclassified, not otherwise specified	40 (15.4)	0.71
Histiocytosis	7 (2.7)	0.13
Hypersensitivity pneumonitis	7 (2.7)	0.13
Chronic eosinophilic pneumonia	7 (2.7)	0.13
Drug-induced ILD	4 (1.5)	0.07
Occupational	8 (3.1)	0.14
Vasculitides	6 (2.3)	0.11
Alveolar proteinosis	1 (0.4)	0.02
Hemosiderosis	1 (0.4)	0.02
Bronchiolitis obliterans	4 (1.5)	0.07
Total	259	4.63

Idiopathic pulmonary fibrosis
Risk factors

- Cigarette smoking
- Environmental exposures
- Microbial agents
- Gastroesophageal reflux
- Genetic factors (familiar and sporadic cases)

TABLE 5. RELATIONSHIP BETWEEN CIGARETTE SMOKING AND FAMILIAL INTERSTITIAL PNEUMONIA

	OR (*95% CI*)	p Value
Univariate analysis		
Unaffected	1.0	
Probable	4.0 (2.8, 5.9)	< 0.00001
Definite	3.7 (1.9, 7.2)	< 0.00001
Probable/definite	4.0 (2.8, 5.6)	< 0.00001
Multivariate analysis*		
Age at examination	1.2 (1.1, 1.2)	0.0004
Sex	1.5 (0.7, 3.3)	0.34
Ever smoking	3.6 (1.3, 9.8)	0.01

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

* In the multivariate analysis, age at examination, sex, and ever cigarette smoking were evaluated as potential risk factors for the development of probable or definite FIP in sibships that included at least one affected family member and one unaffected sibling control with historical smoking data (n = 79 families).

Steele M, et al. Am J Respir Crit Care Med 2005; 172: 1146-1152

Is Idiopathic Pulmonary Fibrosis an Environmental Disease?

Varsha S. Taskar and David B. Coultas

Department of Medicine, The University of Texas Health Center at Tyler, Tyler, Texas

TABLE 1. CASE-CONTROL STUDIES OF OCCUPATIONAL AND ENVIRONMENTAL RISK FACTORS FOR IDIOPATHIC PULMONARY FIBROSIS

	United Kingdom		United States		Japan	
Exposure	England/Wales Scott and Colleagues, 1990 (45) (40/106)*	Trent Region Hubbard and Colleagues, 1996 (46) (218/569)*	Mullen and Colleagues, 1998 (50) (17/94)*	Baumgartner and Colleagues, 2000 (48) (248/491)*	Iwai and Colleagues, 1994 (43) (86/172)*	Miyake and Colleagues, 2005 (51) (102/59)*
Agriculture/Farming				1.60 (1.0–2.5)	3.01 (1.29–7.43)	
Livestock	10.89 (1.24–96.0)			2.70 (1.30–5.50)		
Wood dust	2.94 (0.87–9.9)	1.71 (1.01–2.92)	3.3 (0.42–25.8)	1.60 (0.80–3.30)		6.71 (0.37–123.59)
Textile dust	0.9 (0.24–3.44)	1.80 (1.10–2.96)		1.90 (0.80–4.40)		
Mold			16.0 (1.62–158)			0.98 (0.48–2.01)
Metal dust	10.97 (2.34–52.4)	1.68 (1.07–2.65)		2.00 (1.00–4.00)	1.34 (1.14–1.59)	9.55 (1.68–181.12)
Stone/sand/silica	1.59 (0.52–4.79)	1.76 (1.01–3.07)	11.0 (1.05–115)	3.90 (1.20–12.70)		
Wood fires	12.55 (1.40–114.0)			0.80 (0.40–1.60)		
Smoking	1.11 (0.13–1.40)	1.57 (1.01–2.43)		1.60 (1.10–2.40)	2.94 (1.37–6.3)	3.23 (1.01–10.84)

Environmental factors likely interact with a genetic variability in epithelial cell function

Proc Am Thorac Soc 2006

Genetic Analysis of Sporadic and Familial Interstitial Pneumonia

David A. Schwartz[1]

[1]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

TABLE 1. GENETIC POLYMORPHISMS ASSOCIATED WITH INTERSTITIAL PNEUMONIA

Mechanism	Gene	Reference
Matrix turnover	TGF-β_1	30, 31
	Fibronectin	37
	IGF-1	38
Inflammation	TNF-α	39–41
	IL-4	43
	IL-6	40
	Complement receptor-1	44
	IFN-γ	45
	HLA genotypes	56–60
Oxidative stress	α_1-Antityrpsin	54, 55
	p53	53
Phagocytosis	ELMOD2	69
Proteolysis	Angiotensin-converting enzyme	51
Surface tension	SP-C	21, 62, 63
Telomere length	TERT and TERC	65, 66

Specific gene products modulate the inflammatory/fibrotic response to fibrogenic agents and provide the pathogenic basis for enhanced genetic risk.

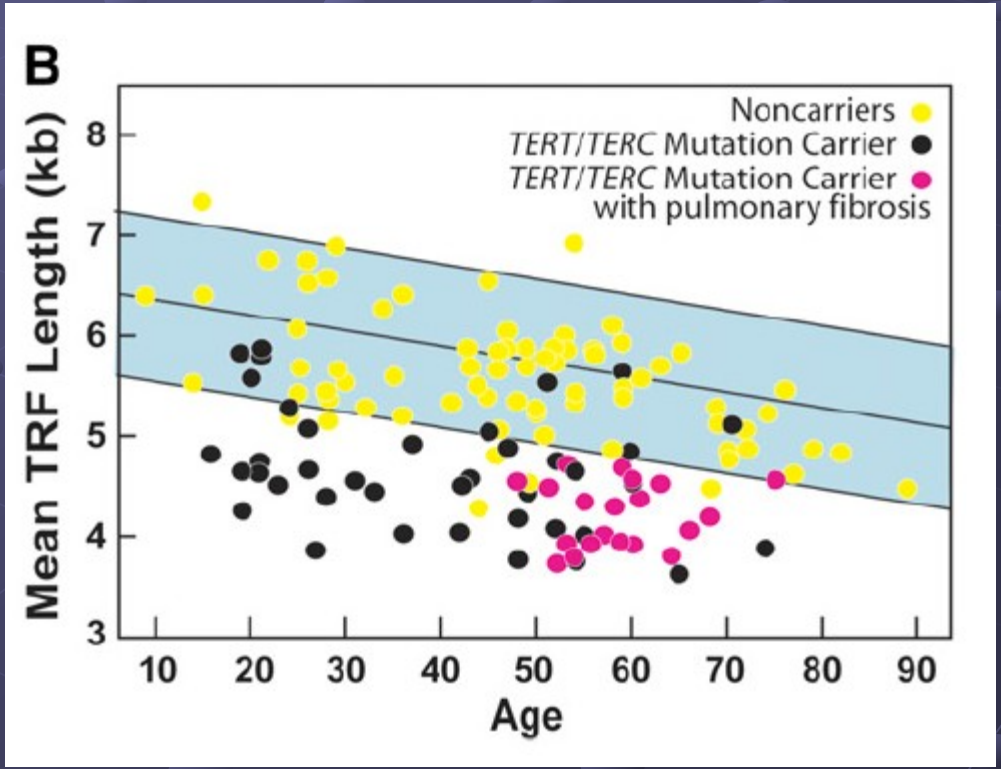
Proc Am Thorac Soc 2008

Telomere Shortening in Familial and Sporadic Pulmonary Fibrosis

Jennifer T. Cronkhite[1], Chao Xing[1], Ganesh Raghu[2], Kelly M. Chin[3], Fernando Torres[3], Randall L. Rosenblatt[3], and Christine Kim Garcia[1,3]

[1]Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, Texas; [2]Division of Pulmonary and Critical Care Medicine, University of Washington Medical Center, Seattle, Washington; and [3]Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

Pulmonary fibrosis affectation status was significantly associated with telomerase restriction fragment lengths, even after controlling for age, sex, and ethnicity . Overall, 25% of sporadic cases and 37% of familial cases of pulmonary fibrosis had telomere lengths less than the 10th percentile.

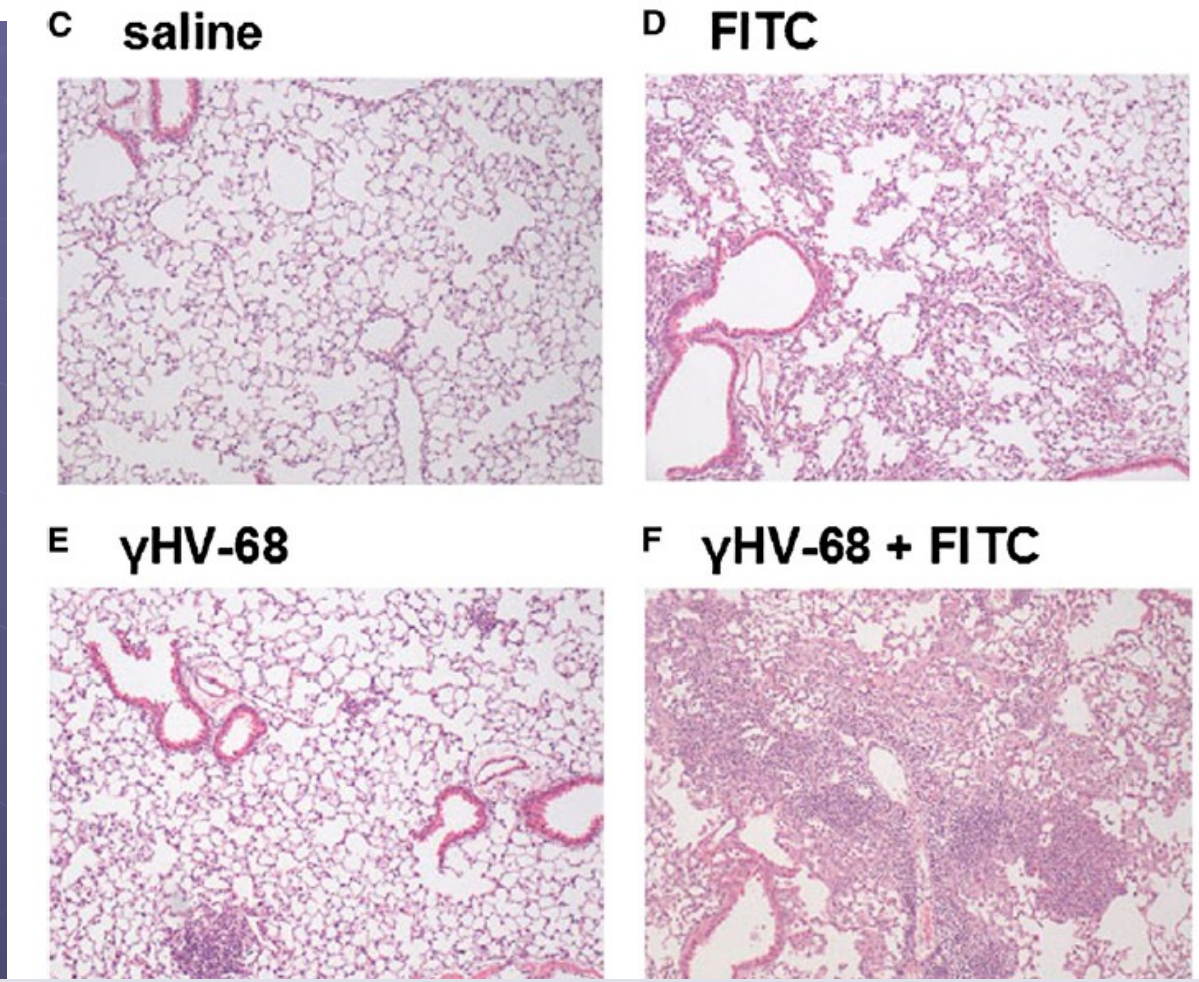


AJRCCM 2008

Latent Herpesvirus Infection Augments Experimental Pulmonary Fibrosis

Kevin M. Vannella[1], Tracy R. Luckhardt[2], Carol A. Wilke[2], Linda F. van Dyk[3], Galen B. Toews[2], and Bethany B. Moore[2,4]

[1]Graduate Program in Immunology, [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, and [4]Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, Michigan; and [3]Department of Microbiology, University of Colorado School of Medicine, Aurora, Colorado



Am J Respir Crit Care Med 2010; 181: 465-477

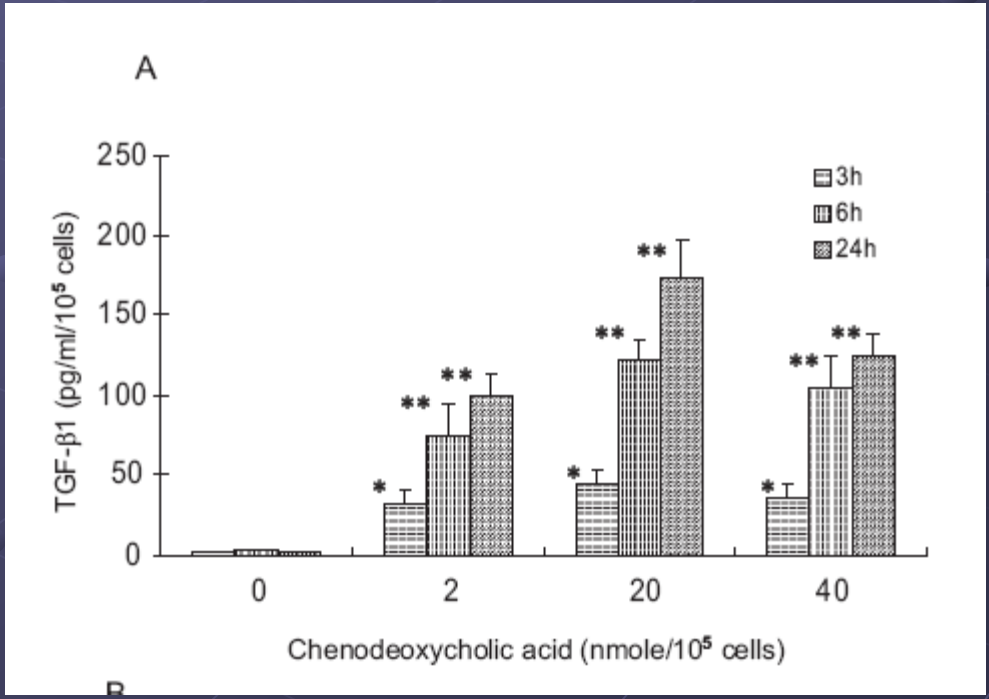
CHEST 2007 Original Research

GERD AND LUNG DISEASE

Exposure of Airway Epithelium to Bile Acids Associated With Gastroesophageal Reflux Symptoms*

A Relation to Transforming Growth Factor-β_1 Production and Fibroblast Proliferation

Aspiration of bile acids may induce airway fibrosis through the production of TGF-1 and fibroblast proliferation



Centennial Review

Back to the Future

Historical Perspective on the Pathogenesis of Idiopathic Pulmonary Fibrosis

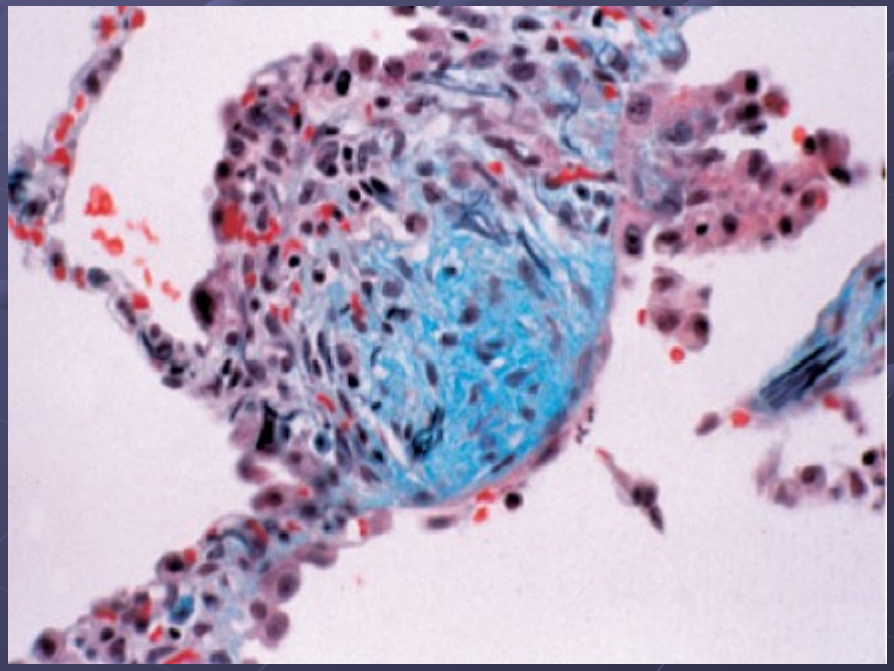
Paul W. Noble and Robert J. Homer

Department of Medicine, Section of Pulmonary and Critical Care Medicine, and Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

THE INFLAMMATION (ALVEOLITIS) HYPOTHESIS

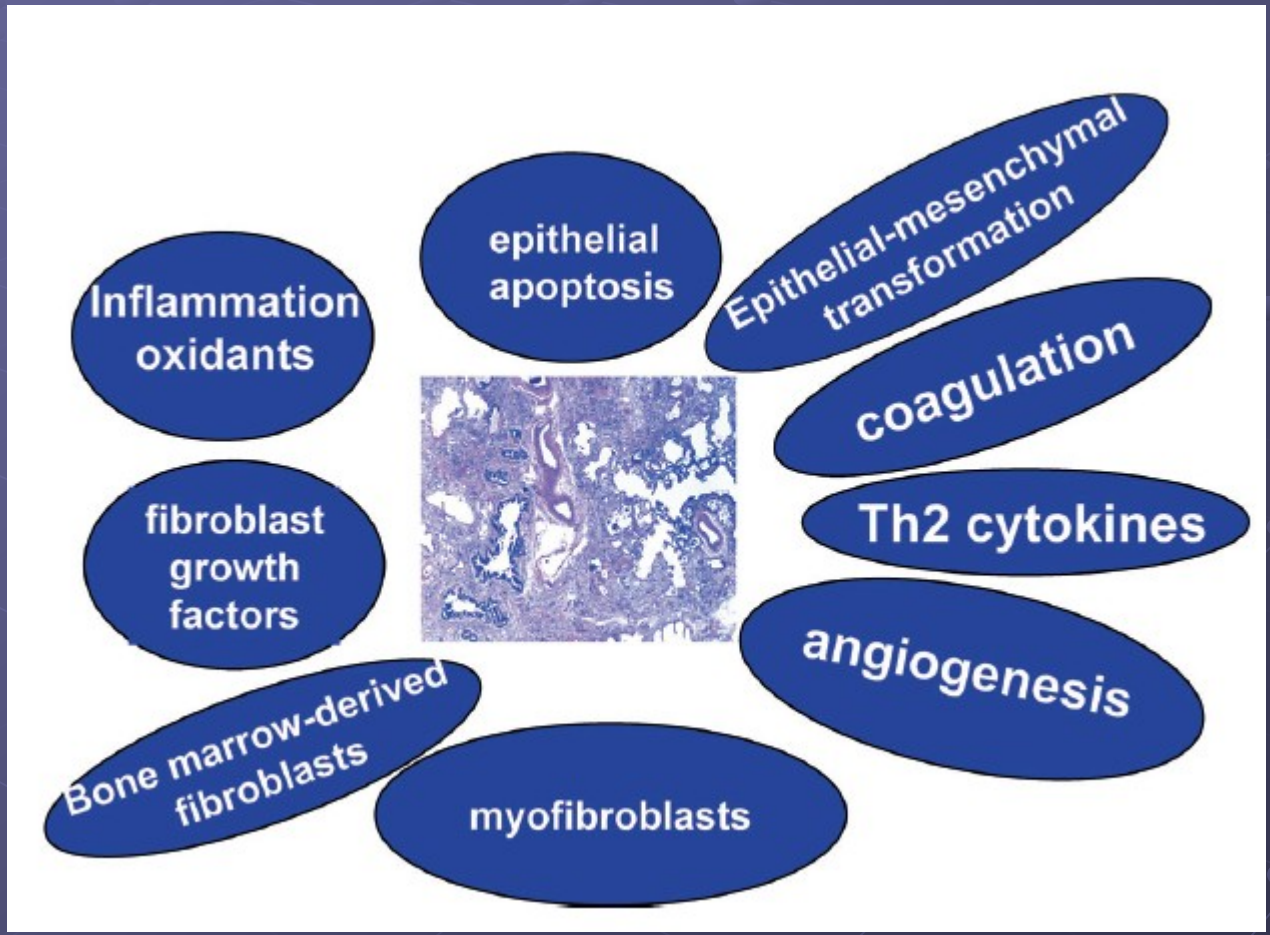
THE GROWTH FACTOR HYPOTHESIS

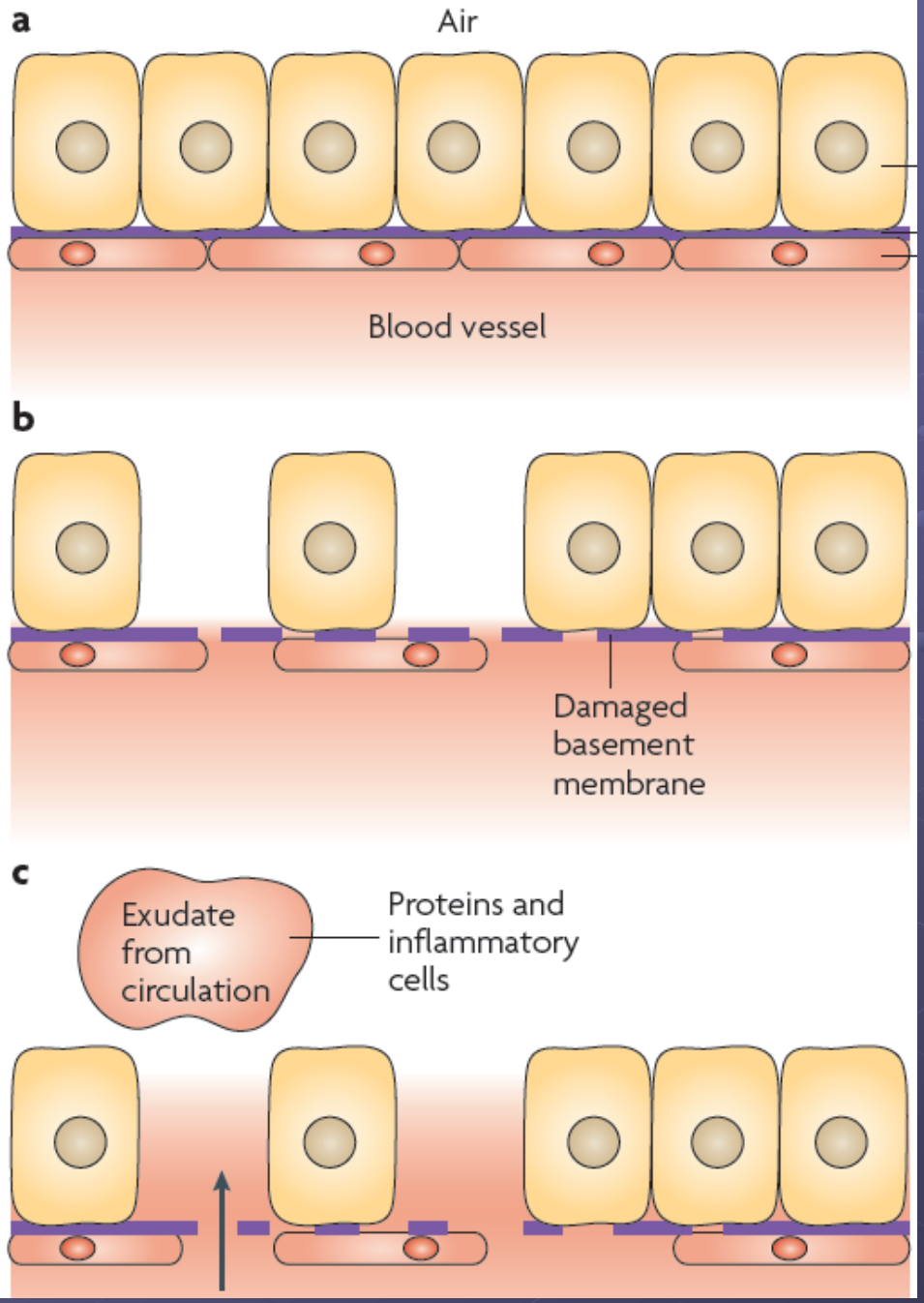
THE EPITHELIAL–MESENCHYMAL HYPOTHESIS



Am J Respir Cell Mol Biol 2005; 33: 113-120

Pathogenesis of IPF





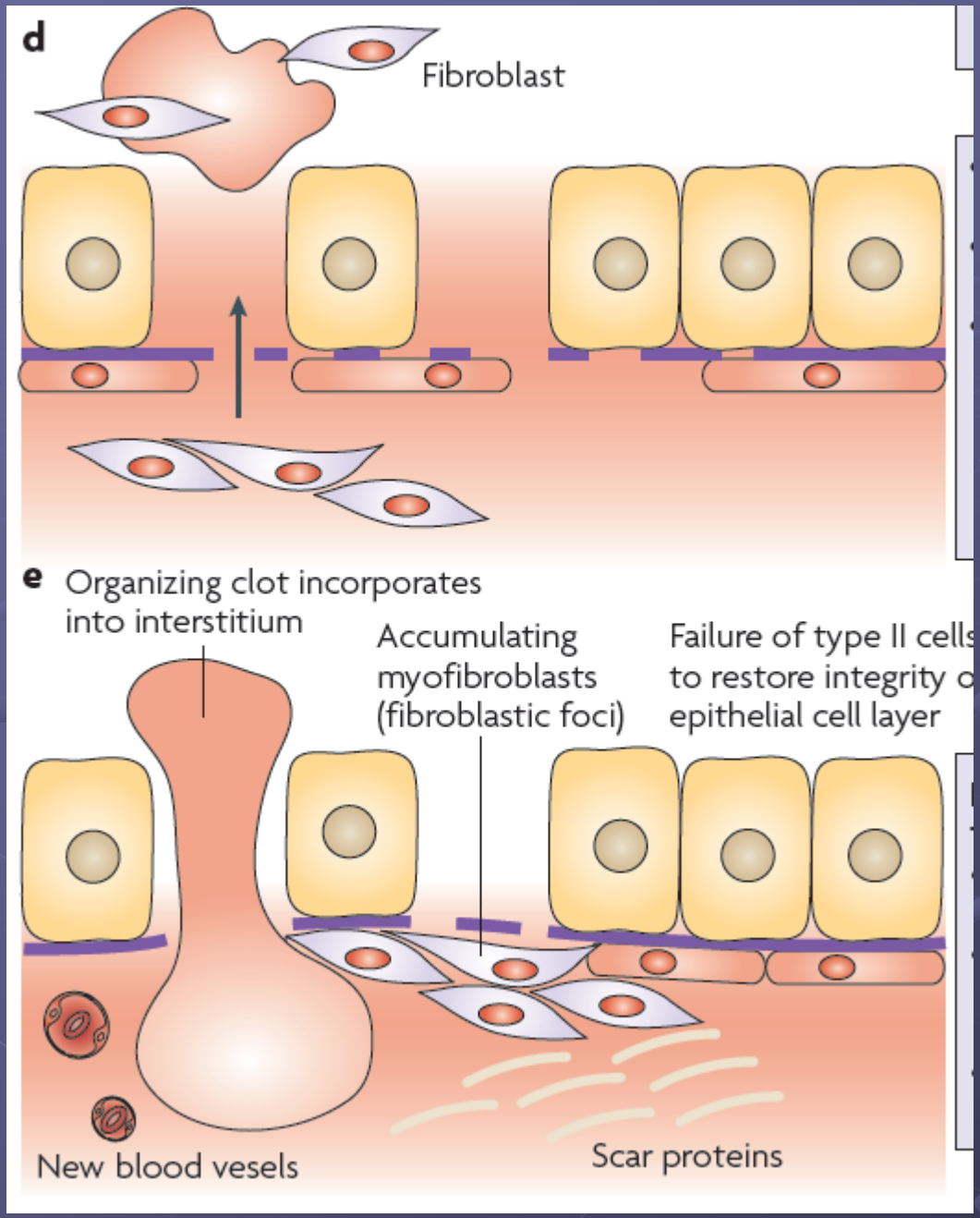
Injury to epithelial and endothelial cells

- Microinjury
- Larger area injury (macroinjury)
- Massive injury (acute exacerbation)

Possible causes

- Smoking
- Viruses
- Wood and metal dust
- Gastro-oesophageal reflux
- Oxidants
- Ageing

RM DuBois. Nat Rev 2010; 9:129



Consequences of injury

- Type II epithelial cell mediator release:
  - Growth factors
  - Metalloproteinases
  - Chemokines
  - Coagulation factor X
- Leakage of protein including coagulant factors into the airspace from the blood

- Organization of intra-alveolar exudate
- Migration of fibroblasts into the area of injury
- Accumulation of myofibroblasts from:
  - Resident fibroblasts
  - Circulating fibrocytes
  - Epithelial to mesenchymal cell transition

RM DuBois. Nat Rev 2010; 9:129

Idiopathic pulmonary fibrosis
Diagnosis

TABLE 4. ATS/ERS CRITERIA FOR DIAGNOSIS OF IDIOPATHIC PULMONARY FIBROSIS IN ABSENCE OF SURGICAL LUNG BIOPSY*†

Major Criteria

Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue diseases

Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV_1/FVC ratio) and impaired gas exchange [increased $P(A–a)O_2$, decreased Pa_{O_2} with rest or exercise or decreased DL_{CO}]

Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans

Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor Criteria

Age > 50 yr

Insidious onset of otherwise unexplained dyspnea on exertion

Duration of illness > 3 mo

Bibasilar, inspiratory crackles (dry or "Velcro"-type in quality)

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

Idiopathic pulmonary fibrosis
Diagnosis

Diagnostic Criteria

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (*see* Table 4).
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (*see* Tables 5 and 6).

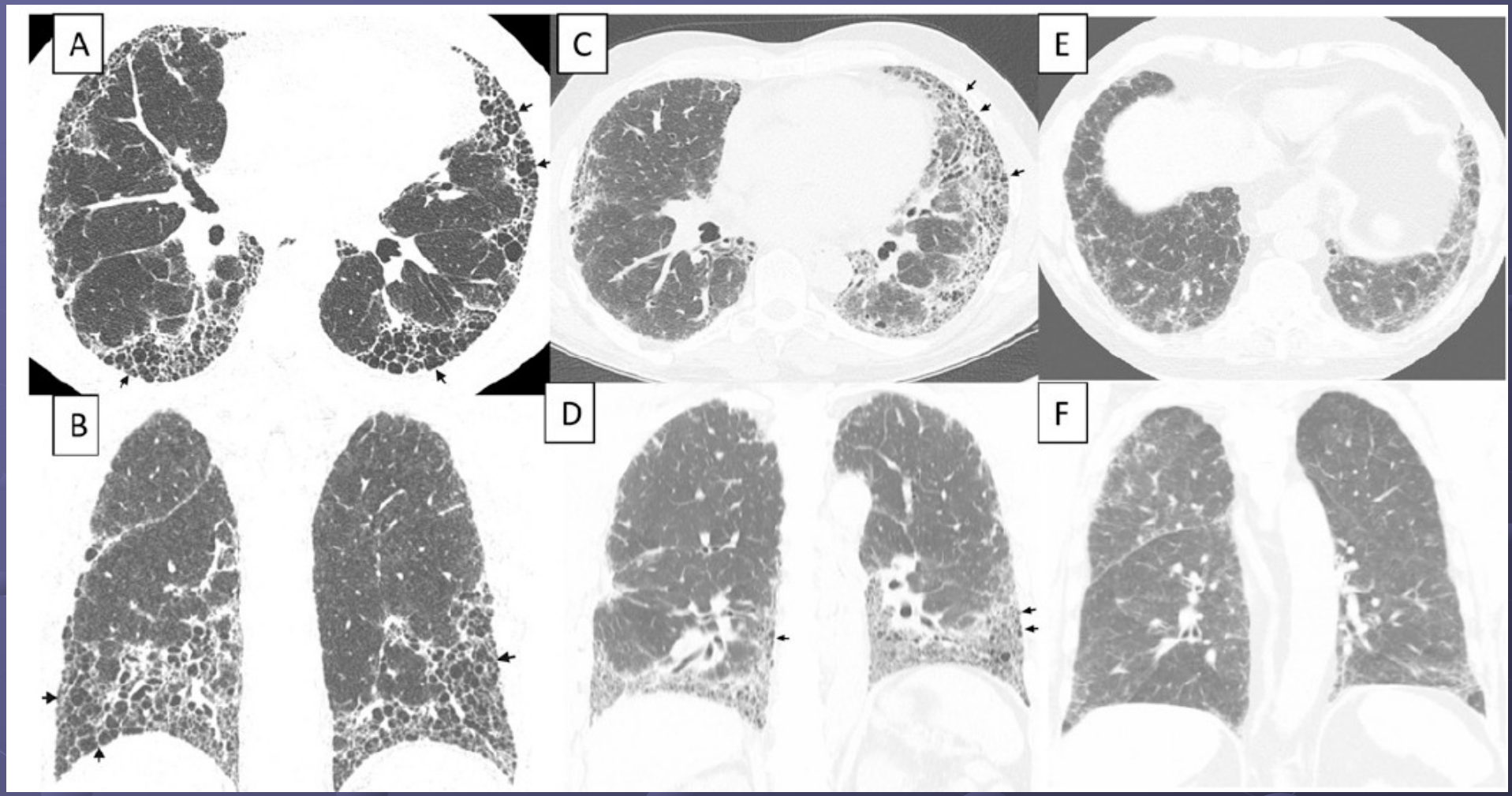
Am J Respir Crit Care Med 2011; 183: 788-824

Idiopathic pulmonary fibrosis
Diagnosis

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

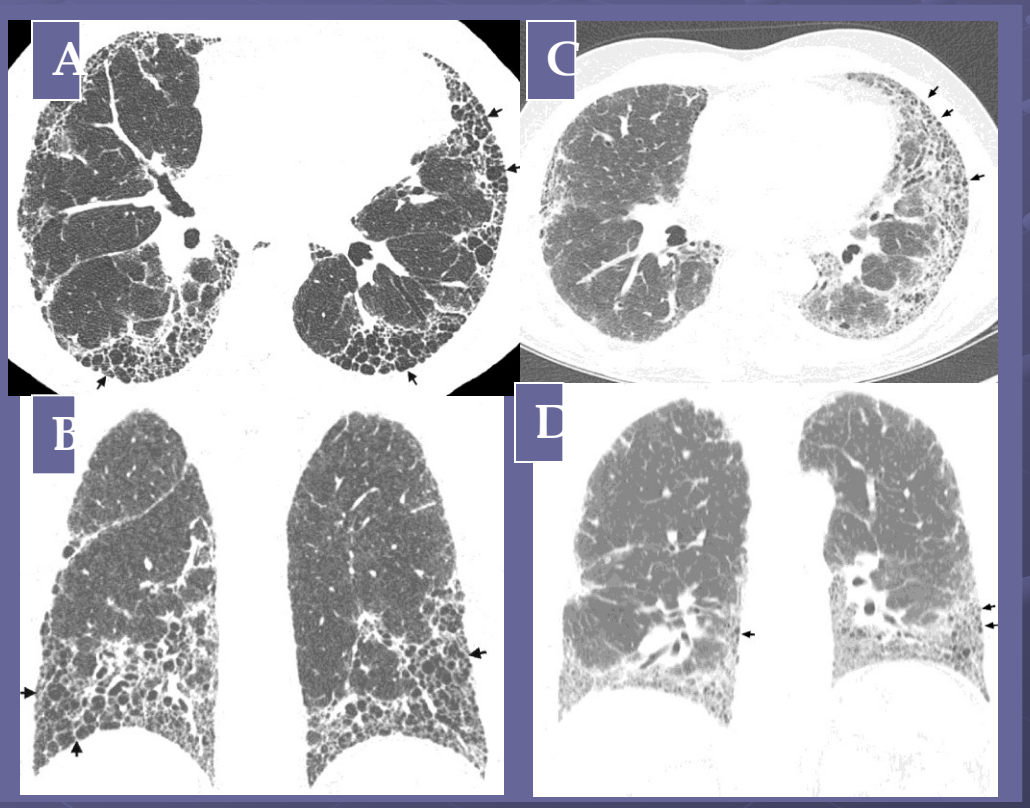
IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause associated with the histopathologic and/or radiologic pattern of UIP.


A
C
E
B
D
F

Idiopathic Pulmonary Fibrosis

HRCT Images: UIP Pattern
Extensive honeycombing

HRCT Images: UIP Pattern
(Less severe honeycombing)



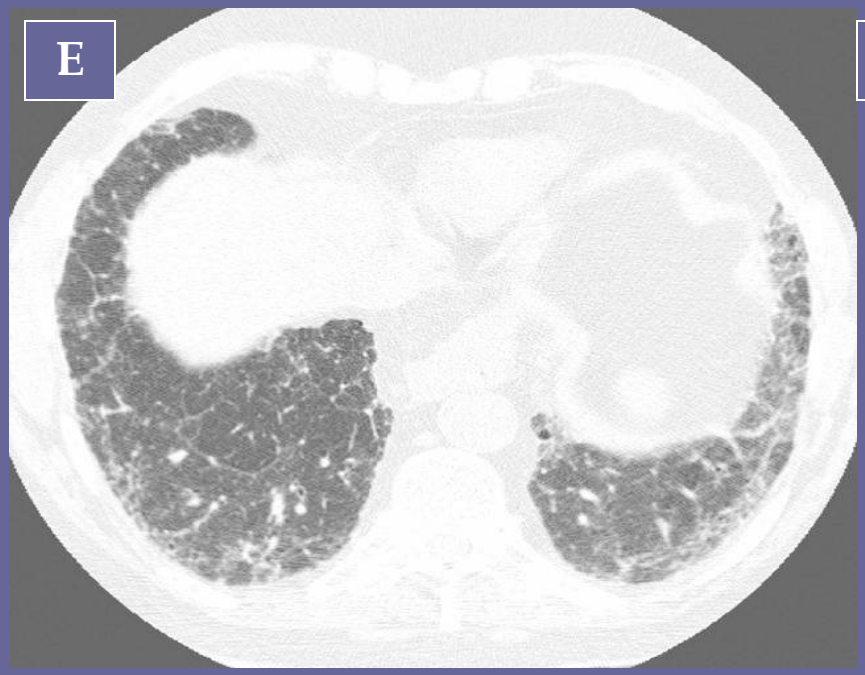
Honeycombing (HRCT)

- Clustered cystic air spaces
- Well defined walls
- Typically comparable diameters

  (3-10 mm; occasionally as large as 2.5 cm)
- Subpleural

Idiopathic Pulmonary Fibrosis

HRCT Images: Consistent with UIP pattern (*no honeycombing*)



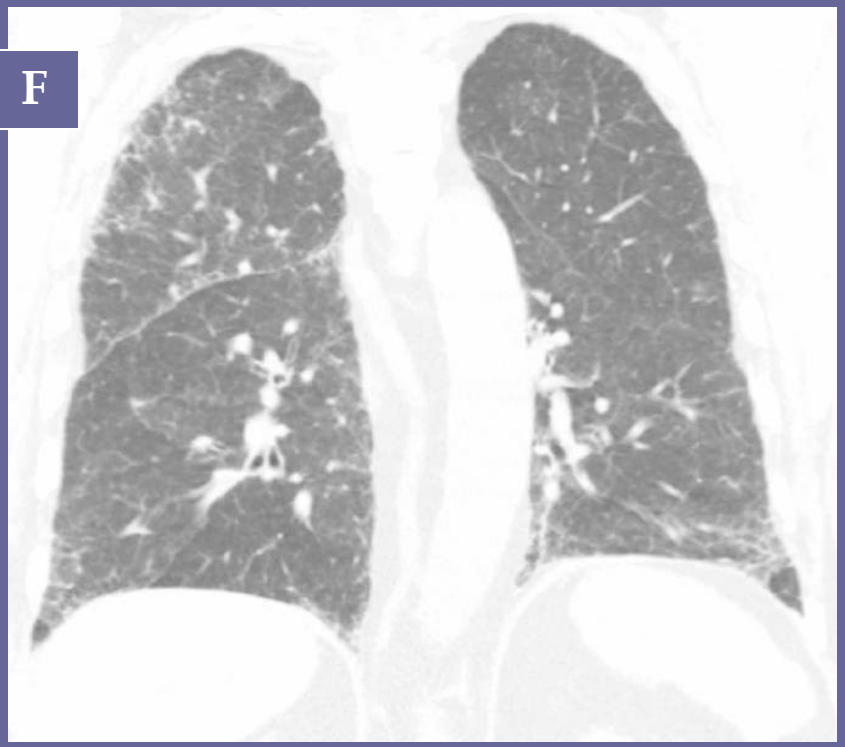
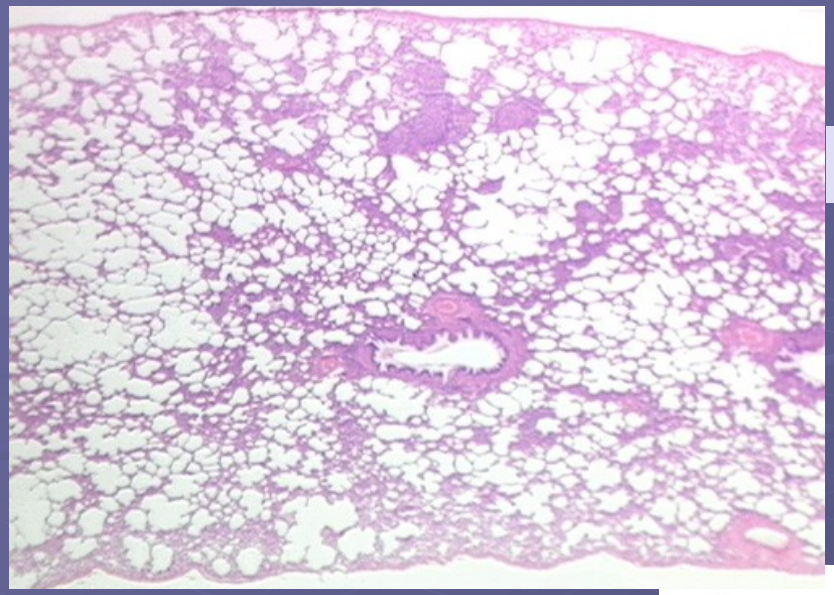


TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

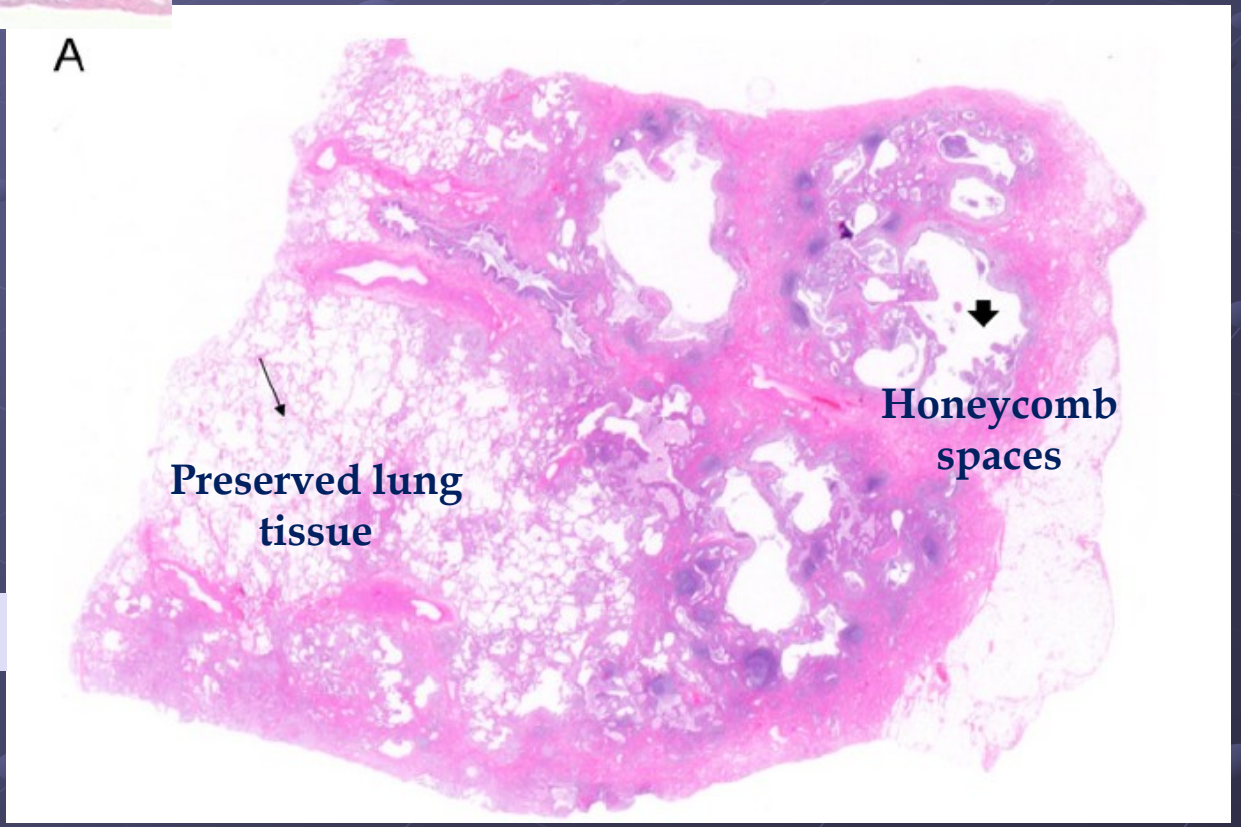
UIP Pattern (All Four Criteria)	Probable UIP Pattern
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis



Normal lung



UIP lung

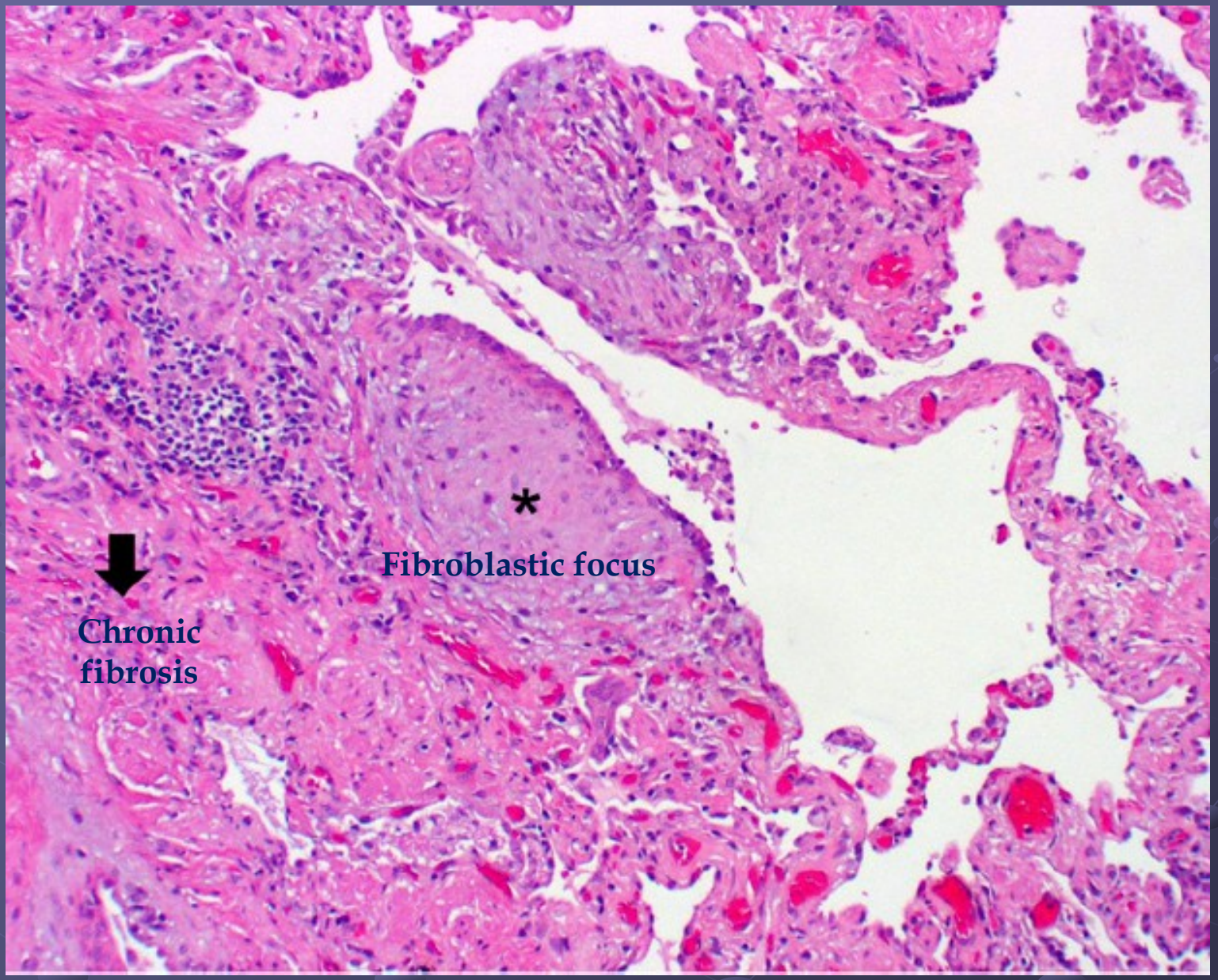

Fibroblastic focus
Chronic fibrosis

TABLE 6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	 fibrosis‡	YES
	Not UIP	No
Possible UIP	UIP Probable UIP	YES
	Possible UIP Nonclassifiable fibrosis	Probable§
	Not UIP	No
Inconsistent with UIP	UIP	Possible§
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

Exclusion of other known causes

- Comorbidities
- Medication use
- Environmental exposure
- Family history

- ***Question***: Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?

- Summary of evidence

-Prominent lymphocytosis (>40%) in BAL suggests diagnosis of chronic hypersensitivity pneumonitis

-8% of patients with UIP pattern on HRCT may have BAL findings suggestive of dx other than IPF

(Ohshimo et al. AJRCCM 2009)

-Unclear whether BAL adds significant diagnostic specificity to a careful exposure history and clinical evaluation

Recommendation: BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence).

Exclusion of other known causes

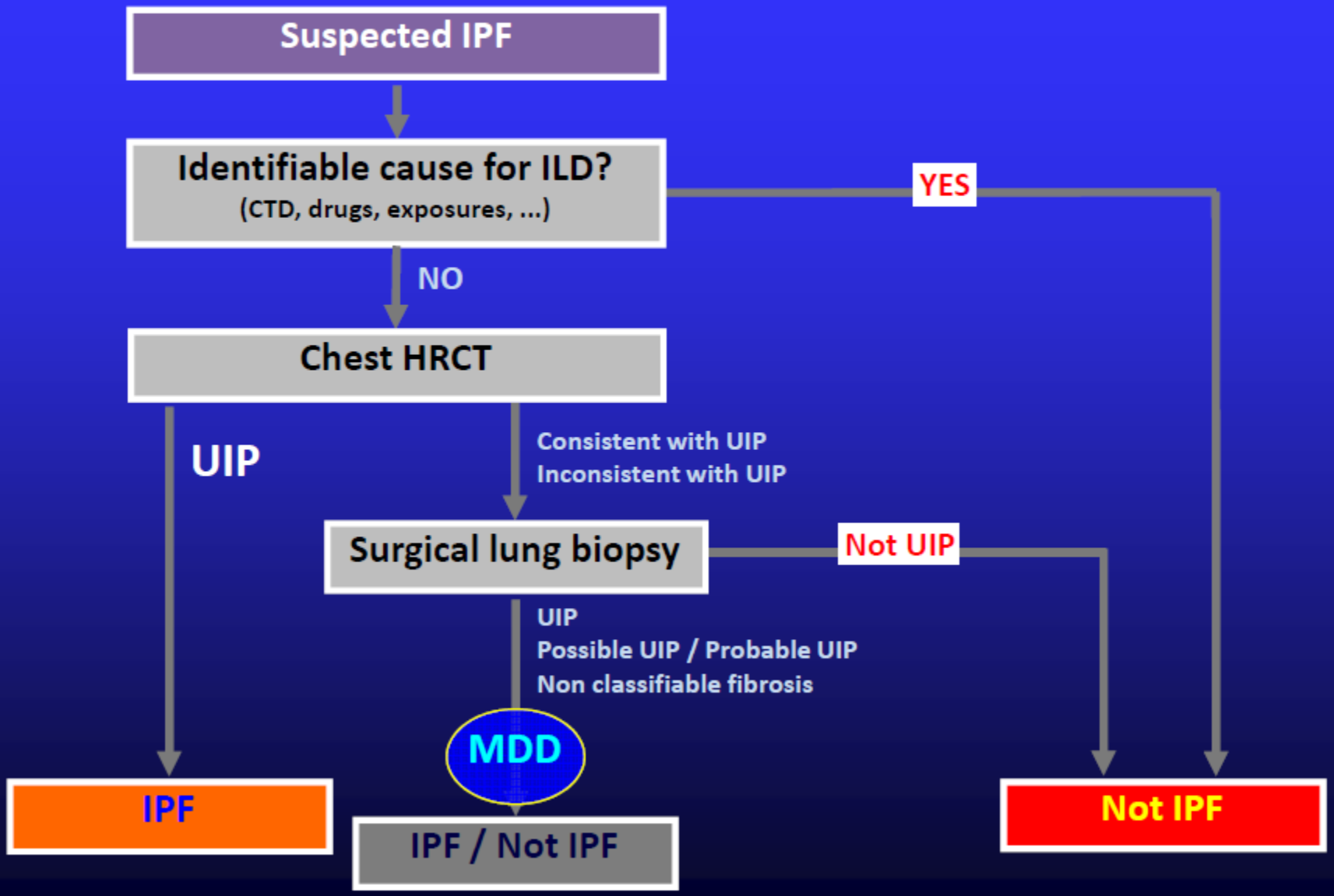
***Question*:** Should transbronchial lung biopsy be used in the evaluation of suspected IPF?

Recommendation: Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation, low-quality evidence).

***Question*:** Should serologic testing for connective tissues disease be used in the evaluation of suspected IPF?

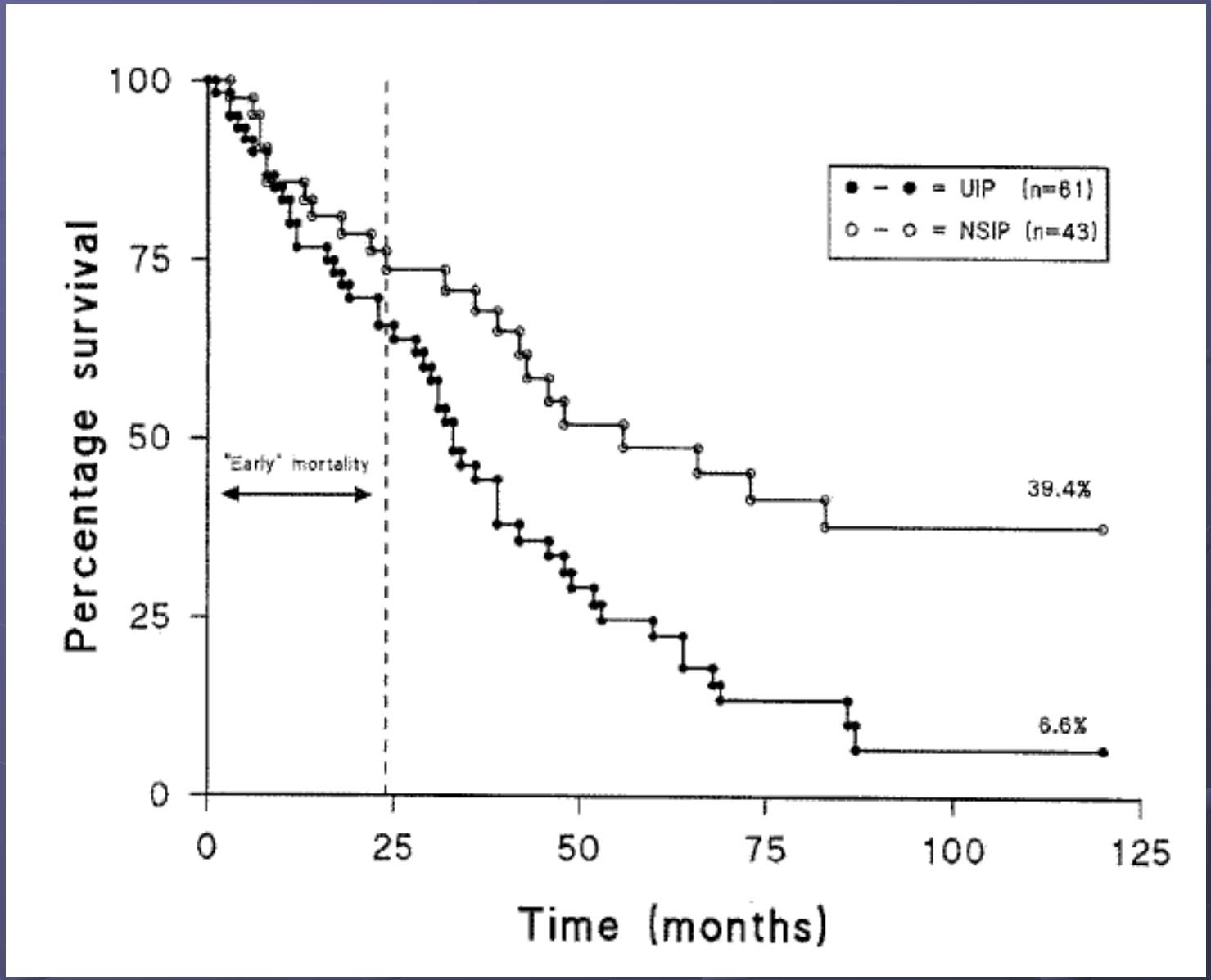
Recommendation: Serologic testing for connective tissue disease should be performed in the evaluation of IPF in the majority of patients, but may not be appropriate in a minority (weak recommendation, very low-quality evidence).

Diagnostic algorithm for IPF

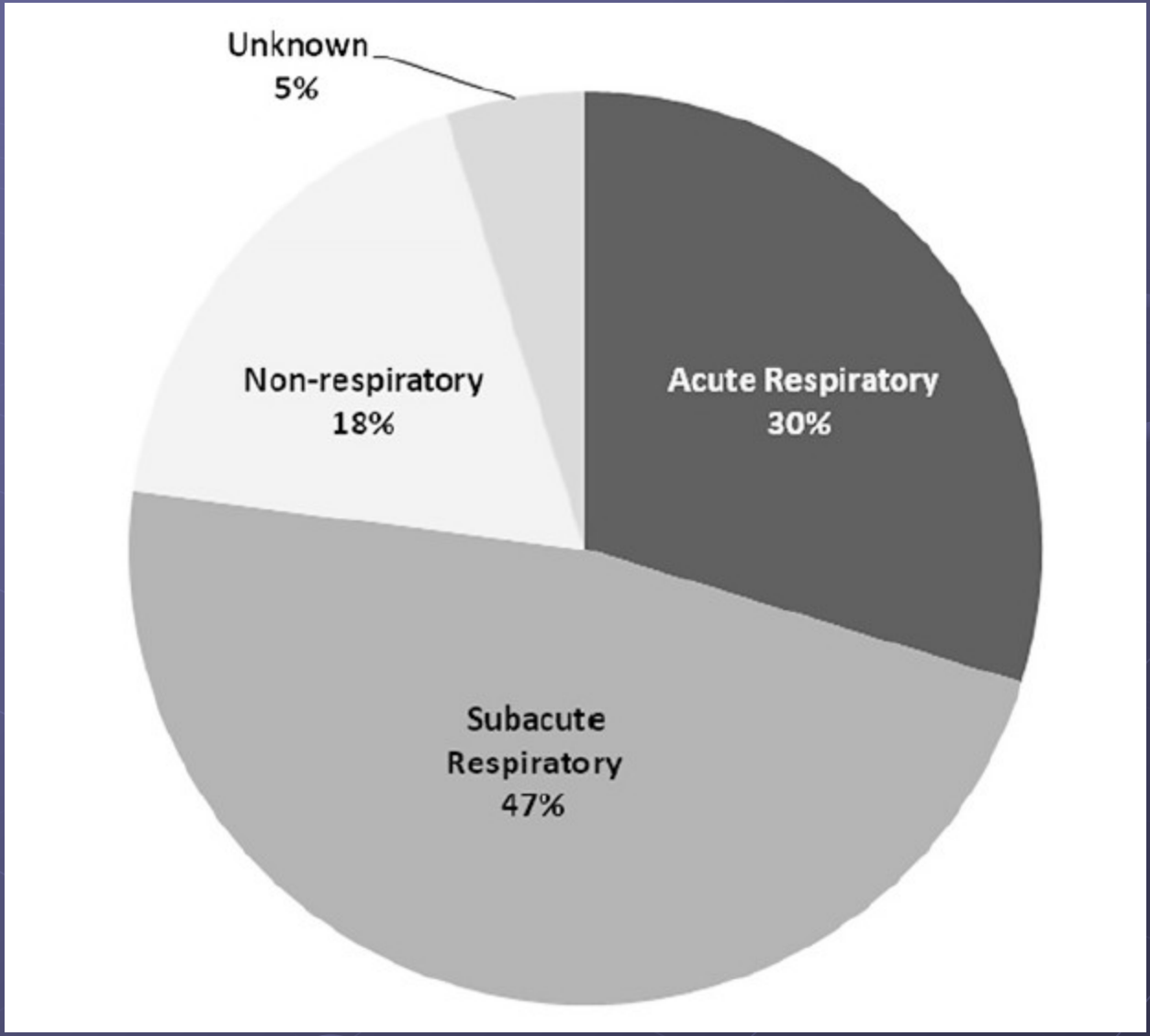


Am J Respir Crit Care Med 2011; 183: 788-824

Survival of UIP patients



Respiratory versus non respiratory causes of death in patients with IPF



Am J Respir Crit Care Med 2011; 183: 431-440

Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis

Brett Ley[1], Harold R. Collard[1], and Talmadge E. King, Jr.[1]

[1]Department of Medicine, University of California San Francisco, San Francisco, California

TABLE 2. INDIVIDUAL PREDICTORS OF SURVIVAL IN IDIOPATHIC PULMONARY FIBROSIS

Clinical Predictors	Radiographic Predictors	Physiologic Predictors	Pathologic Predictors	Biomarker Predictors
Demographic	HRCT	Pulmonary function tests	Histopathology	Blood
Age	UIP pattern	FVC	UIP pattern	BNP
Sex	Extent of fibrosis	TLC	Fibroblastic foci	Albumin
Ethnicity		D_{LCO}		KL-6M
Smoking status		CPI		MP-7
Symptom-based		Change in FVC		CCL-18
Dyspnea scores		Change in D_{LCO}		SP-A & -D
				Circulating fibrocytes
Physical examination		Exercise tests		BAL
Clubbing		6MWT		SP-A & -D
BMI		Desaturation		MMP-3, -7, -8, -9
Comorbidities		Distance		CCL-2, -17, -22
Emphysema		Heart rate recovery		Neutrophilia
Pulmonary hypertension		Others		
		15-step test		
		4-min step test		

Am J Respir Crit Care Med Vol 183. pp 431–440, 2011

TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS

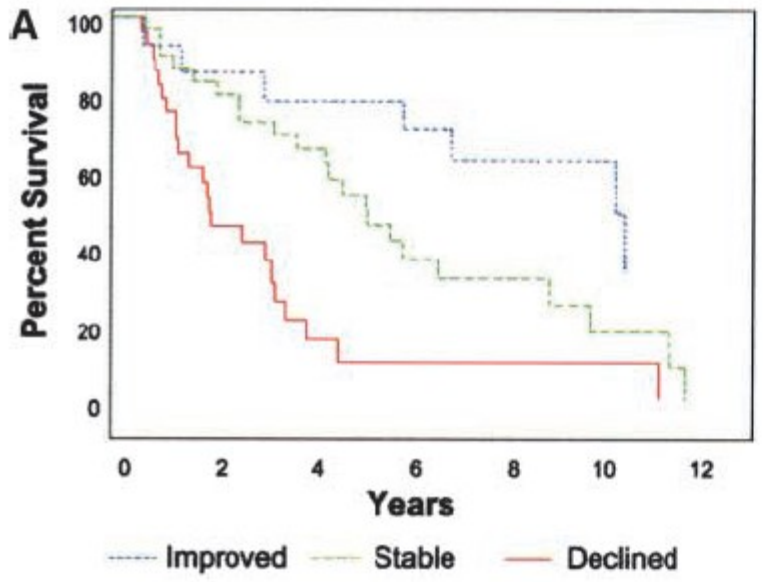
- Baseline factors*
  - Level of dyspnea†
  - D_{LCO} < 40% predicted
  - Desaturation ≤ 88% during 6MWT
  - Extent of honeycombing on HRCT†
  - Pulmonary hypertension
- Longitudinal factors
  - Increase in level of dyspnea†
  - Decrease in Forced Vital Capacity by ≥ 10% absolute value
  - Decrease in D_{LCO} by ≥ 15% absolute value
  - Worsening of fibrosis on HRCT†

Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis

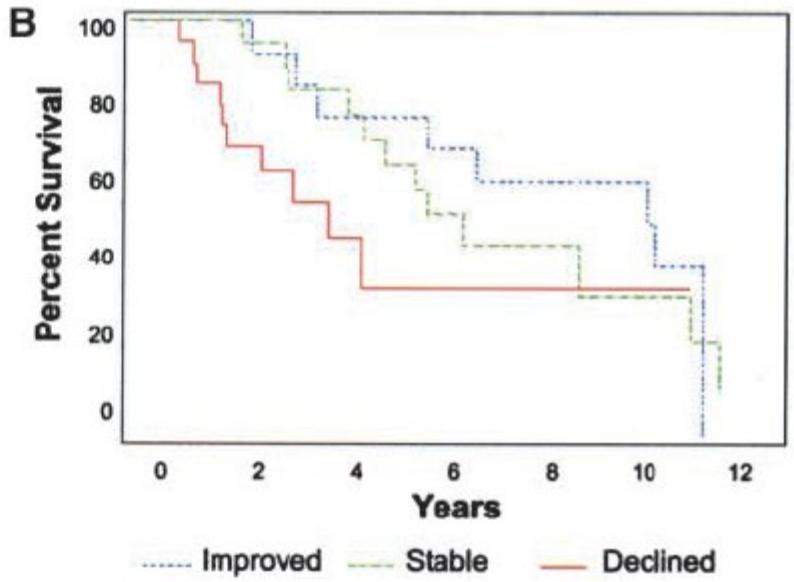
Harold R. Collard, Talmadge E. King, Jr., Becki Bucher Bartelson, Jason S. Vourlekis, Marvin I. Schwarz, and Kevin K. Brown

Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Health Sciences; National Jewish Medical and Research Center, Denver; Department of Biostatistics and Clinical Studies, NetRegulus, Centennial, Colorado; and Department of Medicine, San Francisco General Hospital, University of California at San Francisco, San Francisco, California

Dyspnea change at 6 mo



Dyspnea change at 12 mo

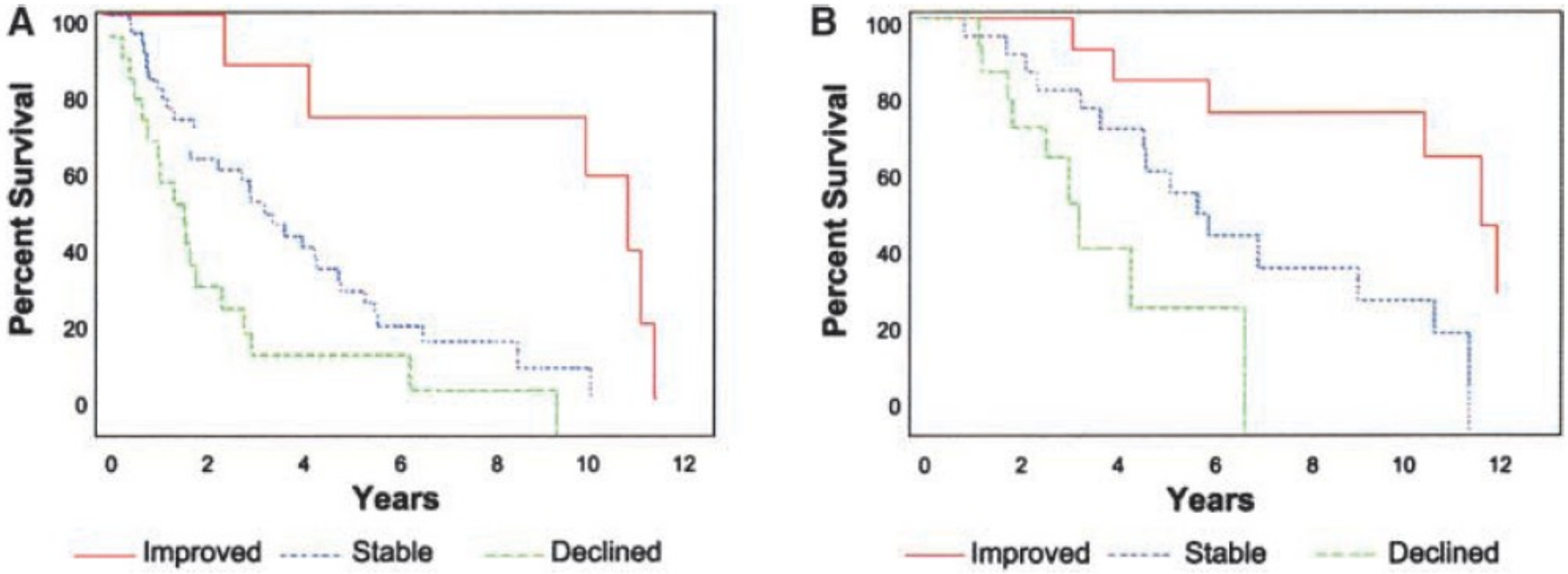


Am J Respir Crit Care Med 2003; 168: 538-542

Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis

Harold R. Collard, Talmadge E. King, Jr., Becki Bucher Bartelson, Jason S. Vourlekis, Marvin I. Schwarz, and Kevin K. Brown

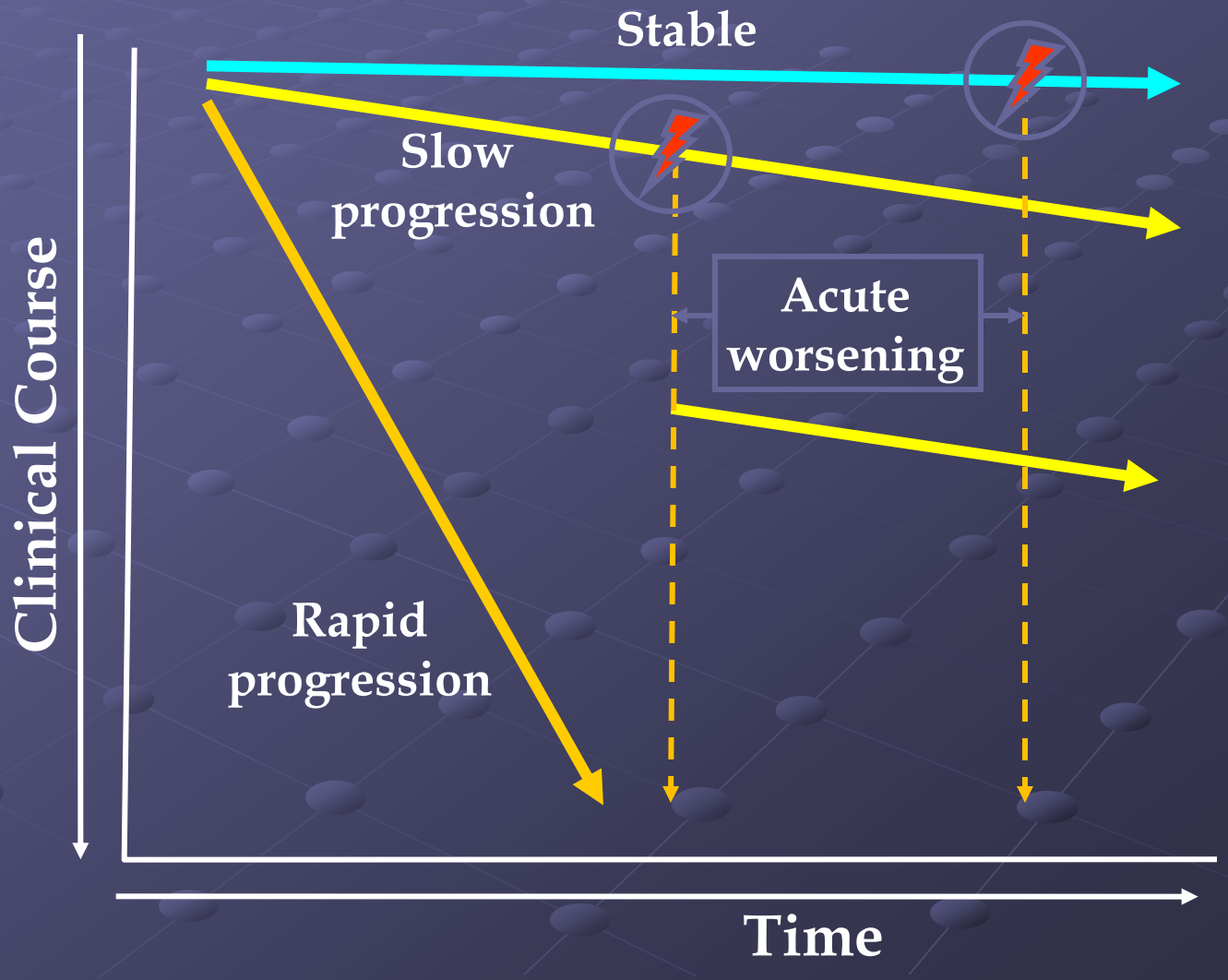
Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Health Sciences; National Jewish Medical and Research Center, Denver; Department of Biostatistics and Clinical Studies, NetRegulus, Centennial, Colorado; and Department of Medicine, San Francisco General Hospital, University of California at San Francisco, San Francisco, California



Am J Respir Crit Care Med 2003; 168: 538-542

IPF is a fatal lung disease; the natural history is variable and unpredictable

Natural History of IPF



Acute exacerbation of IPF

Clinical review: Idiopathic pulmonary fibrosis acute exacerbations - unravelling Ariadne's thread

Spyros A Papiris*[1], Effrosyni D Manali[1], Likurgos Kolilekas[1], Konstantinos Kagouridis[1], Christina Triantafillidou[1], Iraklis Tsangaris[2] and Charis Roussos[3]

- IPF exacerbations constitute the most devastating complication during its course
- IPF exacerbations represent acute and clinically significant deteriorations of unidentifiable cause, transforming the slow and more or less steady disease decline to the unexpected appearance of acute lung injury/ acute respiratory distress syndrome (ALI/ ARDS) ending in death.
- Occasionally, IPF exacerbations may present in a previously apparently healthy or minimally symptomatic individual and might represent acute progression of an unsuspected or undiagnosed early IPF

Crit Care 2010; 14:246

Table 1—*Diagnostic Criteria for AE-IPF*

Previous or concurrent diagnosis of IPF*
Unexplained worsening or development of dyspnea within 30 d
High-resolution CT scan with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with a UIP pattern†
Worsening hypoxemia from a known baseline arterial blood gas‡
No evidence of pulmonary infection by endotracheal aspiration or BAL
Exclusion of alternative causes, including
Left heart failure
Pulmonary embolism
Identifiable cause of acute lung injury§

Huzy R, et al. Chest 2007; 132:1652

sepsis, aspiration, trauma, transfusion of blood products, pulmonary contusion, fat embolization, drug toxicity, acute pancreatitis, inhalational injury,cardiopulmonarybypass.

Incidence and Outcome of AE-IPF

TABLE 1. PUBLISHED STUDIES OF ACUTE EXACERBATION

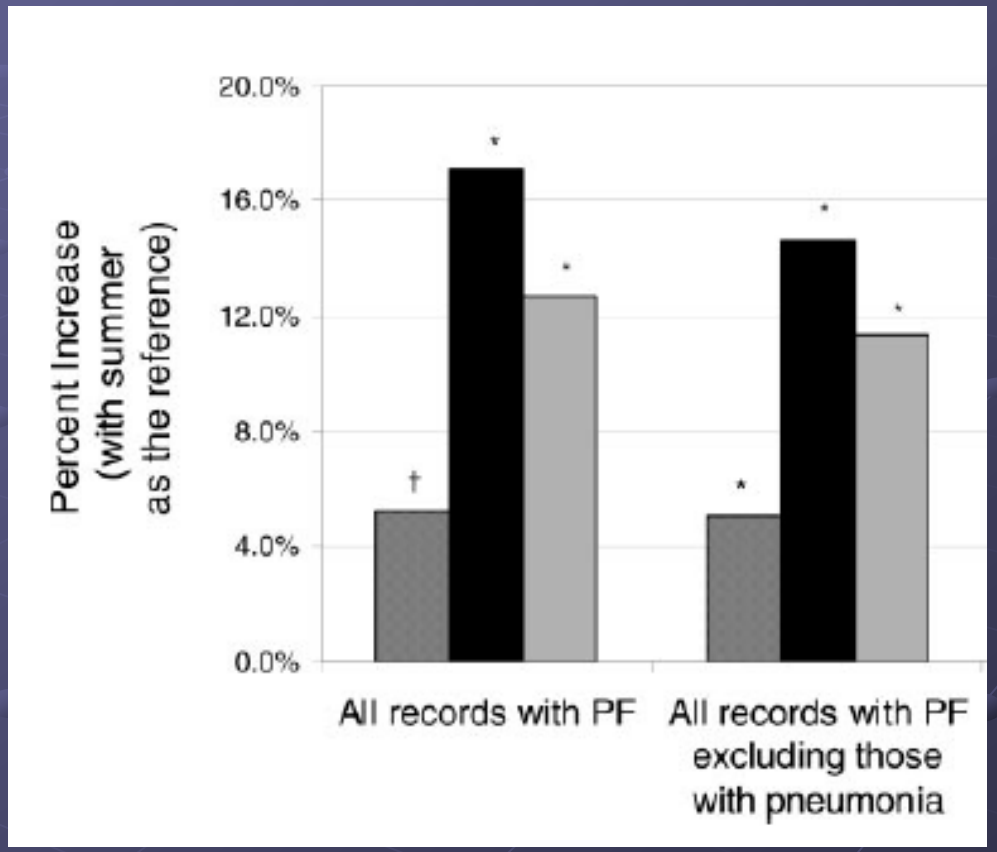
Publication	Study Design	No.*	Age (*yr*)	M/F	Incidence (%)	Mortality Rate (%)
Churg and colleagues, 2007 (27)	Retrospective review of lung biopsy cases	9	62	3/6	N/A	22
Tiitto and colleagues, 2006 (19)	Autopsy review	9	N/A	N/A	21	N/A
Okamoto and colleagues, 2006 (17)	Retrospective review of hospital admissions	28	68	20/8	12.5 (2-yr incidence)	86
Kim and colleagues, 2006 (13)	Retrospective longitudinal cohort	11	63	6/2	9.6 (2-yr incidence)	78
Kondoh and colleagues, 2006 (23)	Retrospective review of post-lung biopsy cases	3	63	3/0	N/A	67
Parambil and colleagues, 2005 (18)	Case series	7	70	5/2	N/A	86
Azuma and colleagues, 2005 (13)	Randomized controlled trial	5	N/A	N/A	5 (9-mo incidence)	20
Kubo and colleagues, 2005 (16)	Randomized controlled trial	32	N/A	N/A	57 (3-yr incidence)	53
Kondoh and colleagues, 2005 (15)	Prospective trial	6	61	3/0	22 (5-yr incidence)	N/A
Homma and colleagues, 2005 (20)	Case series	10	70	10/0	N/A	100
Al-Hameed and Sharma, 2004 (21)	Retrospective review of ICU admissions	25	69	23/2	N/A	96
Rice and colleagues, 2003 (24)	Autopsy review	12	66	10/2	N/A	100
Ambrosini and colleagues, 2003 (12)	Case series	5	70	4/1	N/A	80
Saydain and colleagues, 2002 (25)	Retrospective review of ICU admissions	15	N/A	N/A	47	N/A
Stern and colleagues, 2001 (81)	Retrospective review of ICU admissions	14	N/A	N/A	61	>90
Blivet and colleagues, 2001 (22)	Retrospective review of ICU admissions	6	N/A	N/A	40	100
Akira and colleagues, 1997 (11)	Case series	17	63	14/3	N/A	53
Kondoh and colleagues, 1993 (10)	Case series	3	61	3/0	N/A	0
Kondo and Saiki, 1989 (9)	Survey	51	N/A	N/A	33	96
Kondo and Saiki, 1989 (9)	Retrospective cohort	4	N/A	N/A	18	N/A

Taniguchi et al 2010 107 placebo patients diagnosed with IPF followed up for 12 mo **4.6% at 12 mo**

Huzy R, et al. Chest 2007; 132:1652
Taniguchi H, et al. ERJ 2010; 35:821

Risk Factors

- at any time during the course of disease
- for some patients, may be the presenting manifestation of their disease
- no clear association with age or smoking history or the level of pulmonary function derangement
- surgical lung biopsy and male gender may be a risk factor
- role of treatment- related immunosuppression undefined



Chest 2009; 136:16-22

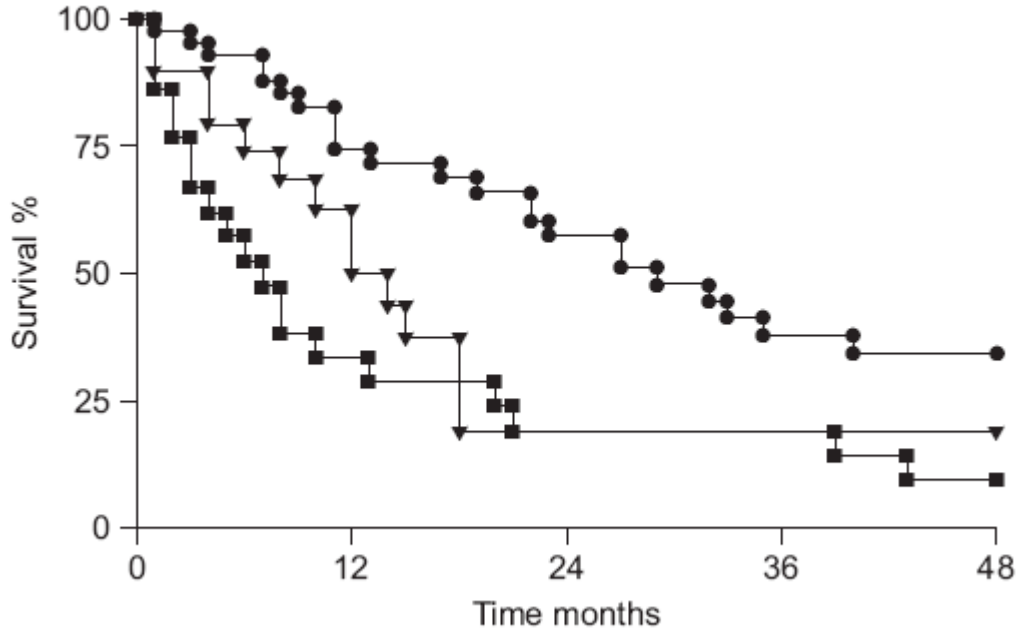
Clinical Features

- Acute to subacute worsening of dyspnea
- Development of new or worsening dyspnea generally occurs within 30 days
- Cough, fever, and flulike symptoms
- Severe hypoxemia and respiratory failure requiring mechanical ventilation

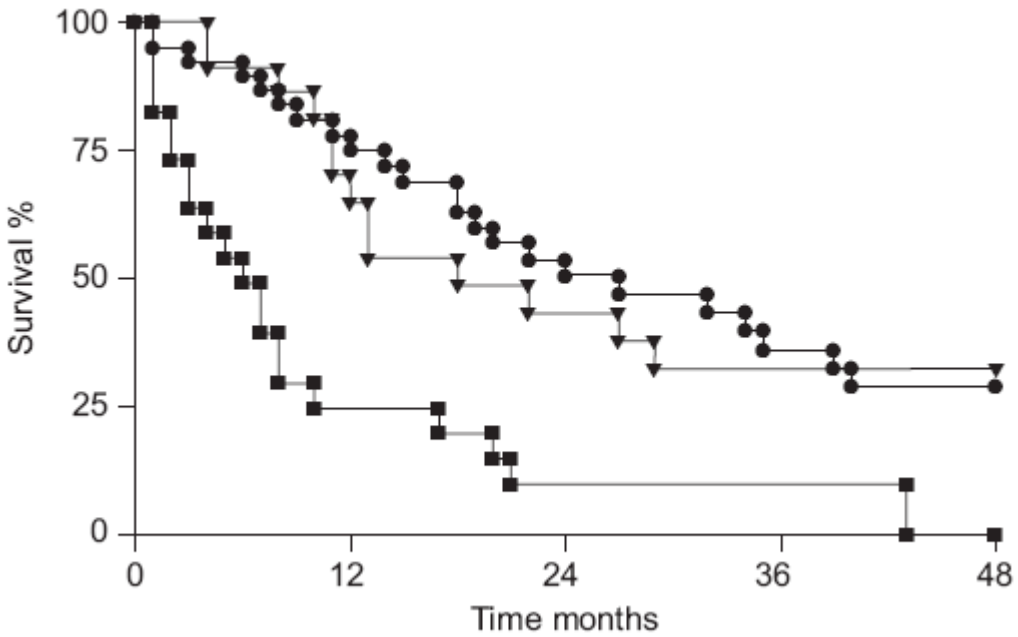
Laboratory Findings

- **There is no laboratory test specific for IPF exacerbation**
- **Most of the tests exclude treatable causes and document severity**
- **a PaO2/FIO2 ratio of less than 225 and a decrease over time in PaO2 of 10 mm Hg or greater**
- **An increase in BALF neutrophils**
- **An increase in serum KL-6, neutrophil elastase, and lactate dehydrogenase (LDH) levels**
- **An increase in ST2 protein, IL-8, and a-defensin levels**

PFTs



Declines of 5–10% (marginal) and > 10% (significant) were both associated with a worse prognosis than stable disease ($p < 0.005$)

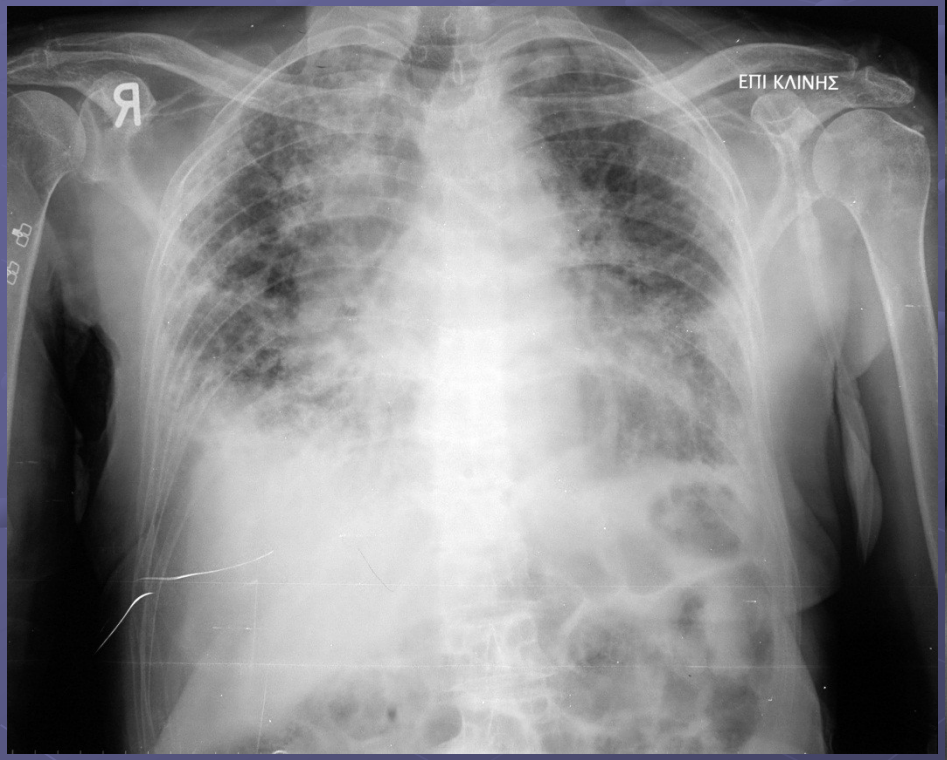


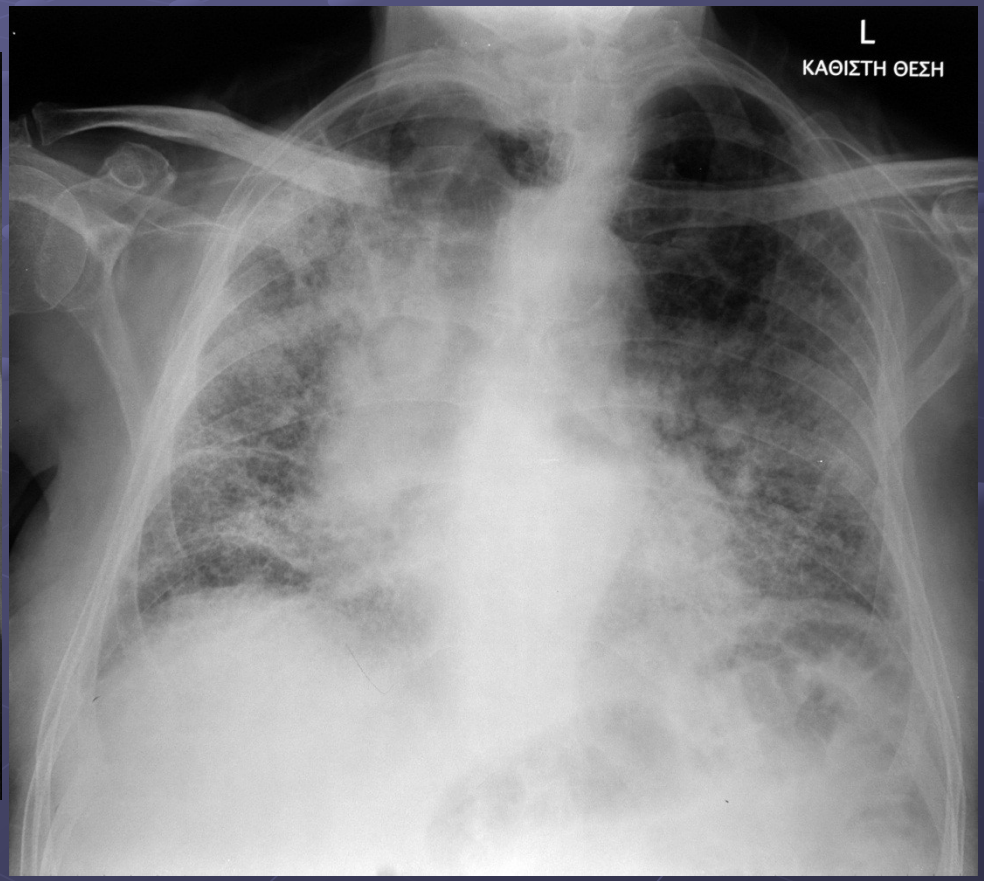
Survival did not differ between those with stable disease or a 7.5–15% (marginal) decline. Patients with a >15% (significant) decline had a worse prognosis than those with stable disease or a marginal decline ($p<0.0005$)

ERJ 2010; 35:830-835

Radiology

Diffuse ground-glass opacities on plain chest radiograph





Computed Tomography Findings in Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Masanori Akira[1], Takenori Kozuka[1], Satoru Yamamoto[2], and Mitsunori Sakatani[3]

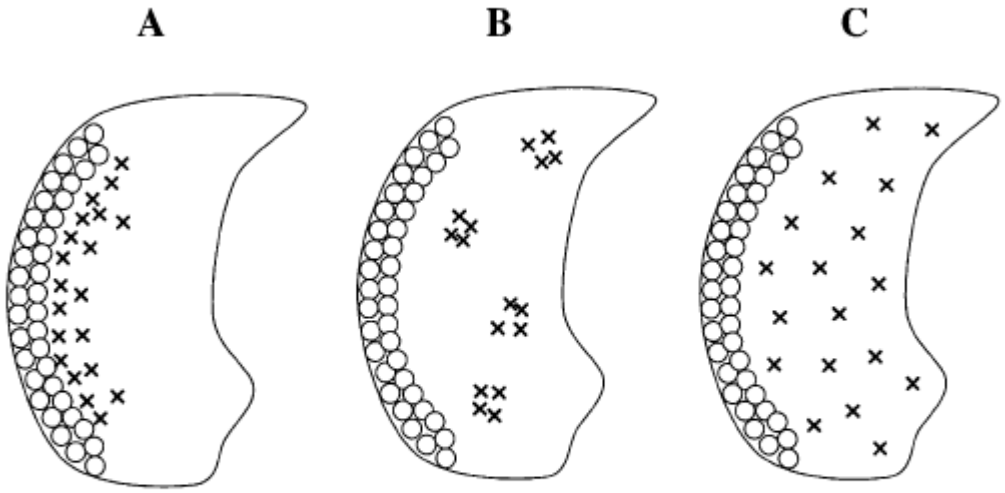
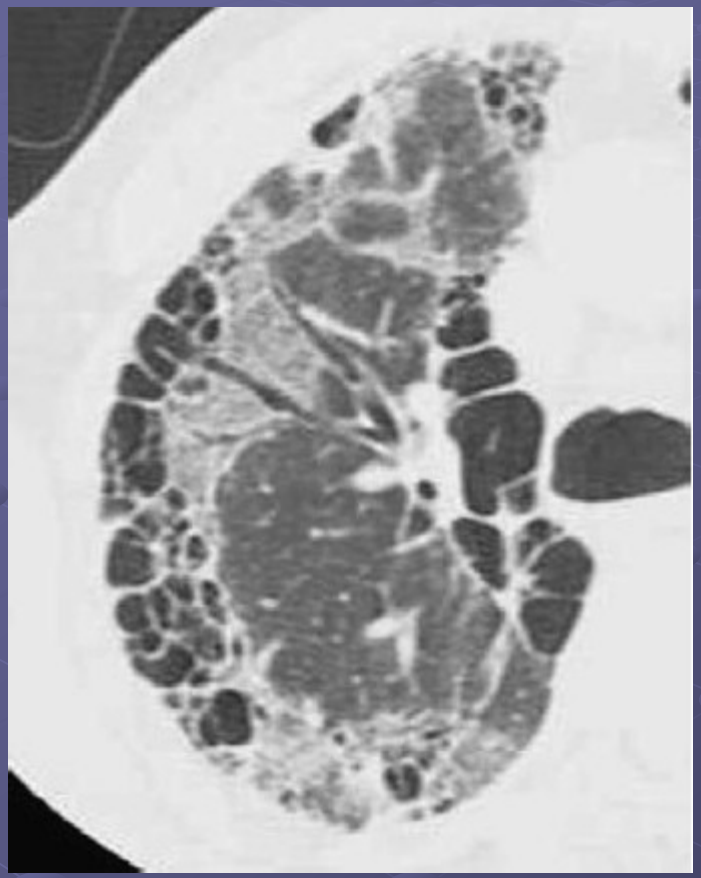
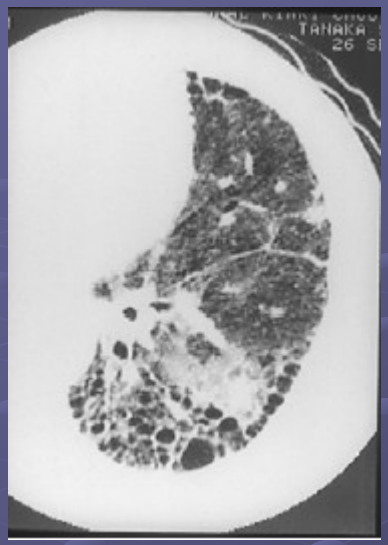


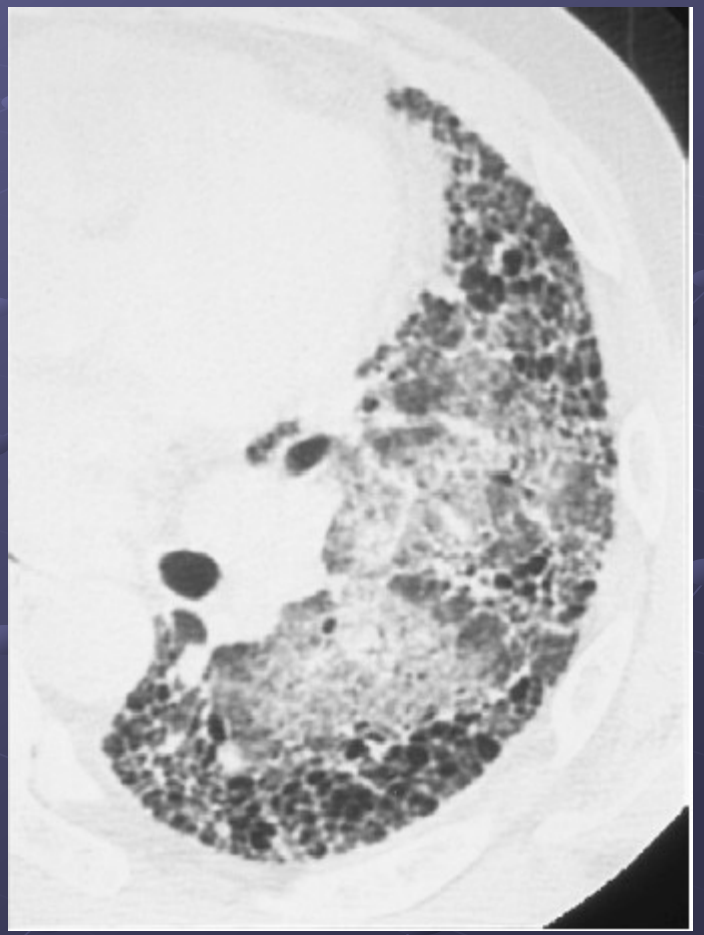
Figure 1. Scheme of computed tomography (CT) patterns. (*A*) Peripheral pattern; (*B*) multifocal pattern; (*C*) diffuse pattern.

- High resolution computed tomography (HRCT) generally demonstrates bilateral ground-glass abnormality with or without areas of consolidation, superimposed on the bibasilar subpleural reticular abnormality, traction bronchiectasis, and honeycomb change typical of usual interstitial pneumonia (UIP) pattern

Am J Respir Crit Care Med 2008; 178: 372–378




TANAKA



Histopathology

- Diffuse alveolar damage superimposed on underlying UIP is the most commonly described finding when surgical lung biopsy is performed

Terminal Diffuse Alveolar Damage in Relation to Interstitial Pneumonias

An Autopsy Study

Alexandra J. Rice, MBBChir,[1] Athol U. Wells, MD,[2] Demos Bouros, MD,[3] Roland M. du Bois, MD,[2] David M. Hansell, MD,[4] Vlasis Polychronopoulos, MD,[5] Dimitris Vassilakis, MD,[3] Jonathan R. Kerr, MD,[6] Timothy W. Evans, MD,[7] and Andrew G. Nicholson, DM[1]

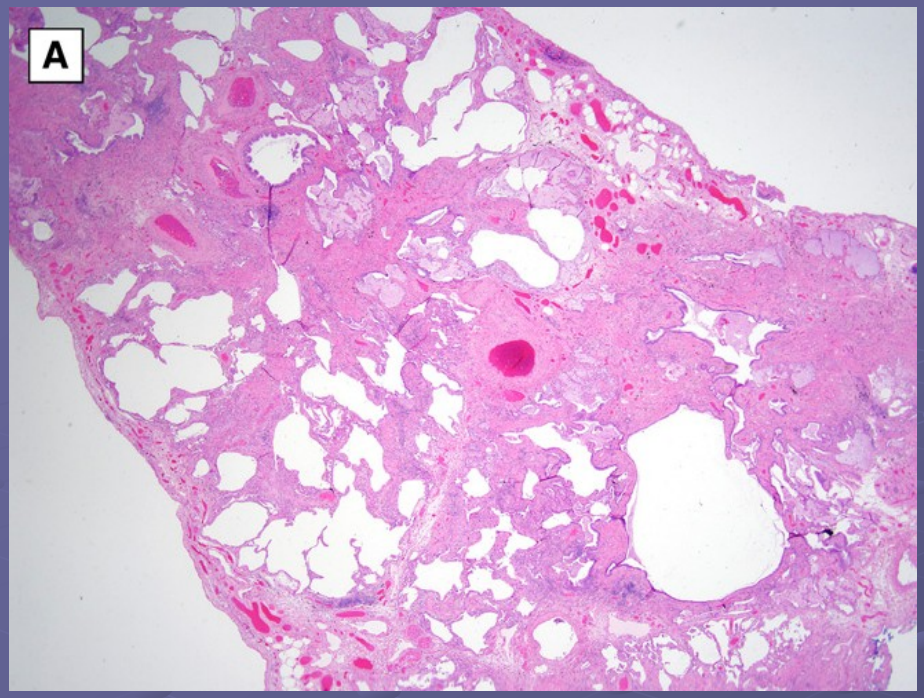
Am J Clin Pathol 2003

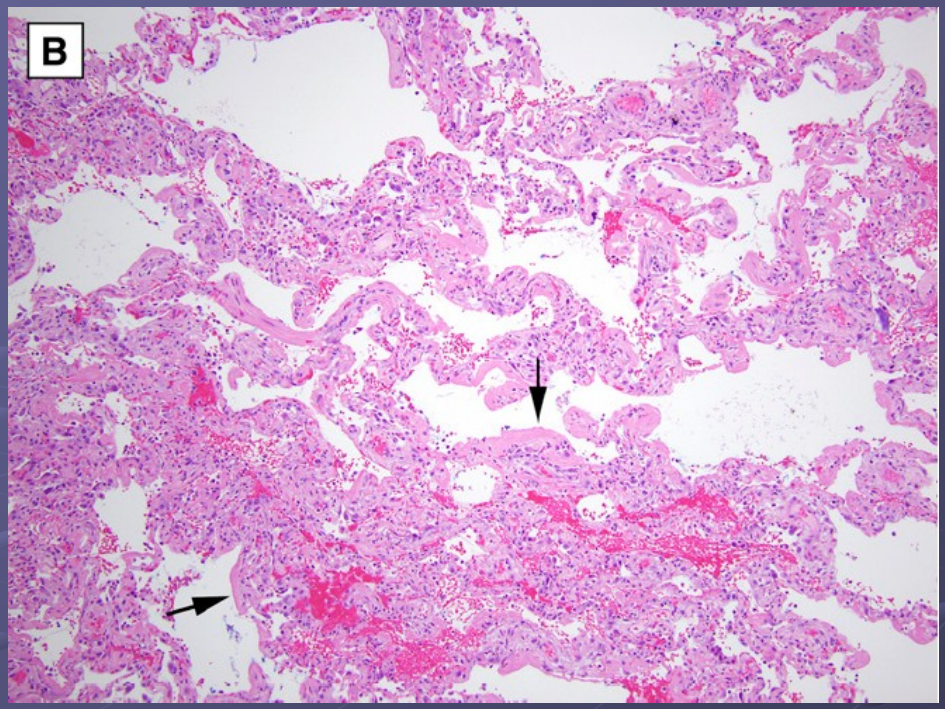
- Organizing pneumonia without other evidence of organizing diffuse alveolar damage and extensive fibroblastic foci have also been described in a few cases

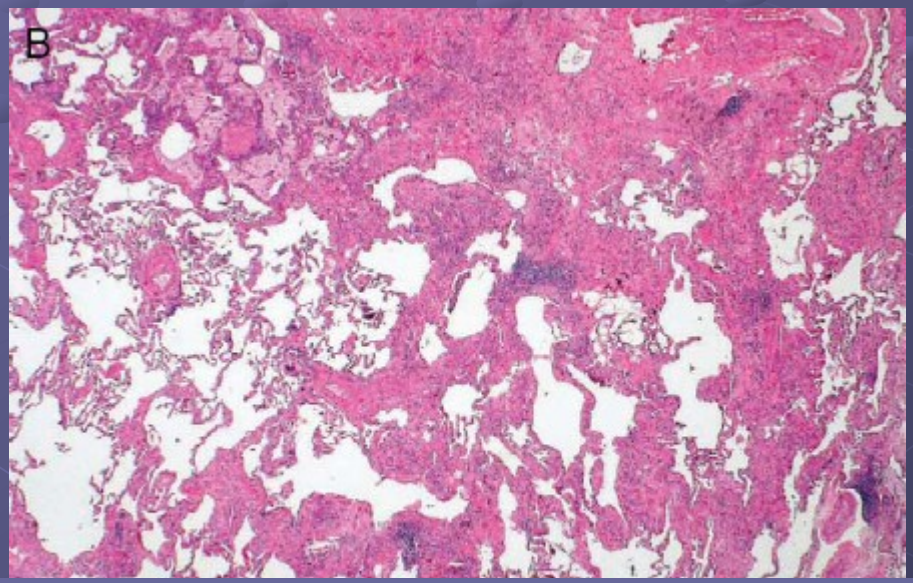
Acute Exacerbation (Acute Lung Injury of Unknown Cause) in UIP and Other Forms of Fibrotic Interstitial Pneumonias

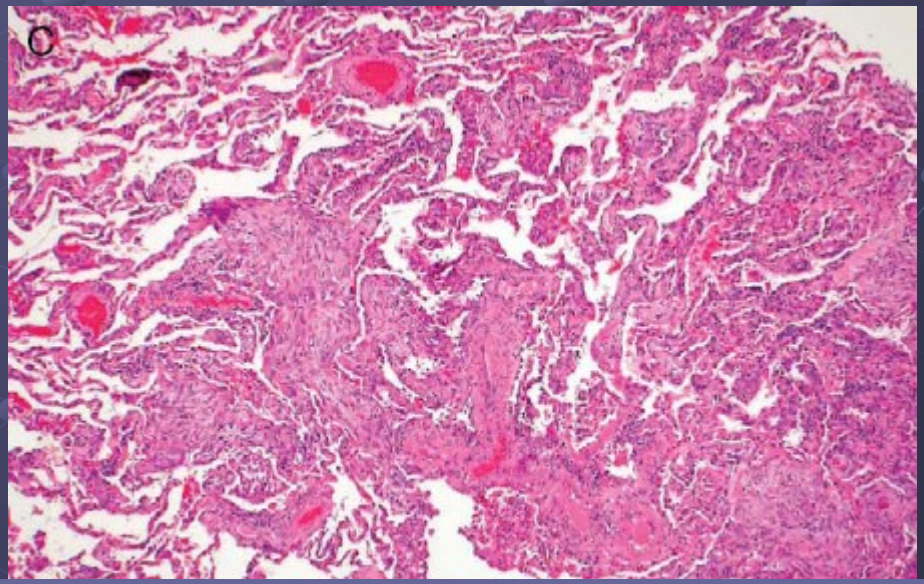
Andrew Churg, MD, Nestor L. Müller, MD, PhD, C. Isabela S. Silva, MD, and Joanne L. Wright, MD

Am J Surg Pathol 2007

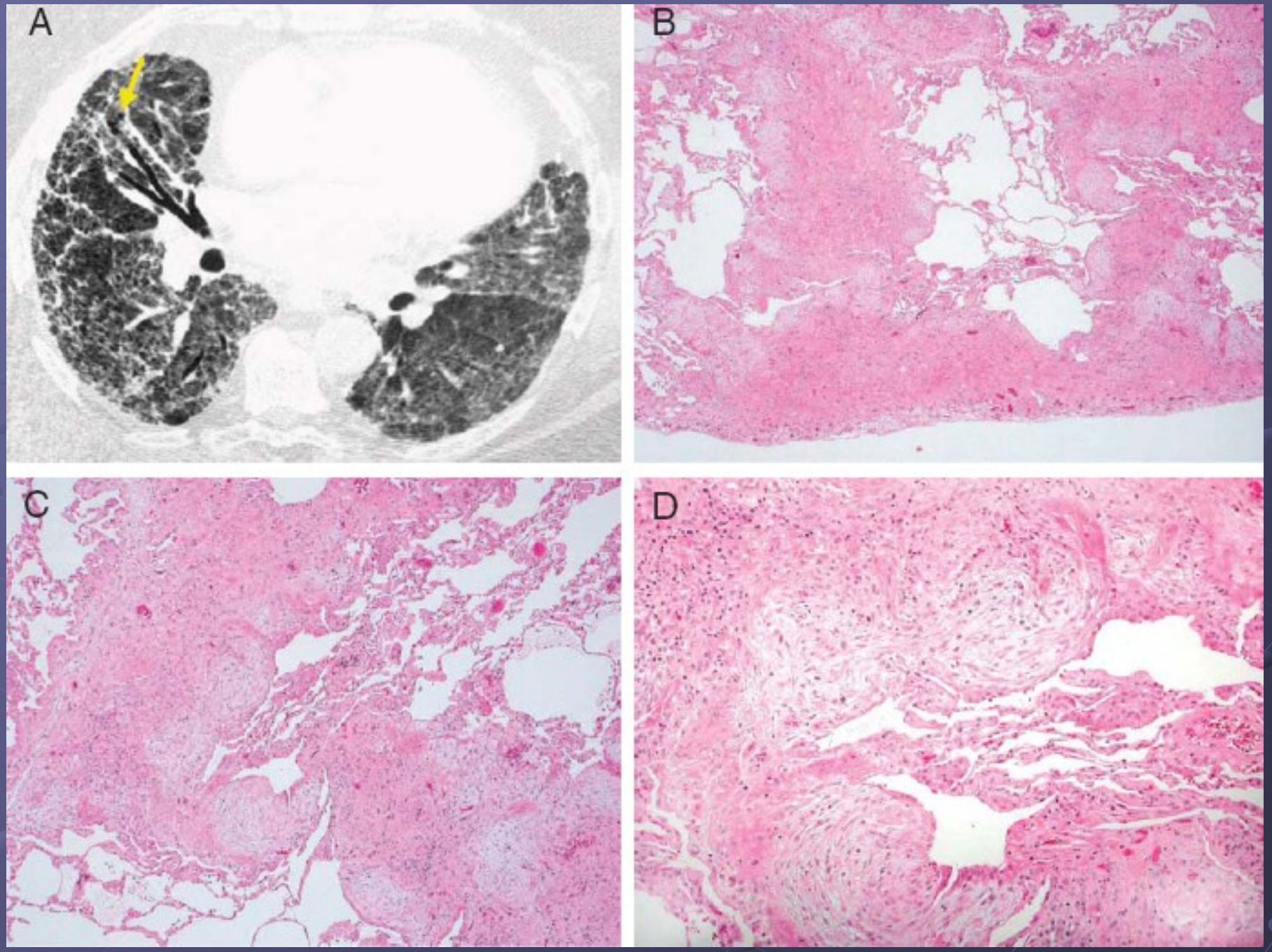


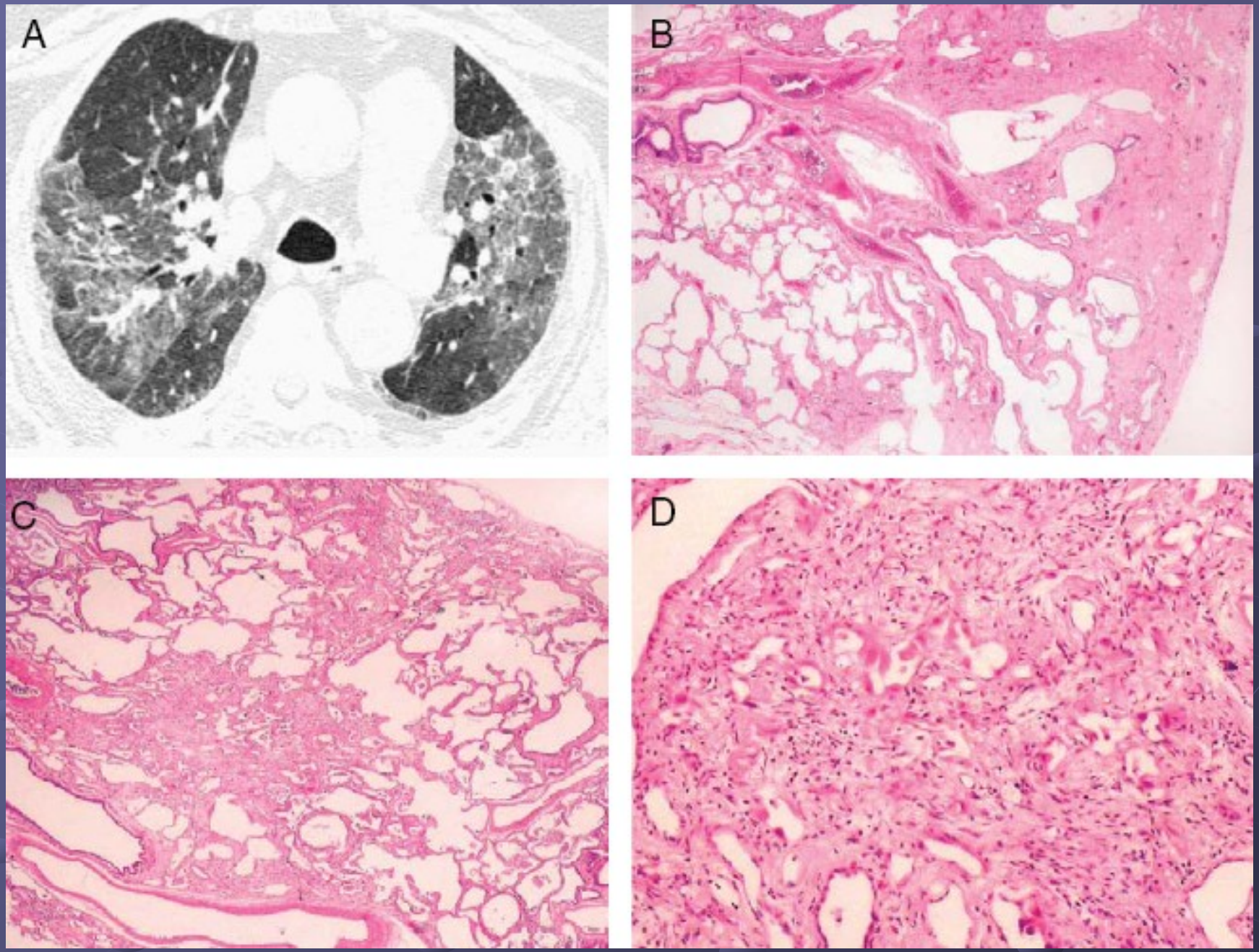






Parambil JG, et al. Chest 2005
Churg A, et al. Am J Surg Pathol 2007


A
B
C
D


A
B
C
D

Clinically occult infection which precipitates an already scarred lung into ALI/ARDS

Fibrogenesis & Tissue Repair

BioMed Central

Review

Open Access

Viruses as co-factors for the initiation or exacerbation of lung fibrosis

Kevin M Vannella[1] and Bethany B Moore*[2]

2008

Table 1: Potential mechanisms to explain how viral infections may predispose the host to develop fibrosis

Lytic infections may kill lung epithelial cells
Latent infections may alter the phenotype (proliferation, apoptosis or mediator secretion) of various lung cells (for example, epithelial and mesenchymal cells)
Persistent viruses may provide repeated insults with reactivation
Infection may increase the production of pro-fibrotic mediators (for example, TGF-β) or diminish the production of anti-fibrotic mediators
Induction of epithelial to mesenchymal transition
Induction of chemokines and fibrocyte recruitment
Surfactant abnormalities
Enhanced inflammation
Alteration of p53 function
Microvascular injury

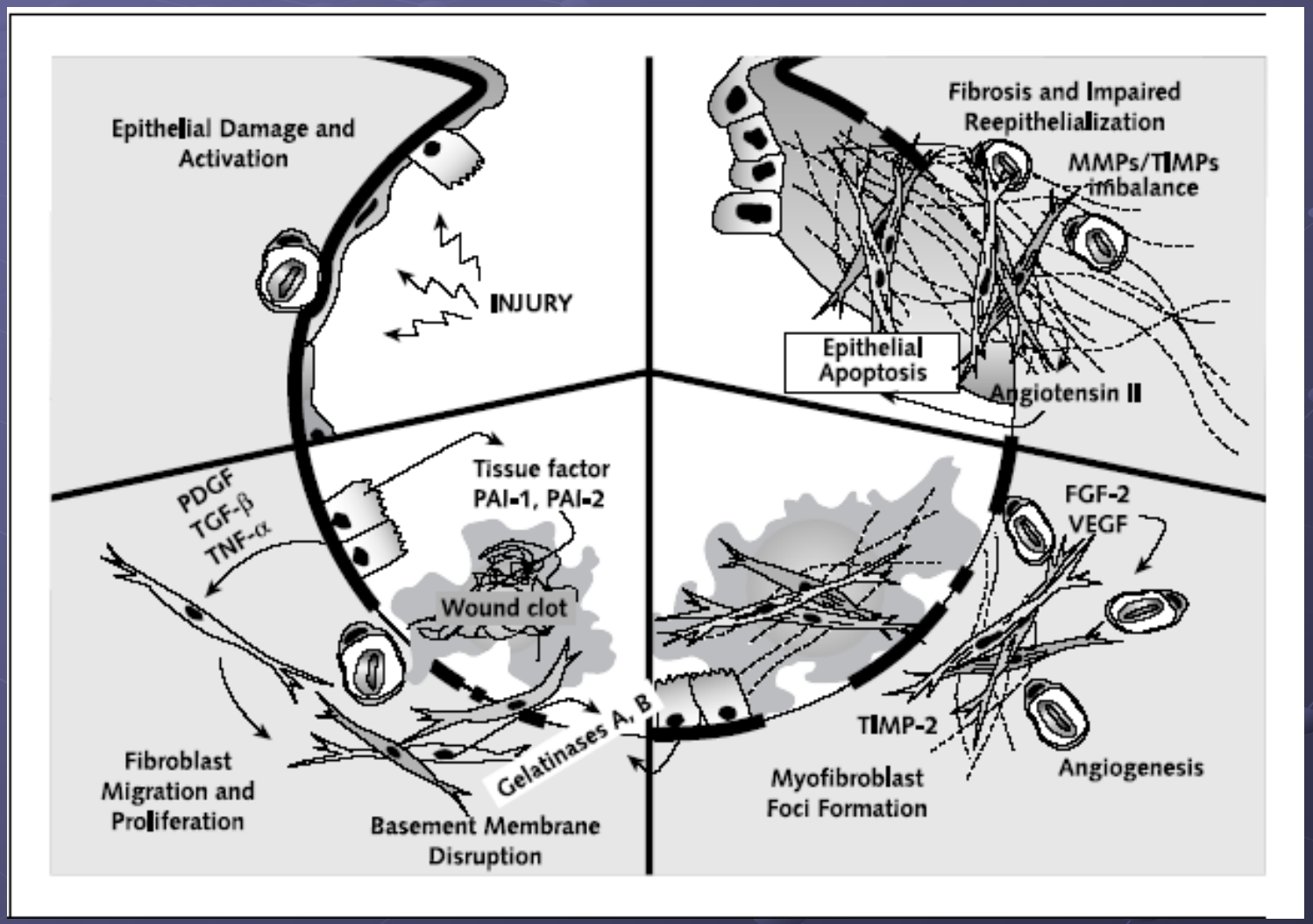
Clinically occult aspiration which precipitates an already scarred lung into ALI/ARDS

TABLE 2. CLINICAL DISORDERS ASSOCIATED WITH THE DEVELOPMENT OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Common causes	**Common causes**
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions
Less common causes	**Less common causes**
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

NEJM 2000

Acute direct stress to the lung with a subsequent acceleration of the already abnormal fibroproliferative process intrinsic to IPF



Circulating Fibrocytes Are an Indicator of Poor Prognosis in Idiopathic Pulmonary Fibrosis

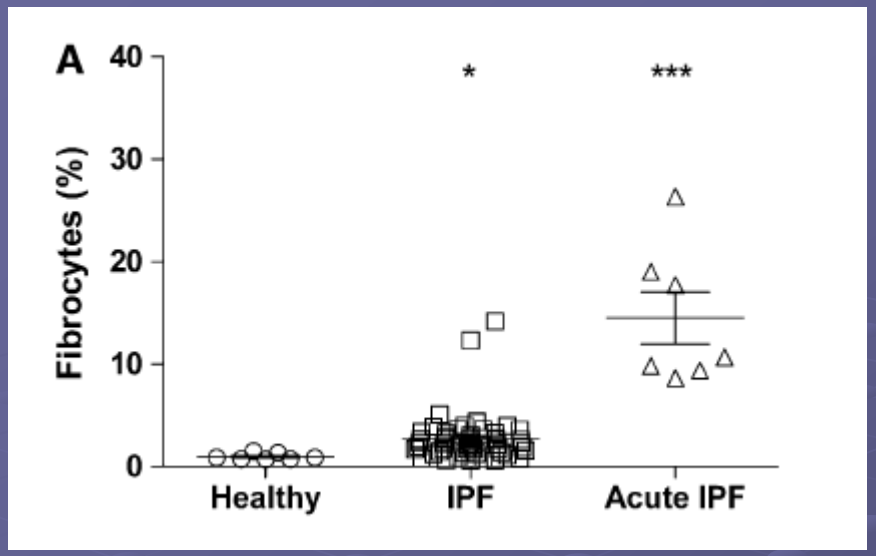
Antje Moeller[1], Sarah E. Gilpin[2], Kjetil Ask[1,2], Gerard Cox[1], Deborah Cook[1], Jack Gauldie[2], Peter J. Margetts[1,2], Laszlo Farkas[1], Julian Dobranowski[3], Colm Boylan[3], Paul M. O'Byrne[1], Robert M. Strieter[4], and Martin Kolb[1,2]

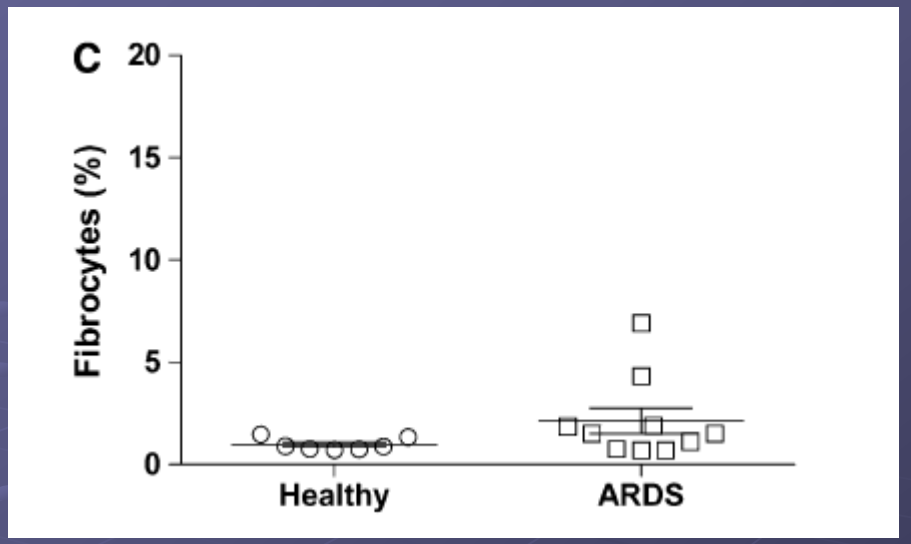
[1]Department of Medicine, McMaster University, and Firestone Institute for Respiratory Health, St. Joseph's Healthcare; [2]Department of Pathology and Molecular Medicine, Center for Gene Therapeutics, McMaster University; [3]Department of Diagnostic Imaging, McMaster University, and St. Joseph's Healthcare, Hamilton, Ontario, Canada; and [4]University of Virginia School of Medicine, Charlottesville, Virginia

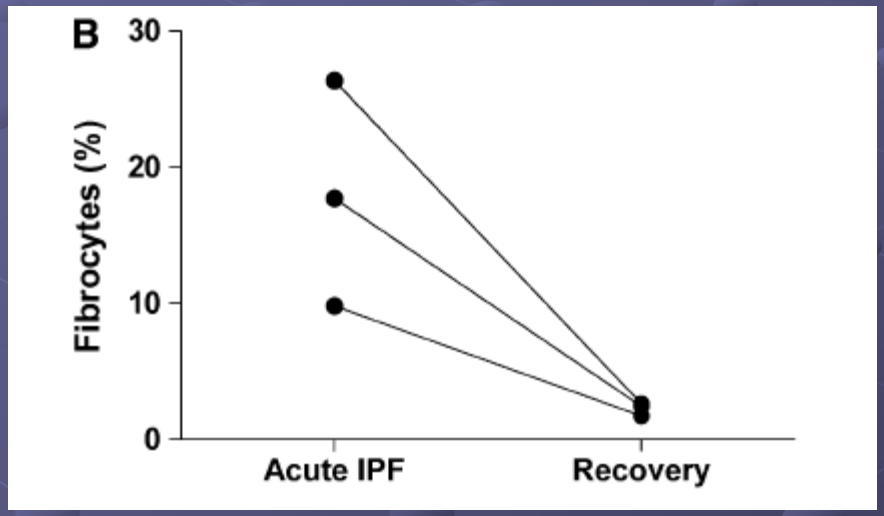
TABLE 1. PATIENT DEMOGRAPHICS

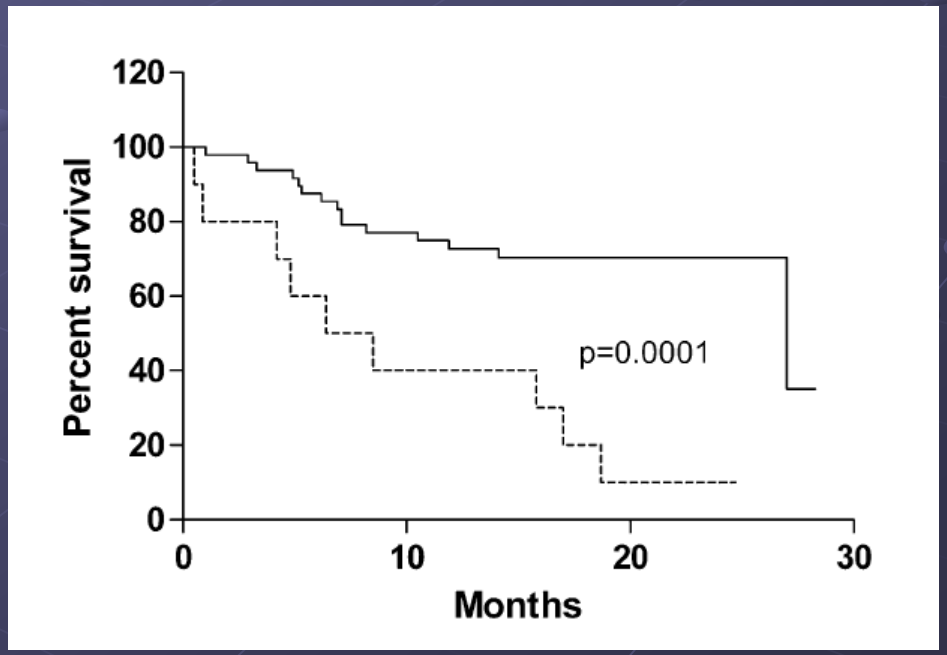
	IPF (Stable)	IPF (Acute)	ARDS
Total, n	51	7	10
Female, n	12	0	4
Male, n	39	7	6
Age (yr), mean ± SEM	68 ± 9.8	72.4 ± 6	69.5 ± 10.1
Treatment with immunosuppressants*	18	5	N/A
Survival from diagnosis (mo), mean ± SEM	44.8 ± 29.8	28.7 ± 18.5	5.6 ± 5.8
Survival from blood sample (mo), mean ± SEM	15.4 ± 7.5	10.1 ± 7.1	5.6 ± 5.8
Patients deceased within 2-yr study period, n/total n	17/51	7/7	7/10
FVC (% predicted), mean ± SEM	65.3 ± 18.1	56.3 ± 17.6	N/A
Etiology, n (septic)/n (other)	N/A	N/A	7/3

Am J Respir Crit Care Med 2009


A
Fibrocytes (%)
40
30
20
10
0
*
***
Healthy
IPF
Acute IPF


C
Fibrocytes (%)
20
15
10
5
0
Healthy
ARDS


B
Fibrocytes (%)
30
20
10
0
Acute IPF
Recovery


Percent survival
120
100
80
60
40
20
0
p=0.0001
0
10
20
30
Months

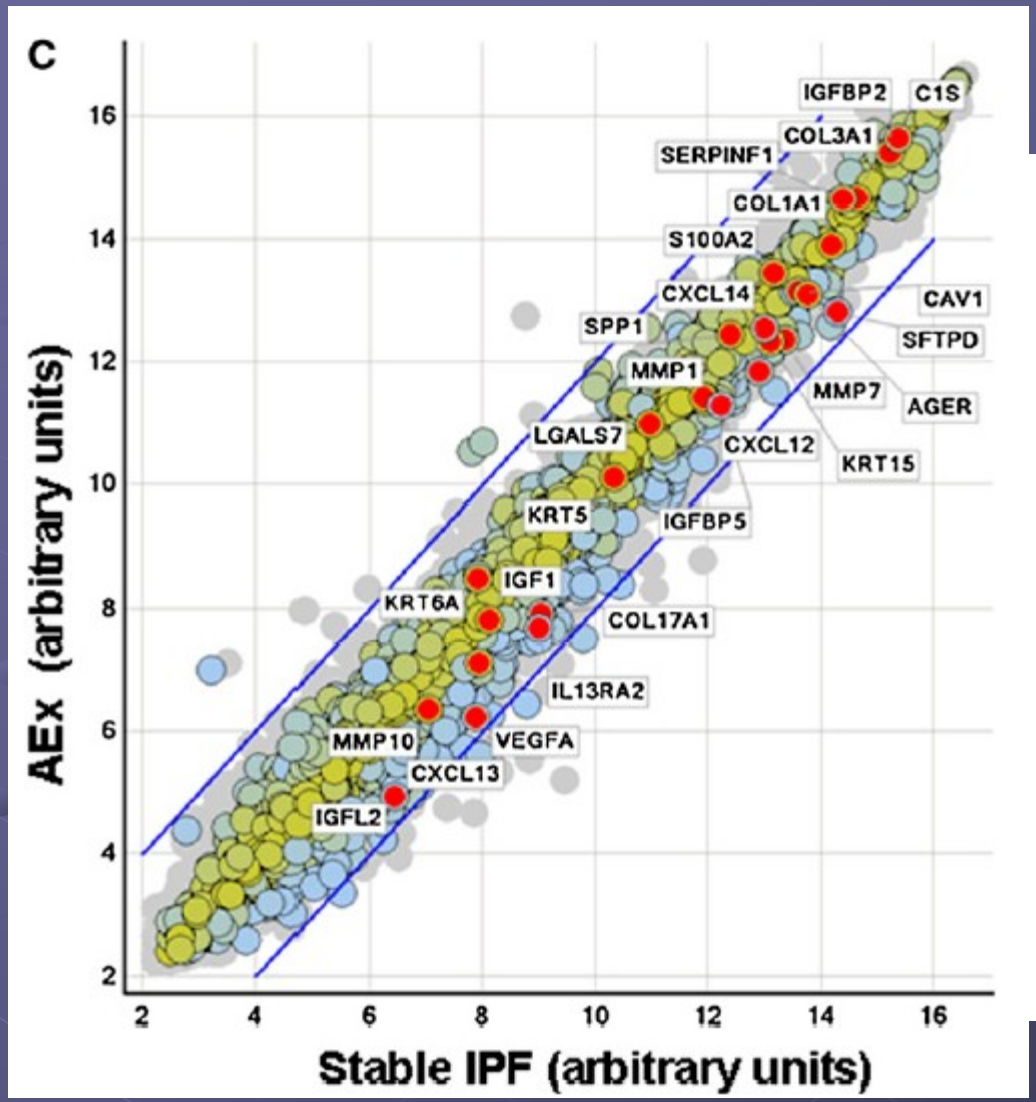
Gene Expression Profiles of Acute Exacerbations of Idiopathic Pulmonary Fibrosis

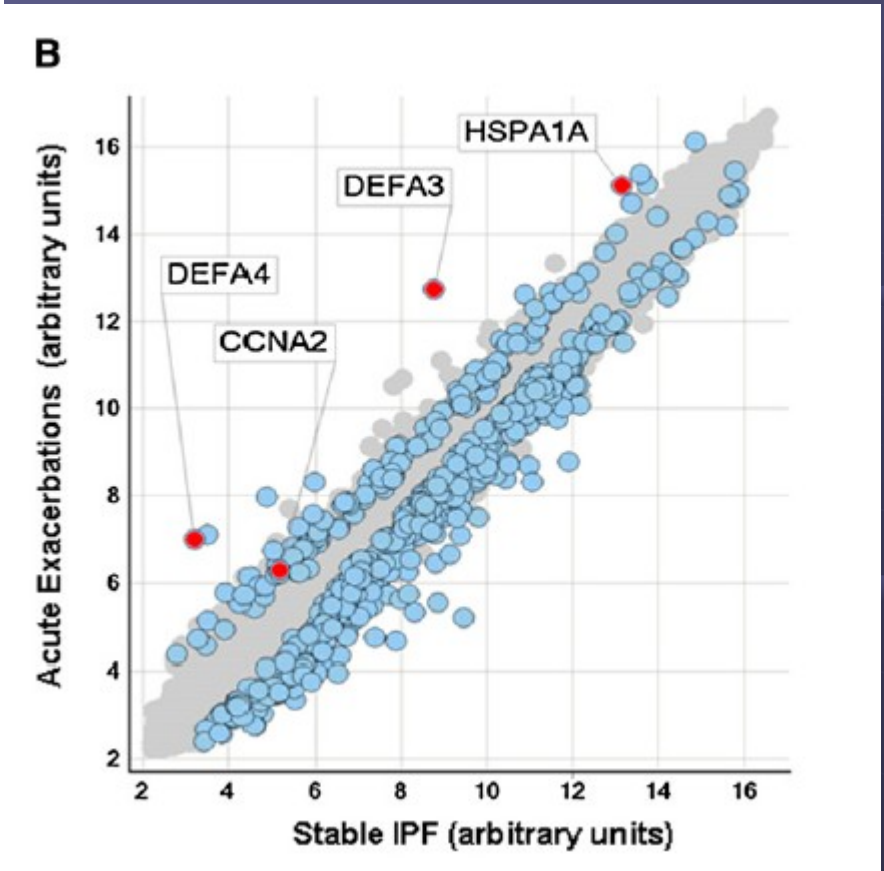
Kazuhisa Konishi[1], Kevin F. Gibson[1], Kathleen O. Lindell[1], Thomas J. Richards[1], Yingze Zhang[1], Rajiv Dhir[2], Michelle Bisceglia[2], Sebastien Gilbert[3], Samuel A. Yousem[2], Jin Woo Song[4], Dong Soon Kim[4], and Naftali Kaminski[1]

TABLE 1. CHARACTERISTICS OF PATIENTS WITH STABLE IDIOPATHIC PULMONARY FIBROSIS (IPF) AND PATIENTS WITH ACUTE EXACERBATION OF IPF

Variable	Stable IPF	IPF-AEx
A. Patients from University of Pittsburgh Medical Center		
Number of subjects	23	8
Average age, yr	61.71 (±5.51)	68.25 (±10.22)
Average FVC%	51.49 (±11.29)	55.73 (±15.85)*
Average D_{LCO}%	40.26 (±16.19)	36.61 (±12.06)*
Male/female	19/4	6/2
B. Patients from Asan Medical Center		
Number of subjects	10	16
Average age, yr	63.60 (±9.94)	65.50 (±10.30)
Average FVC%	81.1 (±11.97)	55.0 (±8.3)† (n = 7)
Average D_{LCO}%	66.40 (±12.77)	38.9 (±13.3)† (n = 7)
Male/female	10/0	9/7

Am J Respir Crit Care Med 2009


C
AEx (arbitrary units)
Stable IPF (arbitrary units)
IGFBP2
C1S
COL3A1
SERPINF1
COL1A1
S100A2
CXCL14
CAV1
SPP1
SFTPD
MMP1
MMP7
AGER
LGALS7
CXCL12
KRT15
KRT5
IGFBP5
IGF1
KRT6A
COL17A1
IL13RA2
MMP10
VEGFA
CXCL13
IGFL2


B
Acute Exacerbations (arbitrary units)
Stable IPF (arbitrary units)
HSPA1A
DEFA3
DEFA4
CCNA2

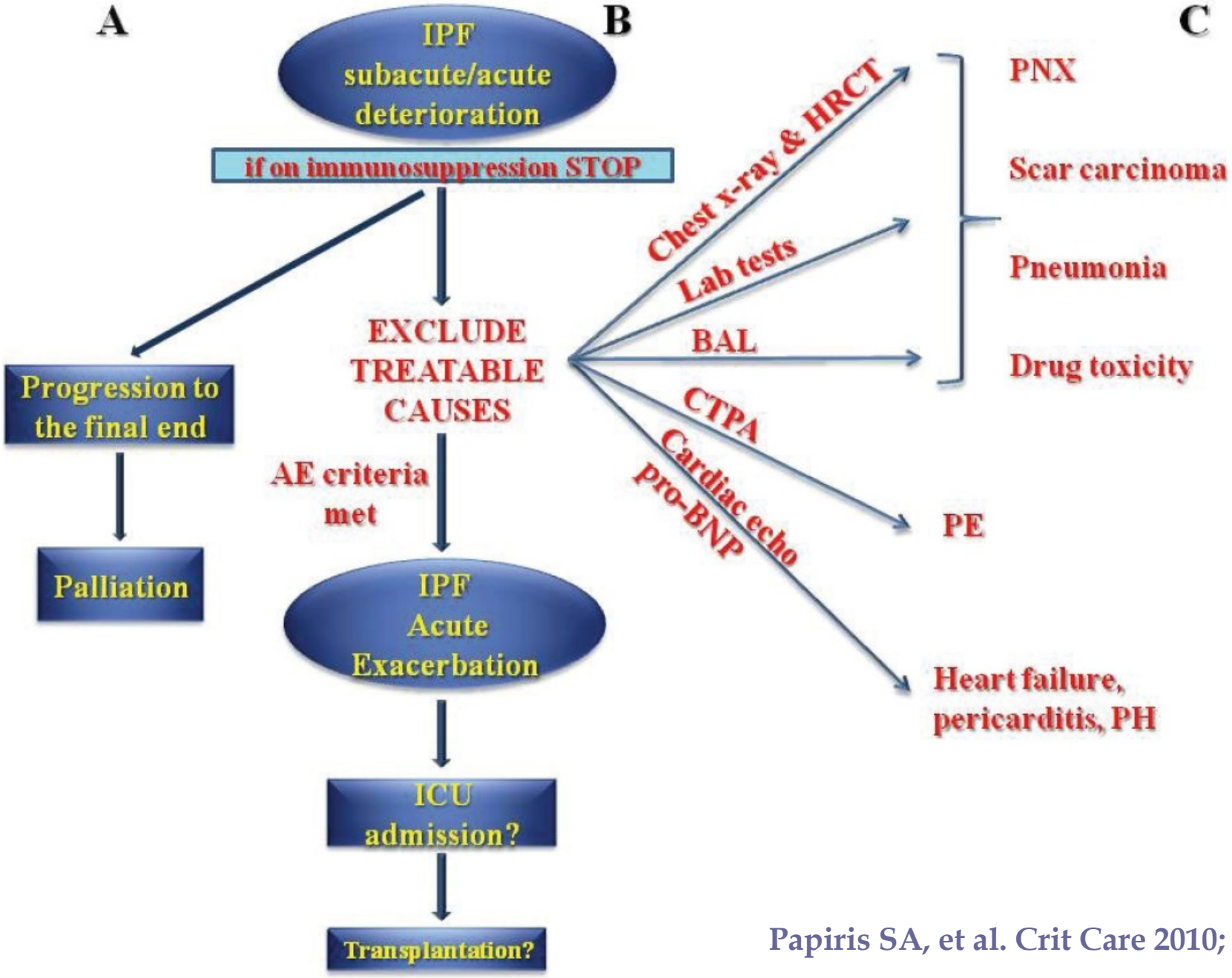
Gene expression patterns in IPF-AEx and IPF samples were similar for the genes that distinguish IPF from control lungs

1. **CCNA2 is overexpressed in IPF-AEx**

2. **IPF-AEx Lungs Exhibit Widespread Epithelial Apoptosis**

3. **a- Defensin Expression Is Increased in Lungs and Peripheral Blood of Patients with IPF-AEx**

- Taken together, these results indicate the central role of the pulmonary epithelium in IPF-AEx and suggest a potential role for a-defensins as peripheral blood biomarkers in IPF-AEx
- Results do they support a role for an active infection during the last phase of the syndrome
- It is entirely possible that by the time the patients experienced the final deterioration all evidence of response to an infection or infected tissue was destroyed. In this context the finding of increased a-defensins levels and the evidence of epithelial injury may be interpreted as remnants of an infectious process that triggered the acute lung injury but was cleared by the time the lungs were harvested.



Papiris SA, et al. Crit Care 2010; 14:246

Management of IPF

- It seems likely that the most effective approach to treatment would be to target multiple fibrosis pathways simultaneously
- Given the similarities between ARDS and AE-IPF, treatment approaches targeting patients with ARDS could be beneficial to patients with AE-IPF

TABLE 2. QUALITY OF THE EVIDENCE RATING AND IMPLICATIONS

Quality of the Evidence (GRADE)	The **quality of the evidence** is a judgment about the extent to which we can be confident that the estimates of effect are correct. These judgments are made using the GRADE system, and are provided for each outcome. The judgments are based on the type of study design (randomized trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall estimate across studies. For each outcome, the quality of the evidence is rated as high, moderate, low, or very low using the following definitions:
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	We are very uncertain about the estimate. (For more information about the GRADE system, see: www.gradeworkinggroup.org)

TABLE 3. IMPLICATIONS OF RECOMMENDATIONS FOR PATIENTS, CLINICIANS, AND POLICY MAKERS

	Strong		Weak	
	"Strong Yes"	"Strong No"	"Weak Yes"	"Weak No"
Patients	**Most people** in this situation **would want** the intervention and only a small proportion would not	**Most people** in this situation **would not want** the intervention and only a small proportion would	**The majority of people** in this situation **would want** the intervention, **but many would not**	**The majority of people** in this situation **would not want** the intervention, **but many would**
Clinicians	Most patients should receive the recommended course of action		Be more prepared to help patients to make a decision that is consistent with the patient's own values	
Policy Makers	The recommendation can be adopted as a policy in most situations		There is a need for substantial debate and involvement of stakeholders	

Treatment I

- Corticosteroid monotherapy: NO strong (⊕○○○)
- Colchicine: NO strong (⊕○○○)
- Cyclosporine A: NO strong (⊕○○○)
- Combination corticosteroid and immunomodulator therapy: NO strong (⊕⊕○○)
- Combination corticosteroid, azathioprine, and acetylcysteine therapy: NO weak (⊕⊕○○)

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

For Immediate Release
Friday, October 21, 2011
Contact:
NHLBI Communications Office
301-496-4236

Commonly used three-drug regimen for idiopathic pulmonary fibrosis found harmful

NIH stops one treatment arm of trial; other two treatments to continue

The interim results from this study showed that compared to placebo, those assigned to triple therapy had greater mortality (11 percent versus 1 percent), more hospitalizations (29 percent versus 8 percent), and more serious adverse events (31 percent versus 9 percent) and also had no difference in lung function test changes. Participants randomly assigned to the triple- therapy arm also remained on their assigned treatment at a much lower rate (78 percent adherence versus 98 percent adherence).

Treatment II

- Acetylcysteine monotherapy: NO weak (⊕⊕◯◯)
- Interferon-gamma 1b: NO strong (⊕⊕⊕⊕)
- Bosentan: NO strong (⊕⊕⊕◯)
- Etanercept: NO strong (⊕⊕⊕◯)
- Anticoagulants: NO weak (⊕◯◯◯)
- Pirfenidone: NO weak (⊕⊕◯◯)

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Double-blind, Placebo-controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Arata Azuma, Toshihiro Nukiwa, Eiyasu Tsuboi, Moritaka Suga, Shosaku Abe, Koichiro Nakata, Yoshio Taguchi, Sonoko Nagai, Harumi Itoh, Motoharu Ohi, Atsuhiko Sato, and Shoji Kudoh for the members of the Research Group for Diffuse Lung Diseases in Japan; and Ganesh Raghu

Am J Respir Crit Care Med Vol 171. pp 1040–1047, 2005

Pirfenidone in idiopathic pulmonary fibrosis

H. Taniguchi*, M. Ebina#, Y. Kondoh*, T. Ogura¶, A. Azuma+, M. Suga§, Y. Taguchiƒ, H. Takahashi**, K. Nakata##, A. Sato¶¶, M. Takeuchi++, G. Raghu§§, S. Kudoh+ and T. Nukiwa#, and the Pirfenidone Clinical Study Group in Japanƒƒ

Eur Respir J 2010; 35: 821–829

Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

www.thelancet.com **Published online May 14, 2011 DOI:10.1016/S0140-6736(11)60405-4**

	Study 004				Study 006				Pooled data			
	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Absolute difference (95% CI)	p value*
Categorical change in FVC ≥10%	35 (20%)	60 (35%)	14·4 (7·4 to 21·3)	0·001†	39 (23%)	46 (27%)	3·8 (–2·7 to 10·2)	0·440†	74 (21%)	106 (31%)	9·1 (4·3 to 13·9)	0·003†
Progression-free survival time‡	..	..	0·64 (0·44 to 0·95)	0·023§	..	..	0·84 (0·58 to 1·22)	0·355§	..	..	0·74 (0·57 to 0·96)	0·025§
Mean change in 6MWT distance (m)	–60·4	–76·8	16·4 (–10·9 to 43·7)	0·171	–45·1	–76·9	31·8 (3·2 to 60·4)	0·0009	–52·8	–76·8	24·0 (4·3 to 43·7)	0·0009
Mean change in DLco (% predicted)	–7·9	–9·9	2·0 (–0·4 to 4·4)	0·145	–9·8	–9·2	–0·5 (–3·2 to 2·2)	0·996	–8·8	–9·6	0·7 (–1·1 to 2·5)	0·301
Mean change in dyspnoea score¶	12·1	15·2	–3·1 (–8·5 to 2·3)	0·509	11·9	13·9	–2·0 (–7·6 to 3·6)	0·604	12·0	14·5	–2·5 (–6·4 to 1·4)	0·405
Mean change in worst SpO_2 during 6MWT (%)	–1·5	–2·3	0·8 (–0·2 to 1·8)	0·087	–1·9	–1·3	–0·5 (–1·7 to 0·7)	0·893	–1·7	–1·8	0·1 (–0·7 to 0·9)	0·261
Time to worsening in idiopathic pulmonary fibrosis	..	..	0·84 (0·50 to 1·42)‡	0·515§	..	..	0·73 (0·43 to 1·24)‡	0·248§	..	..	0·78 (0·54 to 1·14)‡	0·201§
Categorical change in HRCT-diagnosed fibrosis‖	NA	NA	NA	NA	NA	NA	NA	0·894	NA	NA	NA	NA

Nonpharmacological therapies

- Long-term Oxygen Therapy: YES strong (⊕○○○).
- Lung Transplantation: YES strong (⊕○○○).
- Mechanical ventilation: NO weak (⊕⊕○○).
- Pulmonary rehabilitation: YES weak (⊕⊕○○).
- Should patients with acute exacerbation of IPF be treated with corticosteroids? YES weak (⊕○○○).
- Should pulmonary hypertension be treated? YES weak (⊕○○○).
- Should asymptomatic GER be treated? YES weak (⊕○○○).

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial

Hossein Ardeschir Ghofrani, Ralph Wiedemann, Frank Rose, Ralph T Schermuly, Horst Olschewski, Norbert Weissmann, Andreas Gunther, Dieter Walmrath, Werner Seeger, Friedrich Grimminger

Lancet 2002; **360:** 895–900

	Treatment group		
	Sildenafil (n=8)	Epoprostenol (n=8)	Total (n=16)
Age (years)	61·5 (38 to 79)	46·0 (27 to 75)	56·5 (27 to 79)
Heart rate (beats per min)	78·0 (60 to 108)	96·0 (61 to 123)	86·0 (60 to 123)
Mean pulmonary arterial pressure (mm Hg)	41·0 (25 to 62)	33·5 (25 to 59)	40·0 (25 to 62)
Mean systemic arterial pressure (mm Hg)	92·5 (65 to 104)	96·0 (61 to 123)	92·5 (61 to 123)
Cardiac index (L/min/m^2)	2·2 (1·4 to 3·2)	2·4 (1·4 to 4·3)	2·3 (1·4 to 4·3)
Systemic vascular resistance index (dyne/s/cm^{-5}/m^2)	2683·5 (2121 to 3820)	2692·8 (1536 to 5882)	2683·5 (1536 to 5882)
Pulmonary vascular resistance index (dyne/s/cm^{-5}/m^2)	1186·1 (515 to 3296)	961·8 (448 to 3057)	1108·7 (448 to 3296)
Mixed venous oxygen saturation (%)	70·4 (57 to 76)	66·5 (38 to 75)	69·5 (38 to 76)
Partial pressure of arterial oxygen (mm Hg)	77·0 (72 to 104)	63·0 (50 to 102)	73·5 (50 to 104)
Partial pressure of carbon dioxide (mm Hg)	41·0 (32 to 49)	36·3 (27 to 57)	37·3 (27 to 57)
Vital capacity (%)*	65·8 (25 to 87)	49·0 (23 to 75)	55·0 (23 to 87)
Diffusion capacity for carbon monoxide gas*	23·0 (13 to 72)	27·5 (14 to 63)	24·5 (13 to 72)
Pulmonary shunt flow	4·0 (0 to 17)	4·8 (3 to 28)	4·8 (0 to 28)

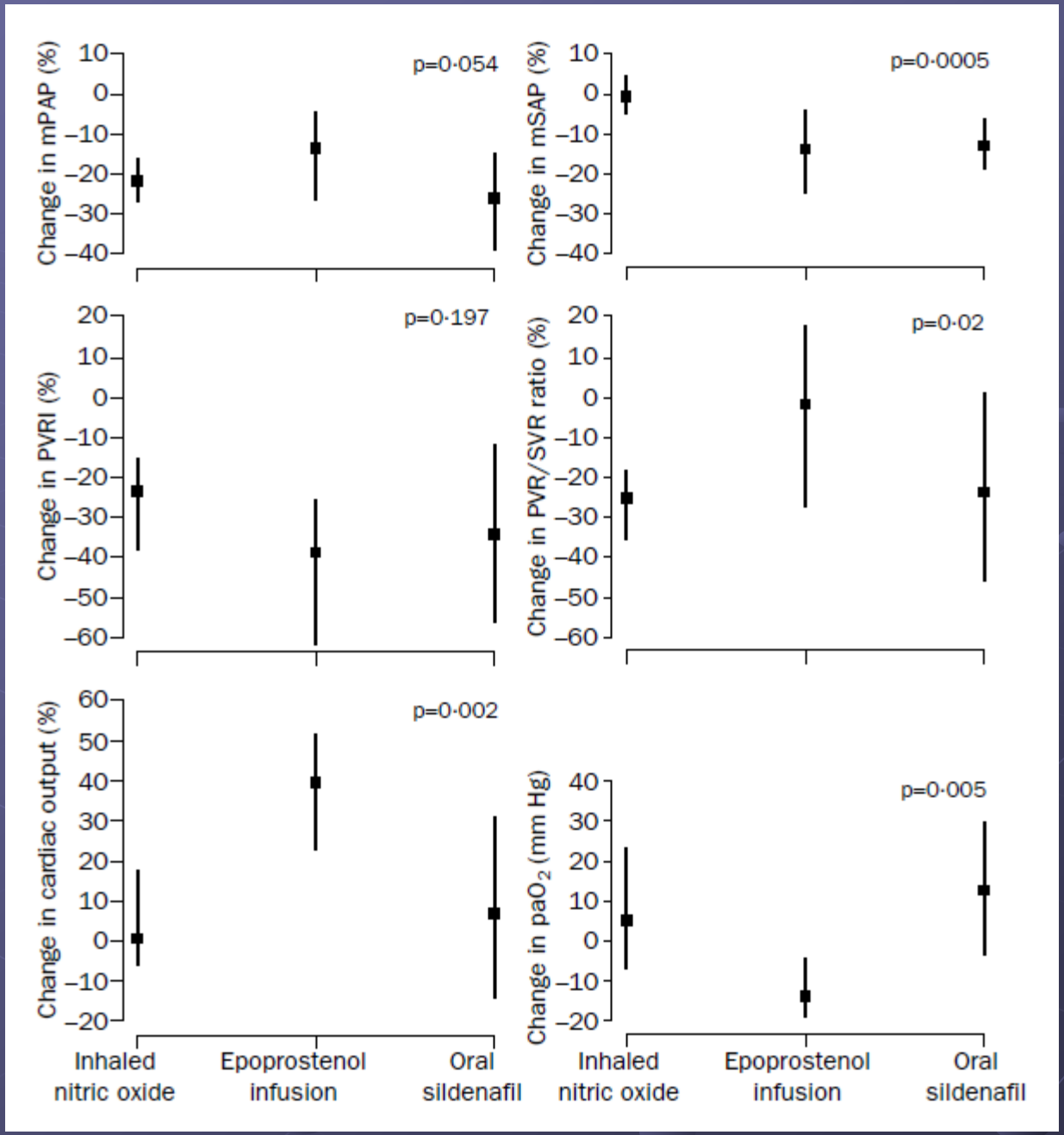

Change in mPAP (%)
10
0
−10
−20
−30
−40
p=0·054
Change in mSAP (%)
p=0·0005
Change in PVRI (%)
20
10
0
−10
−20
−30
−40
−50
−60
p=0·197
Change in PVR/SVR ratio (%)
p=0·02
Change in cardiac output (%)
60
50
40
30
20
10
0
−10
−20
p=0·002
Change in paO2 (mm Hg)
p=0·005
Inhaled nitric oxide
Epoprostenol infusion
Oral sildenafil

Table 32 Recommendations for PH due to lung diseases

Statement	Class[a]	Level[b]
Echocardiography is recommended as a screening tool for the assessment of PH due to lung diseases	I	C
RHC is recommended for a definite diagnosis of PH due to lung diseases	I	C
The optimal treatment of the underlying lung disease including long-term O_2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases	I	C
Patients with 'out of proportion' PH due to lung diseases should be enrolled in RCTs targeting PAH-specific drugs	IIa	C
The use of PAH-specific drug therapy is not recommended in patients with PH due to lung diseases	III	C

Eur Heart J 2009; 30(20):2493-2537

Guidelines for Referral and Listing for Trasnplantation in patients with IPF

Orens JB et al. J Heart Lung Transplant 2006; 25: 745

Guidelines	Description
For referral	Histologic or radiographic evidence of UIP irrespectively of vital capacity Histologic evidence of fibrotic NSIP
For listing	Histologic or radiographic evidence of UIP and any of the following: DLCO of < 39% predicted; ≥ 10% decrement in FVC during 6 mo of follow-up; decrease in pulse oximetry below 88% during a 6MWT; and honeycombing seen on HRCT scan (fibrosis score > 2) Histologic evidence of NSIP and any of following: DLCO < 35% predicted; and ≥ 10% decrement in FVC or 15% decrease in DLCO during 6 mo of follow-up

Conclusions

- Based on the evidence published to date, there is no proven pharmacological therapy for IPF.
- Continued, concerted efforts should be made by physicians, patients, and sponsors to pursue well-designed clinical trials aimed at improving outcomes, including quality of life, in patients with IPF.

Am J Respir Crit Care Med 2011; 183: 788-824

Thorax ONLINE

Interstitial lung disease guideline

A U Wells, N Hirani and on behalf of the BTS Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society

Thorax 2008;63;v1-v58

Best supportive care should be considered a specific and important treatment strategy in all patients with IPF. It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, antireflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. [D]

Thorax ONLINE

Interstitial lung disease guideline

A U Wells, N Hirani and on behalf of the BTS Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society

Thorax 2008;63;v1-v58

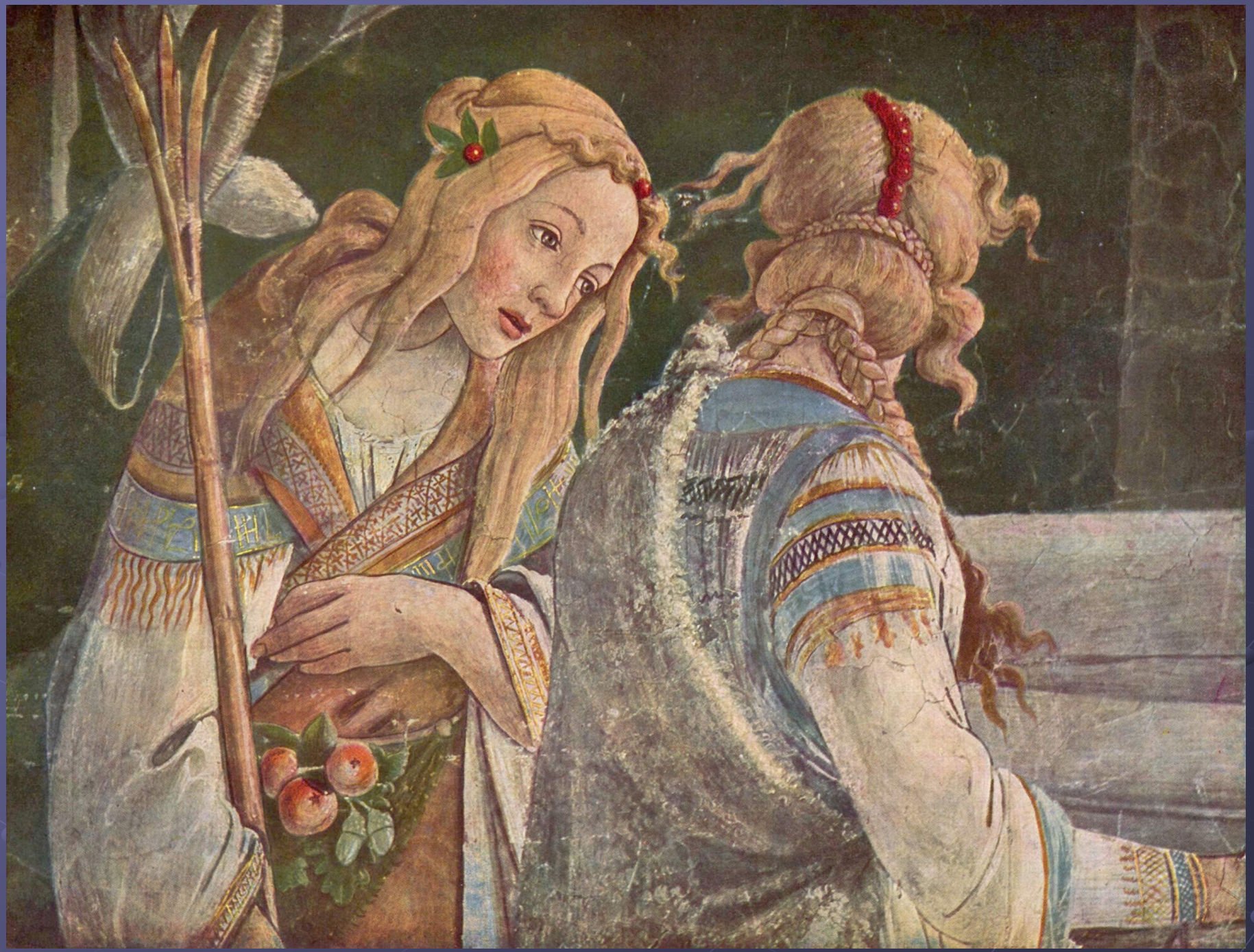
To date there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF. As such, it is recommended that all patients be considered for recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate. [C]

Monitoring for progressive disease

Every 3-6 months

- **Dyspnea Score**
- **Decrease in absolute FVC (<10%)** (emphysema ?)
- **Decrease in absolute DLco (<15%)** (PH ?)
- **Oxygen saturation and 6MWT** (supplemental O2)
- **Monitoring for Complications and Comorbidities**

Am J Respir Crit Care Med Vol 183. pp 788–824, 2011



The American Journal of Surgical Pathology *18(2): 136–147, 1994*

Nonspecific Interstitial Pneumonia/Fibrosis

Histologic Features and Clinical Significance

Anna-Luise A. Katzenstein, M.D., and Robert F. Fiorelli, B.S.

- Sixty-four cases of interstitial pneumonia were identified that could not be classified into one of three main categories of idiopathic interstitial pneumonia
- It should not be considered a specific disease, however, because it may have varying etiologies including underlying connective tissue diseases, organic dust or other exposures, and prior acute lung injury; less often, it may reflect a non-representative biopsy of another process. Better prognosis

ELSEVIER
SAUNDERS

Clin Chest Med 25 (2004) 705 – 715

CLINICS
IN CHEST
MEDICINE

Nonspecific interstitial pneumonia: a real clinical entity?

Sonoko Nagai, MD, PhD[a,*], Tomohiro Handa, MD[a], Rollin Tabuena, MD[a], Masanori Kitaichi, MD, PhD[b], Takateru Izumi, MD, PhD[c]

[a]*Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 606-8507, Kyoto, Japan*
[b]*Laboratory of Anatomical Pathology, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan*
[c]*Kyoto Central Clinic, Nakagyoku, Sanjo, Kyoto, Japan*

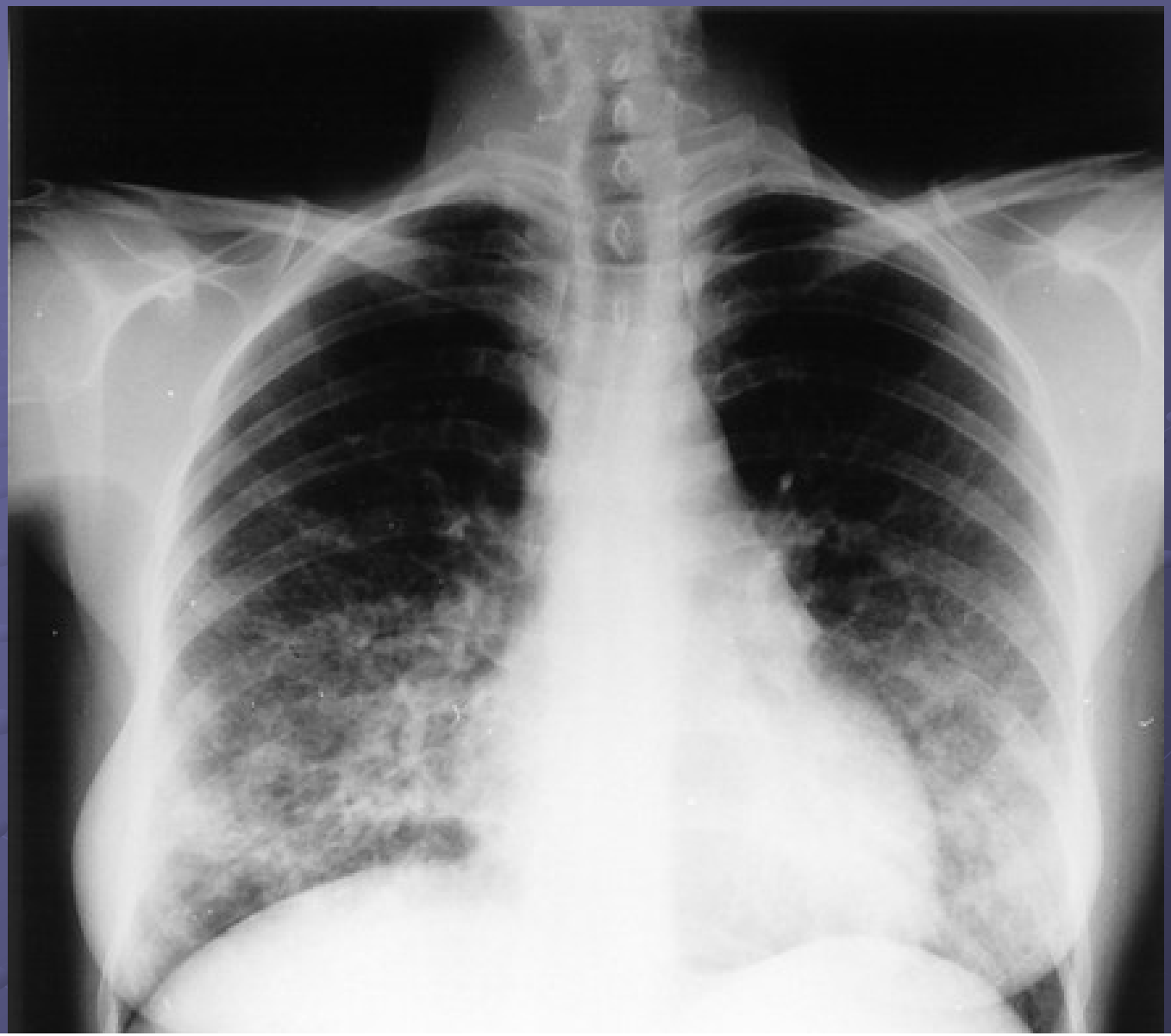
Idiopathic Nonspecific Interstitial Pneumonia

Report of an American Thoracic Society Project

William D. Travis[1*], Gary Hunninghake[2*], Talmadge E. King, Jr.[3*], David A. Lynch[4*], Thomas V. Colby[5*], Jeffrey R. Galvin[6*], Kevin K. Brown[7], Man Pyo Chung[8], Jean-François Cordier[9], Roland M. du Bois[10], Kevin R. Flaherty[11], Teri J. Franks[12], David M. Hansell[13], Thomas E. Hartman[14], Ella A. Kazerooni[15], Dong Soon Kim[16], Masanori Kitaichi[17], Takashi Koyama[18], Fernando J. Martinez[11], Sonoko Nagai[19], David E. Midthun[20], Nestor L. Müller[21], Andrew G. Nicholson[22], Ganesh Raghu[23], Moisés Selman[24], and Athol Wells[10]

Am J Respir Crit Care Med Vol 177. pp 1338–1347, 2008

Idiopathic NSIP is a distinct clinical entity



Infiltrative bilateral opacities in all cases

V.Cottin. Am J Respir Crit Care Med 1998; 158:1286-1293

TABLE 3. CLINICAL FEATURES AT DIAGNOSIS OF 67 PATIENTS WITH IDIOPATHIC NONSPECIFIC INTERSTITIAL PNEUMONIA

Feature	Number (%)*
Age, yr	
Mean	52
Range	26–73
Sex	
Female	45 (67)
Male	22 (33)
Contributing institution	
Asian	31 (46)
Non-Asian	36 (54)
Symptoms	
Dyspnea (n = 67)	64 (96)
Duration dyspnea	
Median	7 mo
Range	1–120 mo
Cough (n = 67)	58 (87)
Duration cough	
Median	6 mo
Range	1–147 mo
Weight loss (n = 64)†	16 (25)
Fever (n = 64)†	14 (22)
Arthralgias (n = 64)†	9 (14)
Clubbing (N = 62)†	5 (8)
Raynauds (n = 63)†	5 (8)
Myalgias (n = 58)†	4 (7)
Skin rash (n = 64)†	3 (5)
Arthritis (n = 64)†	2 (3)

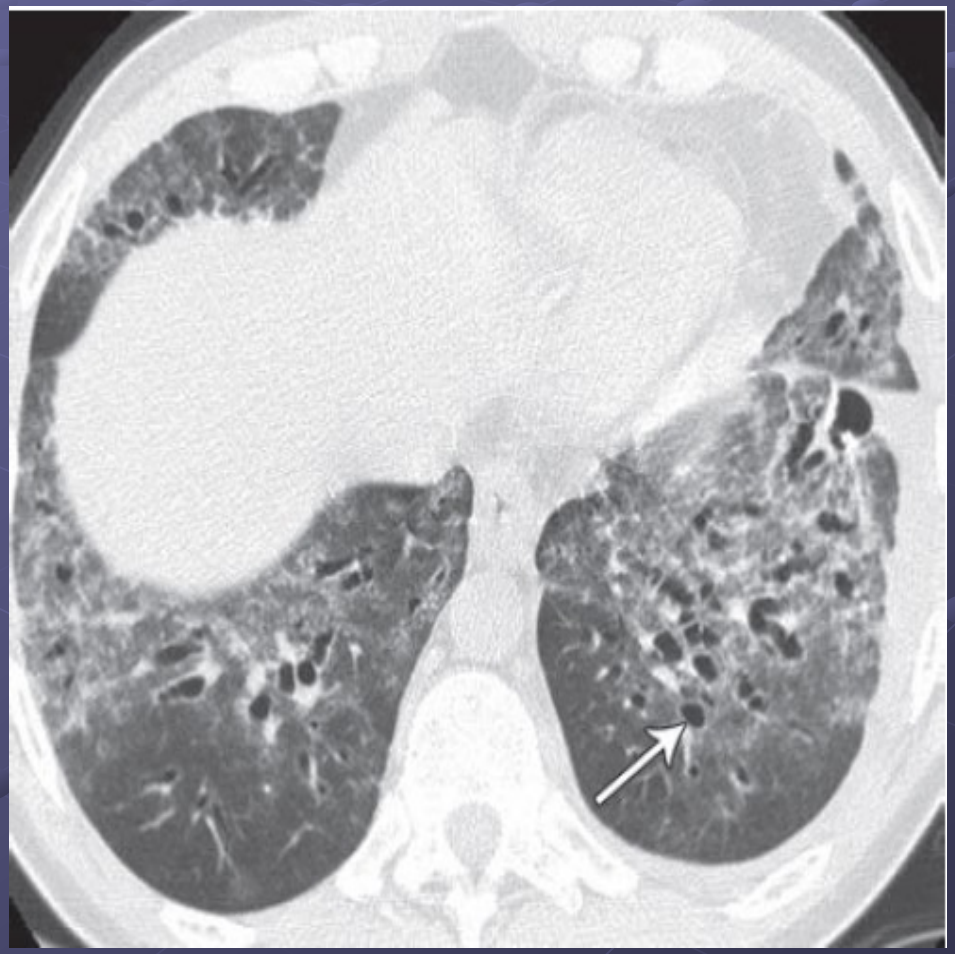
Serology	
Antinuclear antibody (n = 44)†	19 (43)
Rheumatoid factor (n = 44)†	10 (23)
Jo-1 (n = 14)†	0 (0)
Pulmonary function testing (n = 58)†	
Restrictive	46 (79)
Obstructive	2 (3)
Mixed	2 (3)
Normal	8 (14)
Smoking (n = 65)†	
Never	45 (69)
Former	16 (25)
Persistent	4 (6)
Pack-years (n = 19)†	
Mean	26
Range	1–96
Survival (n = 66)†	
5-yr	82.3%
10-yr	73.2%

Crackles and inspiratory squeaks in the majority of cases

RadioGraphics 2009; 29:73–87

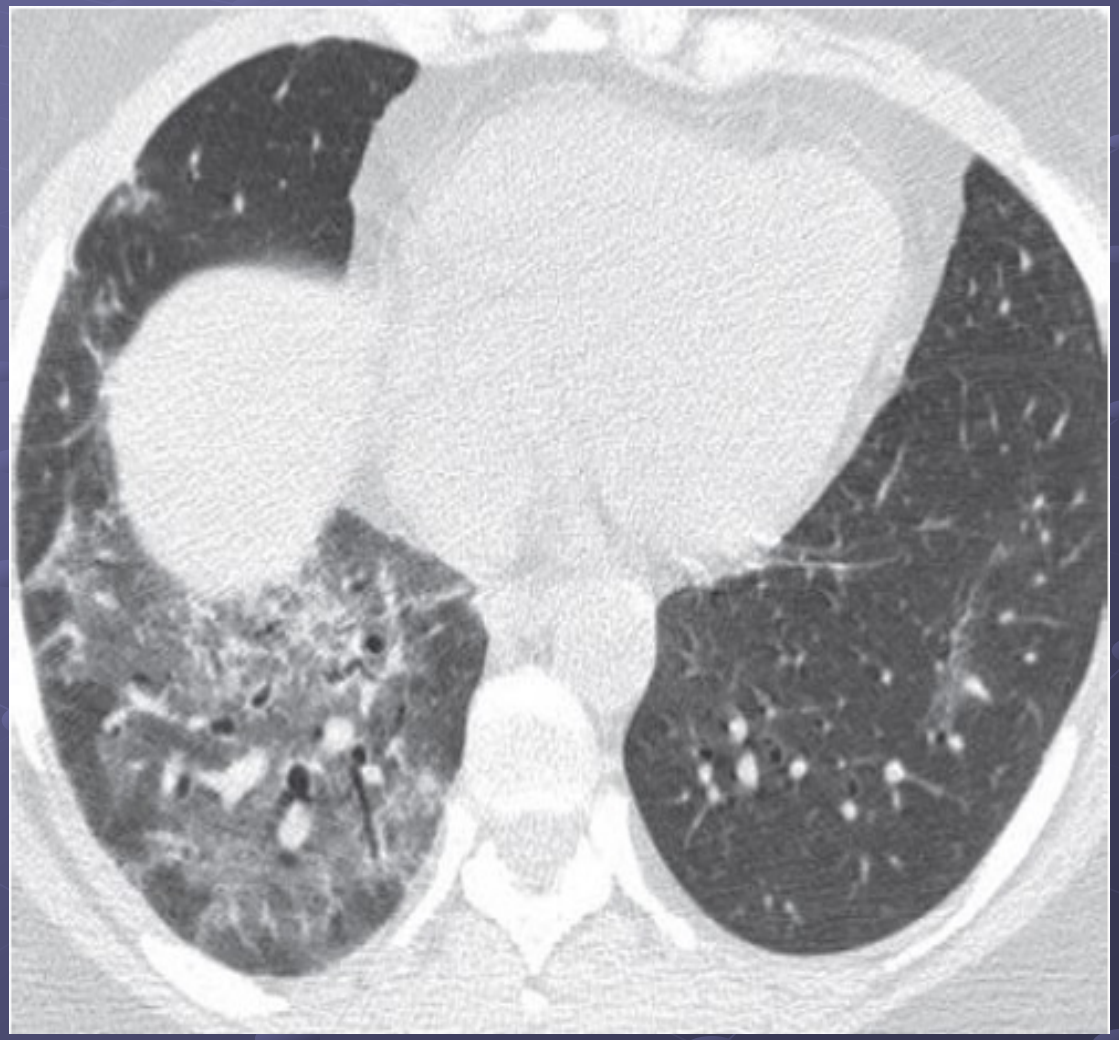
Radiologic Findings Suggesting the Diagnosis of NSIP

Symmetric Lower Lobe Distribution

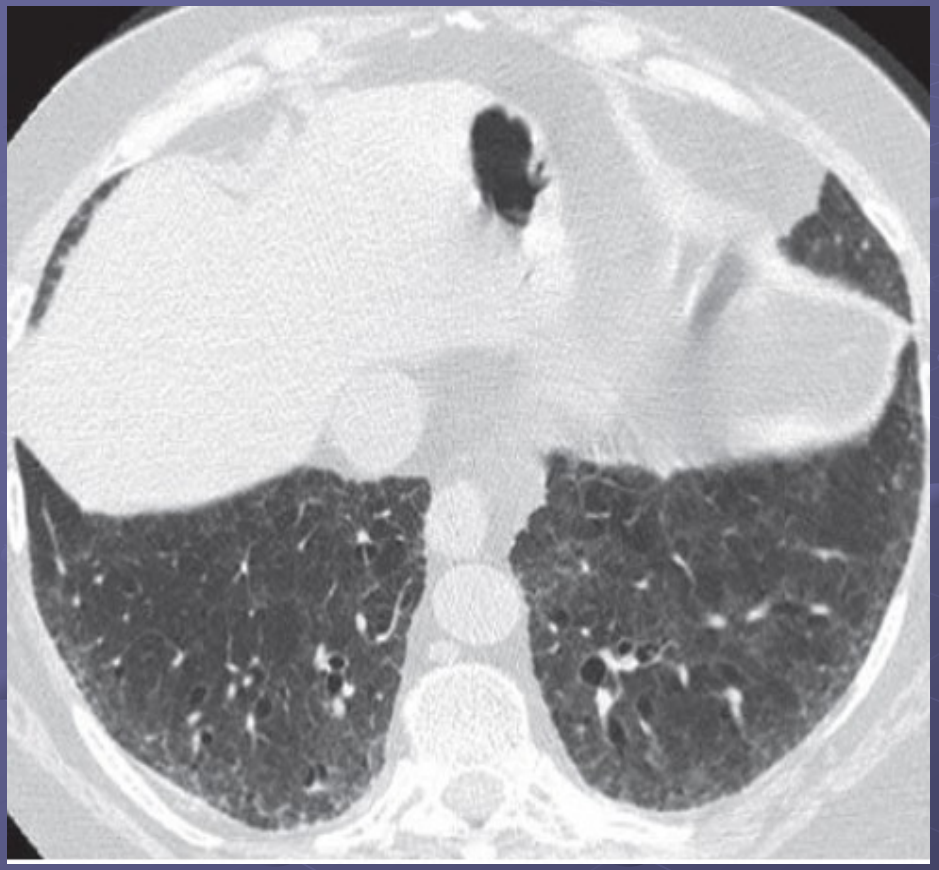


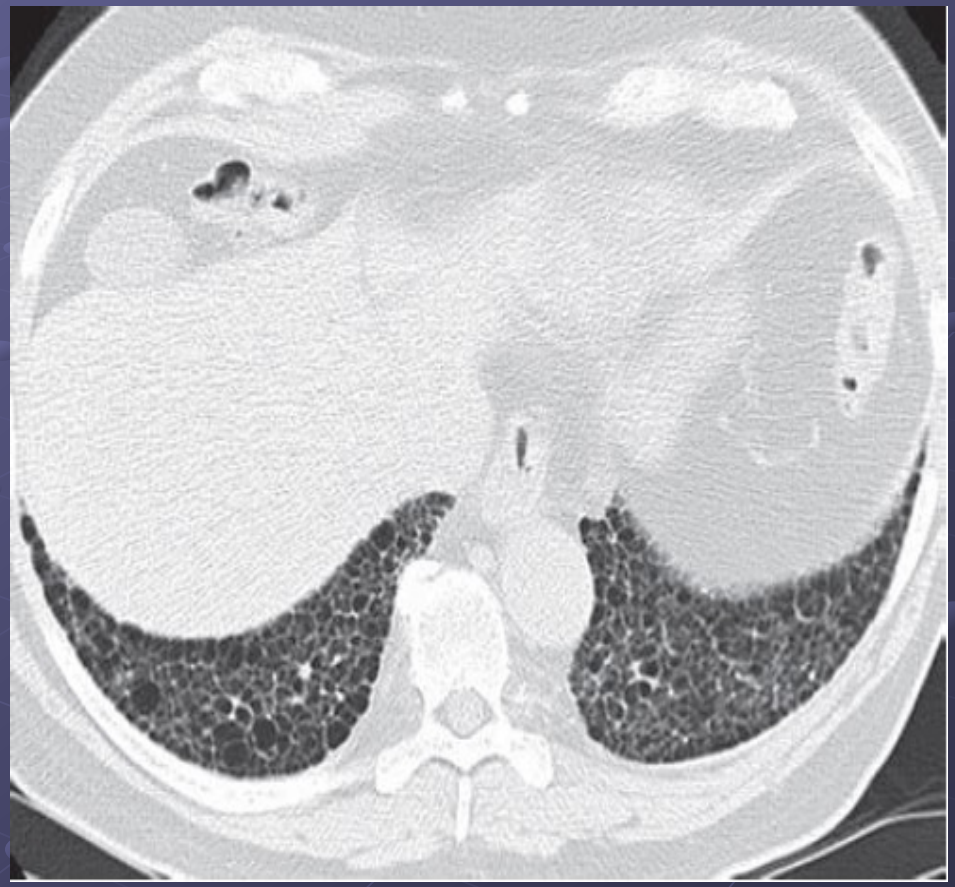
Ground-Glass Abnormality

Ground-glass opacity is the salient CT feature of NSIP and is found in nearly all cases. Areas



Reticular Abnormality

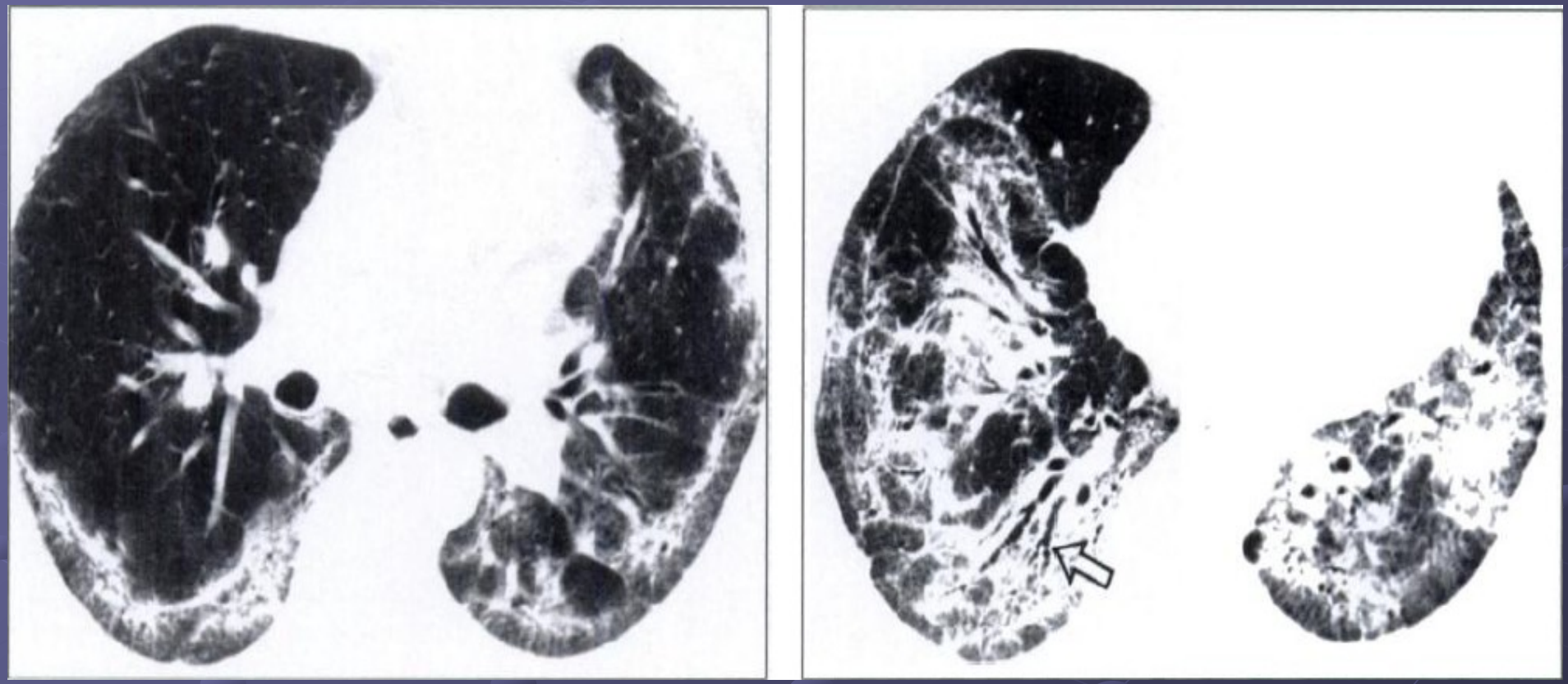




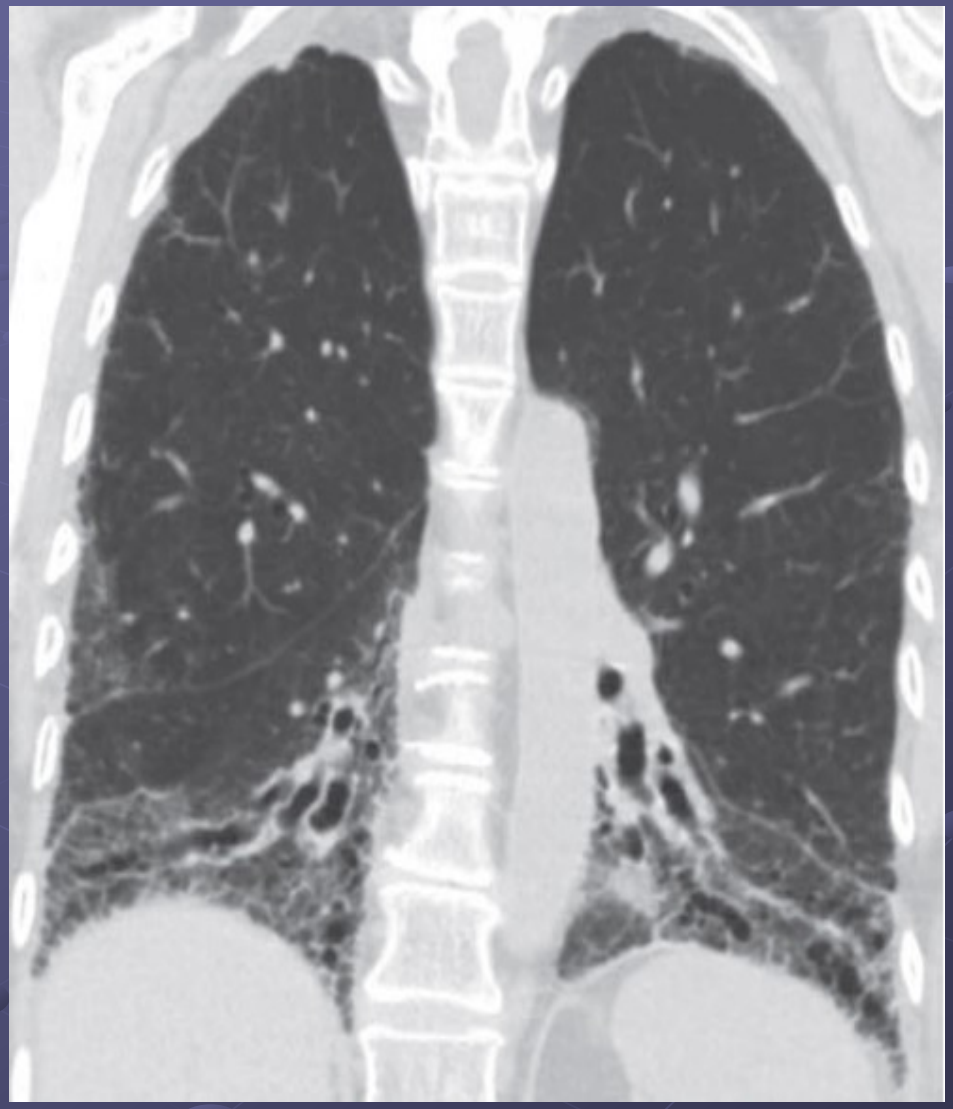
Fibrotic NSIP vs UIP

Reticular abnormality can be seen in many other diseases including UIP, hypersensitivity pneumonitis and sarcoidosis

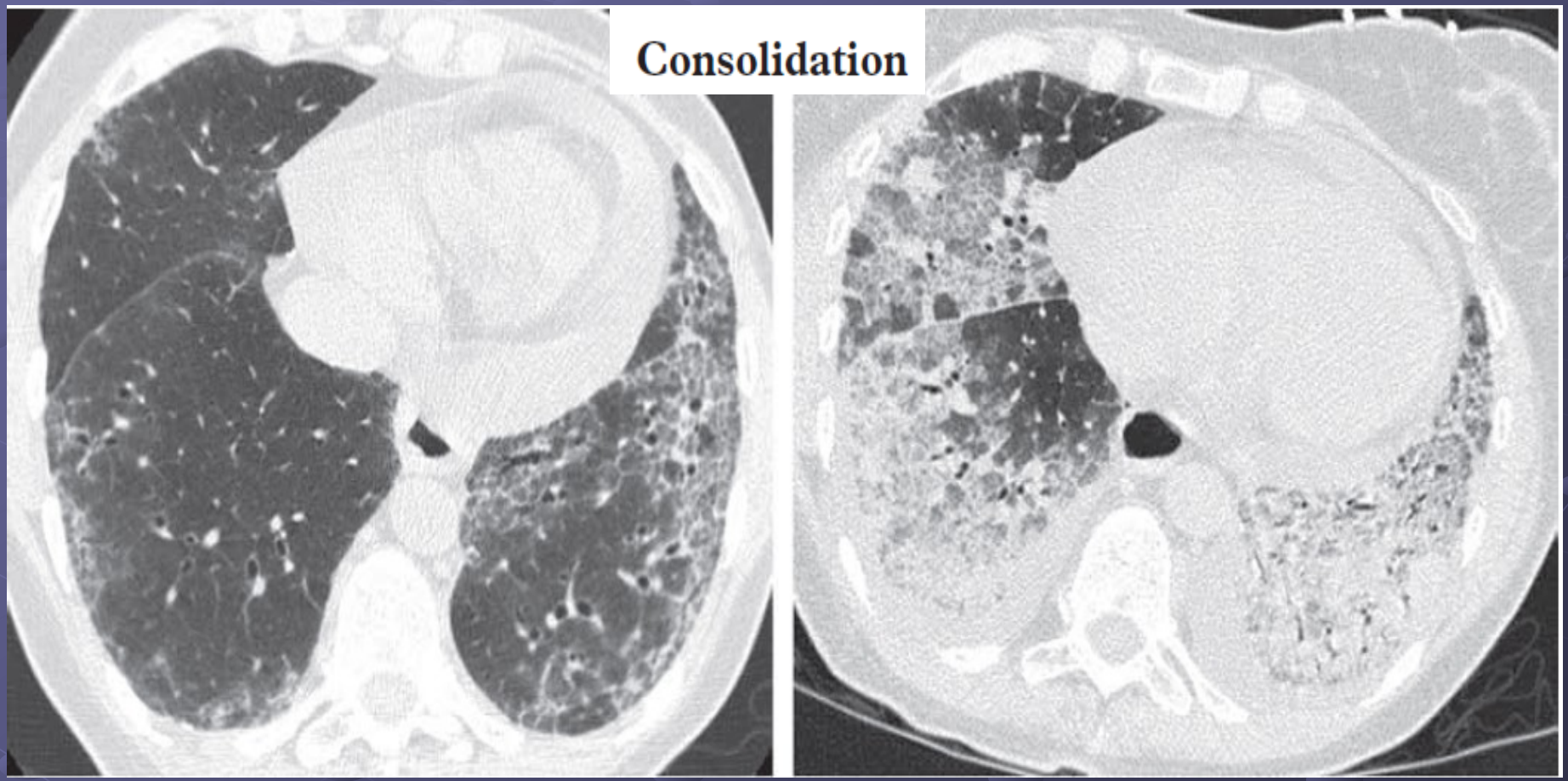
Traction Bronchiectasis



Lower Lobe Volume Loss

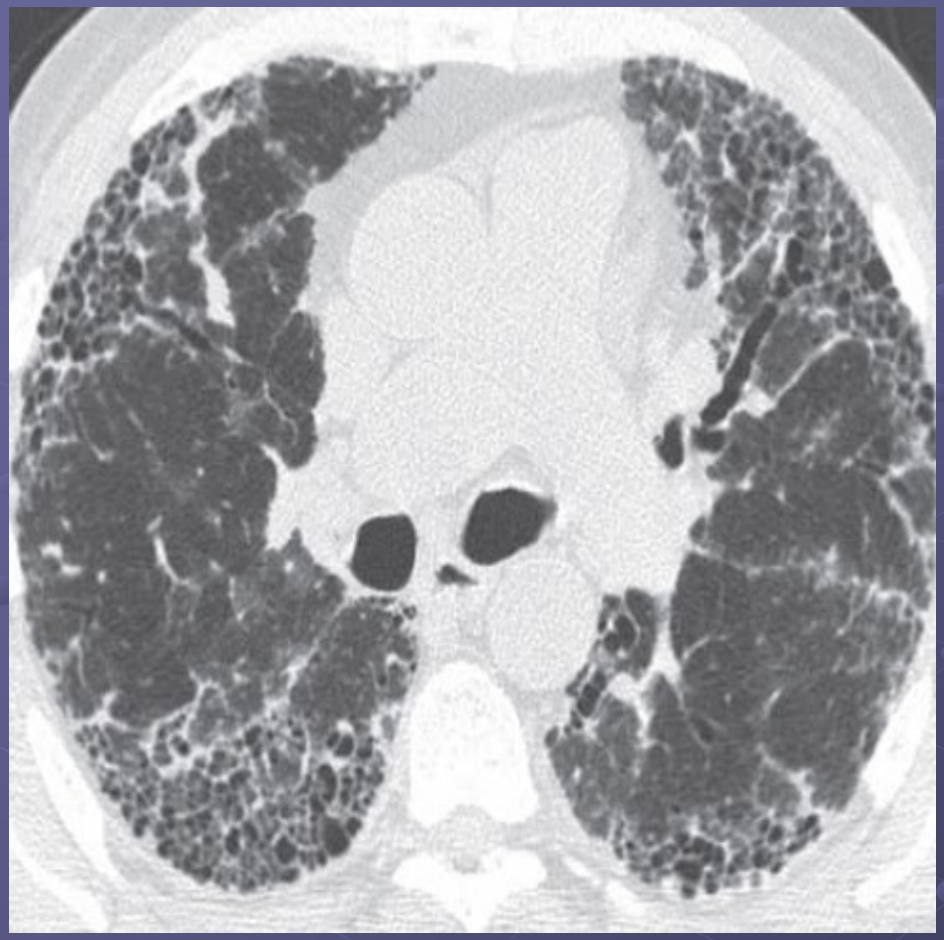


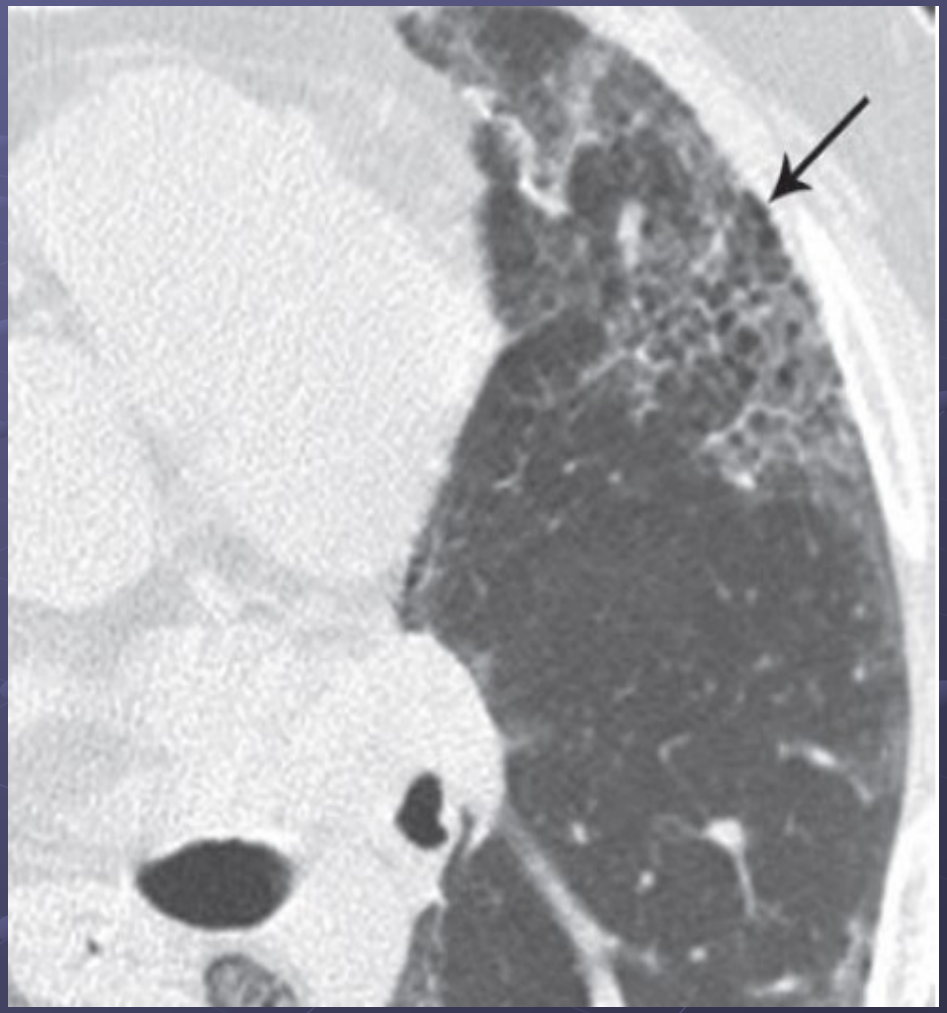
Radiologic Findings That May Be Associated with NSIP



If consolidation is present think of another diagnosis (OP, eosinophilic pneumonia, DAD) or of acute exacerbation

Honeycombing





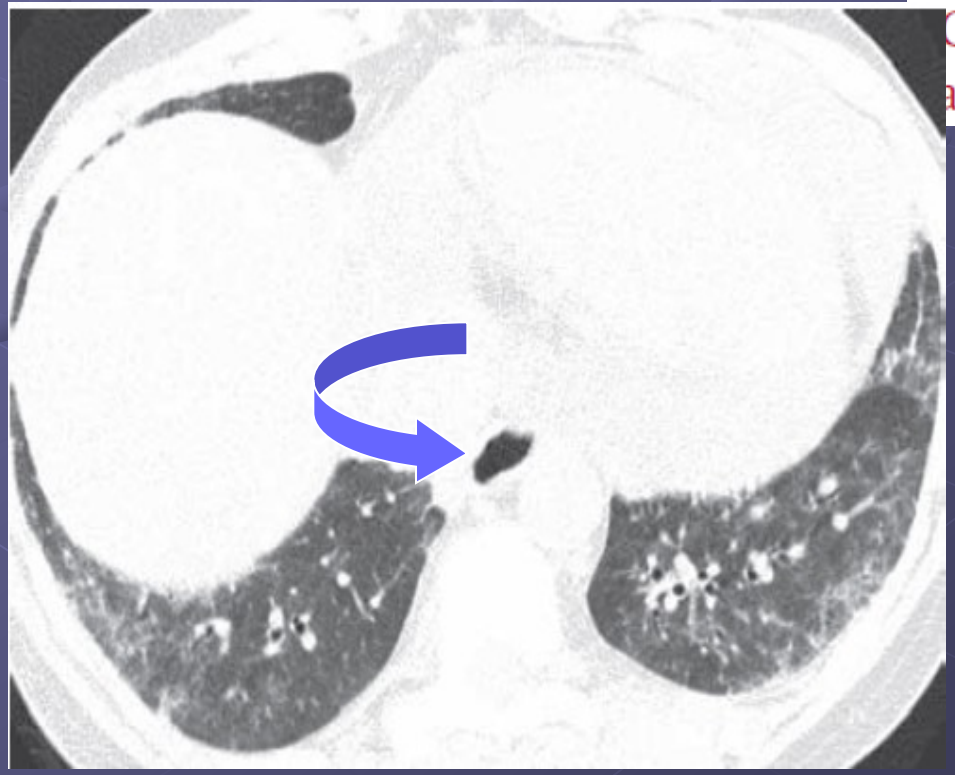
UIP versus fibrotic NSIP

Radiologic Findings That Should Suggest an Alternate Diagnosis

- Nodules
- Low Attenuation
- Cystic Change

Associated Findings Suggesting Underlying Collagen Vascular Diseases

Although many cases of NSIP are idiopathic, NSIP is commonly associated with underlying collagen vascular diseases. Various collagen vascular diseases can be associated with NSIP, including scleroderma, polymyositis or dermatomyositis, Sjögren syndrome, and rheumatoid arthritis. Given this association, it is important to look for additional abnormalities that may aid in diagnosis.



1. Esophageal abnormalities
2. Pleural, pericardial effusion or thickening
3. Bone and joint disease

TABLE 5. IDIOPATHIC NONSPECIFIC INTERSTITIAL PNEUMONIA: HIGH-RESOLUTION COMPUTED TOMOGRAPHY FEATURES IN 61 CASES

Radiologic Feature	Number (*n* = 61)	Percent	95% CI
Craniocaudal Distribution			
Lower	56	92	82–96
Diffuse	5	8	4–18
Upper	0	0	0–6
CT axial distribution			
Diffuse	29	47	36–60
Peripheral	28	46	34–58
Central	4	7	3–16
Reticulation	53	87	76–93
Traction bronchiectasis	50	82	71–90
Lobar volume loss	47	77	65–86
Ground-glass attenuation	27	44	33–57
Subpleural sparing	13	21	13–33
Emphysema/cysts	7	12	6–22
Consolidation	8	13	7–24
Peribronchial thickening	4	7	3–16
Substantial micronodules	2	3	1–11
Honeycombing	3	5	2–13

Eur Respir J 2003; 22: 239–244
DOI: 10.1183/09031936.03.00105202

European Respiratory Journal
ISSN 0903-1936

BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia

S. Veeraraghavan*, P.I. Latsi*, A.U. Wells*, P. Pantelidis*, A.G. Nicholson#, T.V. Colby¶, P.L. Haslam+, E.A. Renzoni*, R.M. du Bois*

Table 2. – Bronchoalveolar lavage (BAL) fluid total cells·mL^{-1} and differential counts in patients with fibrotic nonspecific interstitial pneumonia (NSIP) compared with usual interstitial pneumonia (UIP)

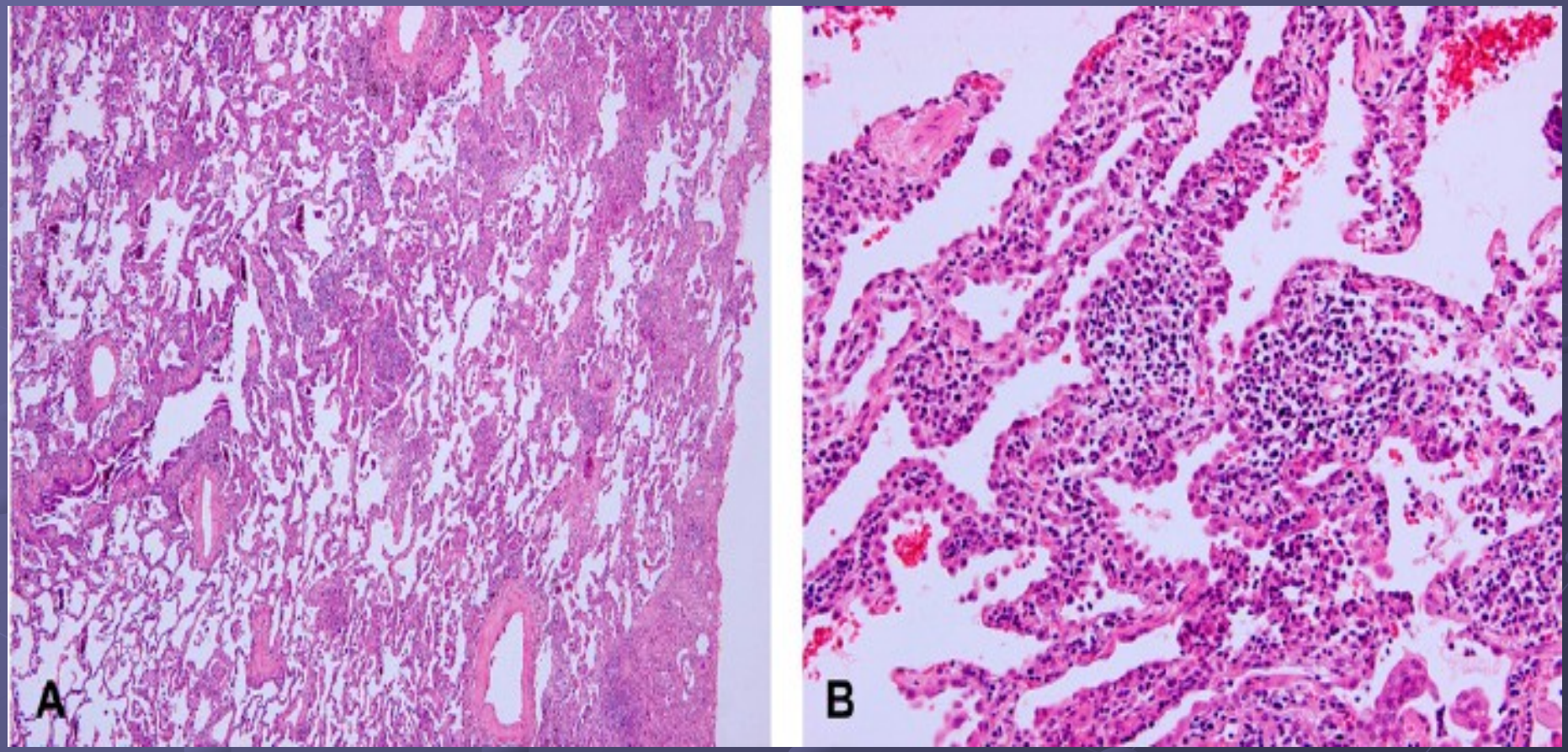
	Fibrotic NSIP	UIP	p-value
Total subjects n	19	35	
Subjects with normal BAL	1	1	NS
Macrophages %	71 (25–92)	73 (24–89)	NS
Neutrophils %	9 (2–57)	9 (1–58)	NS
Lymphocytes %	5 (0–18)	4 (0–42)	NS
Eosinophils %	7 (1–28)	7 (0–32)	NS
Total cells# $\times 10^5$ mL^{-1}	2.02 (0.40–11.43)	2.4 (0.4–11.6)	NS

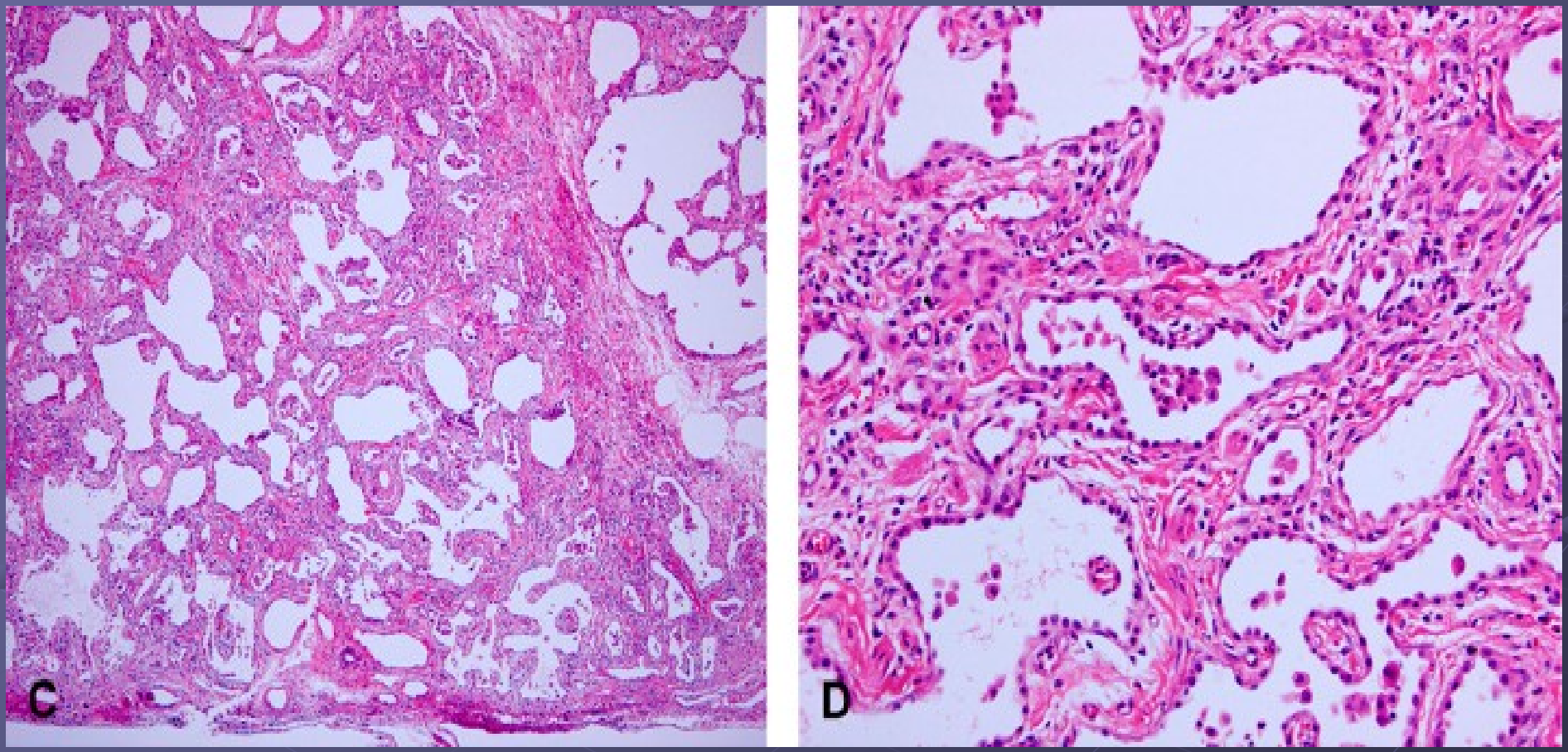
Ιδιοπαθής NSIP: τεκμηρίωση της διάγνωσης

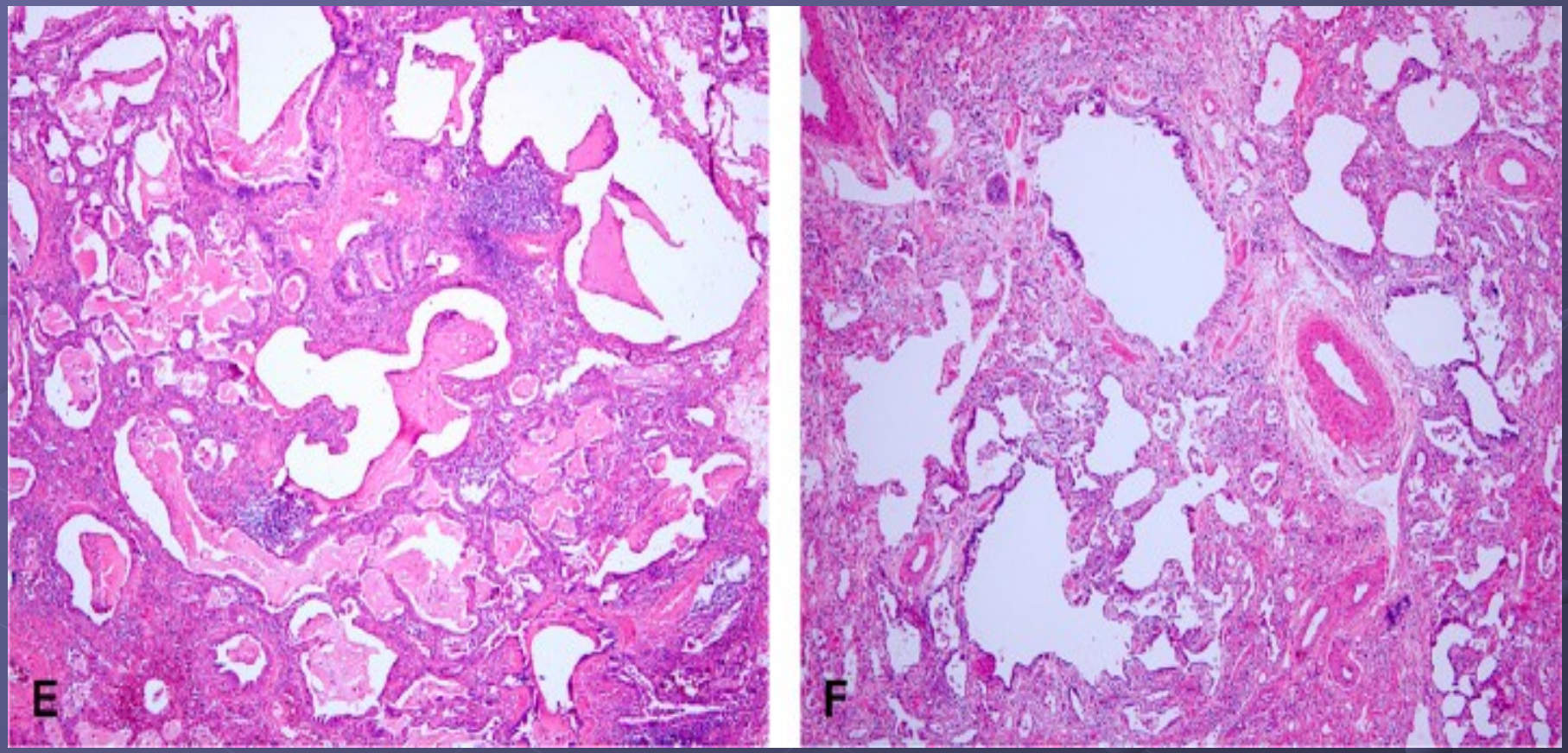
- **Απαραίτητη η ιστολογική τεκμηρίωση με βιοψία πνεύμονα (θωρακοσκοπική ή ανοικτή)**

- **Συνδυασμός πάντοτε των αποτελεσμάτων με τα κλινικά και ακτινολογικά δεδομένα**

Nicholson AG. Classification of idiopathic interstitial pneumonias: making sense of the alphabet soup. Histopathology 2002; 41:381-91


A
B


C
D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F

TABLE 6. PROPOSED REVISED HISTOLOGIC FEATURES OF NONSPECIFIC INTERSTITIAL PNEUMONIA

Key Features

Cellular Pattern*

Mild to moderate interstitial chronic inflammation

Type II pneumocyte hyperplasia in areas of inflammation

Fibrosing Pattern*

Dense or loose interstitial fibrosis *with uniform appearance.*

Lung architecture is frequently preserved

Interstitial chronic inflammation—mild or moderate

Pertinent Negative Findings

Cellular Pattern

Dense interstitial fibrosis: absent

Organizing pneumonia is not the prominent feature *(<20% of biopsy specimen)*

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

Honeycombing inconspicuous or absent

(*Enlarged fibrotic airspaces may be present*)

Both Patterns

Acute lung injury pattern, especially hyaline membranes: absent

Eosinophils: inconspicuous or absent

Granulomas: *absent*

Lack of viral inclusions and organisms on special stains for organisms

Dominant airway disease such as extensive peribronchiolar metaplasia

TABLE 4. IDIOPATHIC NONSPECIFIC INTERSTITIAL PNEUMONIA: PATHOLOGIC FEATURES OF 67 CASES

Pathologic Feature	Number	Percentage	95 CI
NSIP pattern			
Cellular	11	16	9–27
Fibrosing	56	84	73–91
Bronchiolocentric (as a minor finding)	9	13	7–24
Lymphoid follicles	38	57	45–68
Interstitial fibrosis with enlarged airspaces*			
Absent	9	13	7–24
<10%	23	34	24–46
10–50	24	36	25–48
>50%	11	17	9–27
Interstitial cellular inflammation			
Mild	31	46	35–58
Moderate	36	54	42–65
Organizing pneumonia			
Absent	32	48	36–60
0–9%	33	49	38–61
10–19%	2	3	1–10
Smooth muscle hyperplasia	22	36	23–45
Fibroblastic foci	14	21	13–32
Bronchiolar metaplasia	13	19	12–30
Pleural fibrosis	37	55	43–67
Vascular medial thickening	43	64	52–75
Emphysema	4	6	2–14

The relative frequency of fibrosis in NSIP is variable. Patients with fibrotic NSIP outnumber patients with cellular NSIP by a ratio of nearly 4:1 in published

INTERSTITIAL LUNG DISEASE

Radiological versus histological diagnosis in UIP and NSIP: survival implications

K R Flaherty, E L Thwaite, E A Kazerooni, B H Gross, G B Toews, T V Colby, W D Travis, J A Mumford, S Murray, A Flint, J P Lynch III, F J Martinez

Thorax 2003;58:143–148

Table 4 Median survival by diagnostic category

Diagnostic category	Median (95% CI) survival (years)	No (%) of patients	Deaths (n)
Histological diagnoses			
Histological UIP	3.98 (2.71 to 5.81)	73 (76)	34
Histological NSIP	>9 years (NA)	23 (24)	2
HRCT diagnoses			
HRCT definite/probable UIP	2.08 (1.30 to 3.98)	27 (28)	17
HRCT indeterminate	5.76 (4.03 to NA)	25 (26)	9
HRCT definite/probable NSIP	5.81 (5.81 to NA)	44 (46)	10
Histological pattern and HRCT diagnoses			
Histological UIP and HRCT definite/probable UIP	2.08 (1.30 to 3.98)	27 (28)	17
Histological UIP and HRCT indeterminate or definite/probable NSIP	5.76 (4.03 to NA)	46 (48)	17
Histological NSIP and HRCT definite/probable NSIP	>9 years (NA)	18 (19)	2
Histological NSIP and HRCT indeterminate	>6.6 years (NA)	5 (5)	0

UIP=usual interstitial pneumonia; NSIP=non-specific interstitial pneumonia; HRCT=high resolution computed tomography; NA=not available.

TABLE 8. CLINICAL CONDITIONS ASSOCIATED WITH NONSPECIFIC INTERSTITIAL PNEUMONIA HISTOLOGIC PATTERN*

No detectable cause (idiopathic NSIP)
Collagen vascular disease
Hypersensitivity pneumonitis
Drug-induced pneumonitis
Infection
Immunodeficiency including HIV infection

REVIEW SERIES

Challenges in pulmonary fibrosis · 5: The NSIP/UIP debate

Roland du Bois, Talmadge E King Jr

Thorax 2007;**62**:1008–1012. doi: 10.1136/thx.2004.031039

Table 3 Histopathological subsets in connective tissue disease

Pathological feature	Total (n = 177)	Systemic sderosis* (n = 102)	Rheumatoid arthritis† (n = 40)	Polymyositis-dermatomyositis‡ (n = 51)
NSIP	146 (82%)	83	23	46
UIP	31 (18%)	19	17	5

A Histologic Pattern of Nonspecific Interstitial Pneumonia Is Associated with a Better Prognosis Than Usual Interstitial Pneumonia in Patients with Cryptogenic Fibrosing Alveolitis

ZOE D. DANIIL, FRANCES C. GILCHRIST, ANDREW G. NICHOLSON, DAVID M. HANSELL, JESSICA HARRIS, THOMAS V. COLBY, and ROLAND M. du BOIS

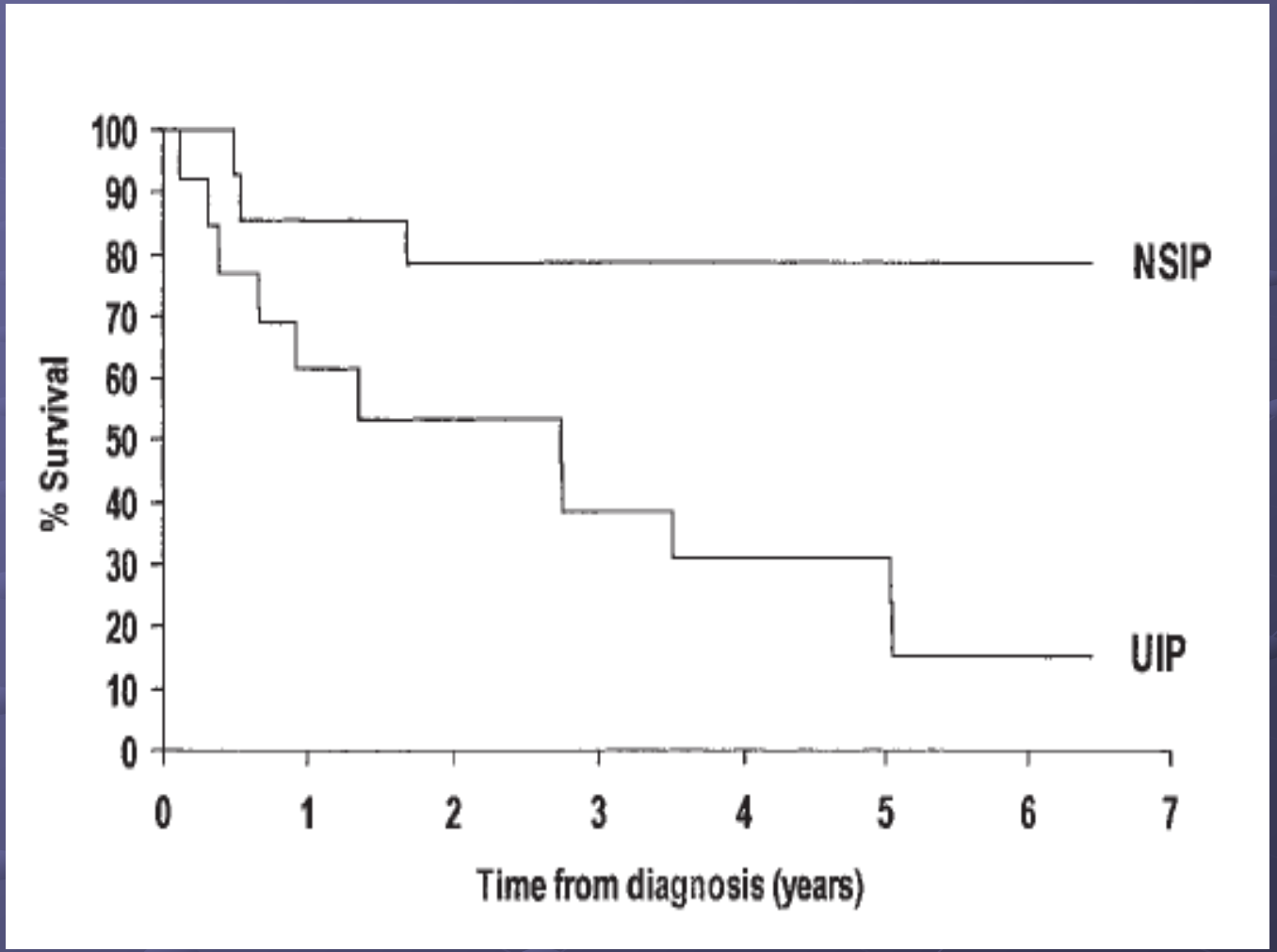
Interstitial Lung Disease Unit and Departments of Histopathology and Radiology, Royal Brompton Hospital, London, United Kingdom; and Department of Pathology, Mayo Clinic, Scottsdale, Arizona

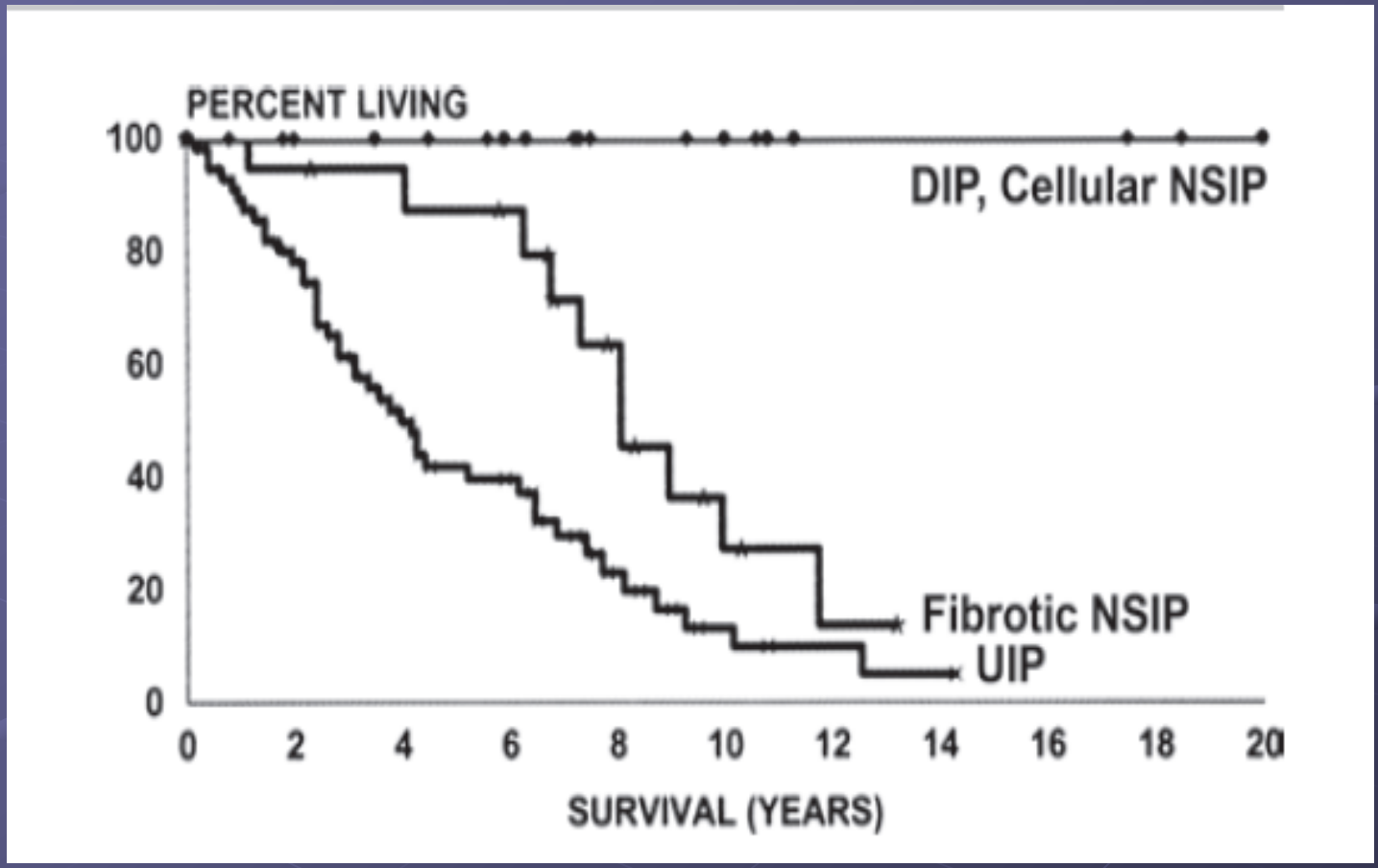
AM J RESPIR CRIT CARE MED 1999;160:899–905.

TABLE 5

CHANGES IN LUNG FUNCTION BETWEEN PRESENTATION AND FINAL LUNG FUNCTION MEASUREMENT IN NSIP AND UIP PATIENTS

	NSIP ($n = 11$)	UIP ($n = 11$)	p Value
Time from biopsy to final lung function assessment			
Median, mo	14	23.5	1.00
Range, mo	3–72.5	1.5–59	
FVC change, mean ± SEM			
ml	78 ± 140	−329 ± 140	0.03
Percentage	7.0 ± 7.1%	−11.8 ± 4.0%	
D_{LCO} change, mean ± SEM			
mmol/min/kPa	0.19 ± 0.35	−0.87 ± 0.31	0.05
Percentage	5.5 ± 9.8%	−19.9 ± 6.4%	
Dead	4 (29%)	13 (93%)	< 0.001
Alive	10 (71%)	1 (7%)	
Total	14	14	


100
90
80
70
60
50
40
30
20
10
0
% Survival
0
1
2
3
4
5
6
7
Time from diagnosis (years)
NSIP
UIP



Klingerman SJ, et al. Radiographics 2009; 29:73-87

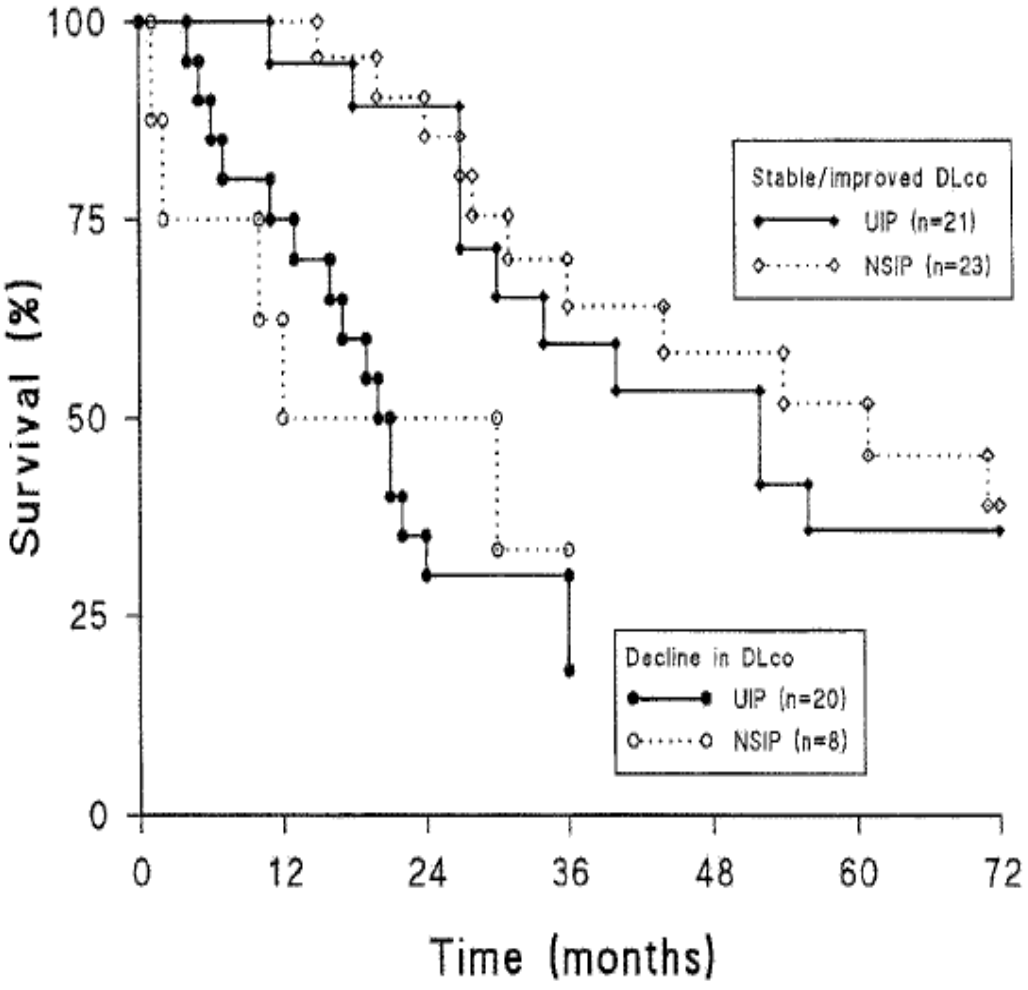
Fibrotic Idiopathic Interstitial Pneumonia

The Prognostic Value of Longitudinal Functional Trends

Panagiota I. Latsi, Roland M. du Bois, Andrew G. Nicholson, Thomas V. Colby, Danai Bisirtzoglou, Ageliki Nikolakopoulou, Srihari Veeraraghavan, David M. Hansell, and Athol U. Wells

Interstitial Lung Disease Unit, Department of Radiology and Department of Pathology, Royal Brompton Hospital, London, United Kingdom; and Department of Pathology, Mayo Clinic, Scottsdale, Arizona

Am J Respir Crit Care Med Vol 168. pp 531–537, 2003



Idiopathic Nonspecific Interstitial Pneumonia

Lung Manifestation of Undifferentiated Connective Tissue Disease?

Brent W. Kinder[1], Harold R. Collard[1], Laura Koth[1], David I. Daikh[1], Paul J. Wolters[1], Brett Elicker[2], Kirk D. Jones[3], and Talmadge E. King, Jr.[1]

Departments of [1]Medicine, [2]Radiology, and [3]Pathology, University of California School of Medicine, San Francisco, California

Am J Respir Crit Care Med Vol 176. pp 691–697, 2007

TABLE 1. DIAGNOSTIC CRITERIA FOR PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE*

Diagnostic Criteria	Presence of
Symptoms associated with connective tissue disease	At least one of the following symptoms: 1. Raynaud's phenomenon 2. Arthralgias/multiple joint swelling 3. Photosensitivity 4. Unintentional weight loss 5. Morning stiffness 6. Dry mouth or dry eyes (sicca features) 7. Dysphagia 8. Recurrent unexplained fever 9. Gastroesophageal reflux 10. Skin changes (rash) 11. Oral ulceration 12. Nonandrogenic alopecia 13. Proximal muscle weakness
Evidence of systemic inflammation in the absence of infection	Positive findings for at least one of the following: 1. Antinuclear antigen 2. Rheumatoid factor 3. Anti–SCL 70 antibody 4. SS-A or SS-B 5. Jo-1 antibody, 6. Sedimentation rate (> two times normal), C-reactive protein

+Absence of criteria for another CTD

TABLE 5. HISTOPATHOLOGIC FINDINGS IN PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE COMPARED WITH PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA

Histopathologic Pattern	All Patients n = 40 (%)	UCTD* n = 18 (%)	Other IIP† n = 22 (%)	OR (95% CI)	p Value‡
Nonspecific interstitial pneumonia pattern	17 (42.5)	15 (83)	2 (9)	50 (6–566)	< 0.0001
Usual interstitial pneumonia	20 (50)	1 (6)	19 (86)	0.009 (0.0002–0.114)	< 0.0001
Organizing pneumonia	1 (2.5)	1 (6)	0 (0)	NS	0.450
Desquamative interstitial pneumonia	1 (2.5)	0 (0)	1 (5)	NS	1
Nonclassifiable fibrosis	1 (2.5)	1 (6)	0 (0)	NS	1

In summary, we have demonstrated that most patients previously classified as having idiopathic NSIP have clinical, serologic, radiographic, and pathologic characteristics that are suggestive of autoimmune disease and meet criteria for UCTD.

Thorax ONLINE

Interstitial lung disease guideline

A U Wells, N Hirani and on behalf of the BTS Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society

Thorax 2008;63;v1-v58
doi:10.1136/thx.2008.101691

14.4 Treatment of NSIP

In the complete absence of data, the Committee argues in favour of basing therapeutic approaches on the clinicoradiological profiles of disease. Patients should be categorised as most closely resembling IPF, COP or HP and the treatment stratagem selected accordingly.

1. Management in patients with the clinical features of IPF and a distribution of disease on HRCT is broadly similar to that of IPF but is grounded in a far poorer evidence base than for those with IPF. This group of patients has a better overall prognosis than those with biopsy-proven UIP, but a higher mortality than other NSIP patient subsets. Treatment, as with IPF, is based on the hope of slowing or preventing disease progression in most cases rather than achieving regression of disease. The options for treatment are summarised in table 5. Prolonged high doses of corticosteroids should be avoided unless there is clear evidence of a response. Of the other options, as for IPF, none can be strongly recommended.

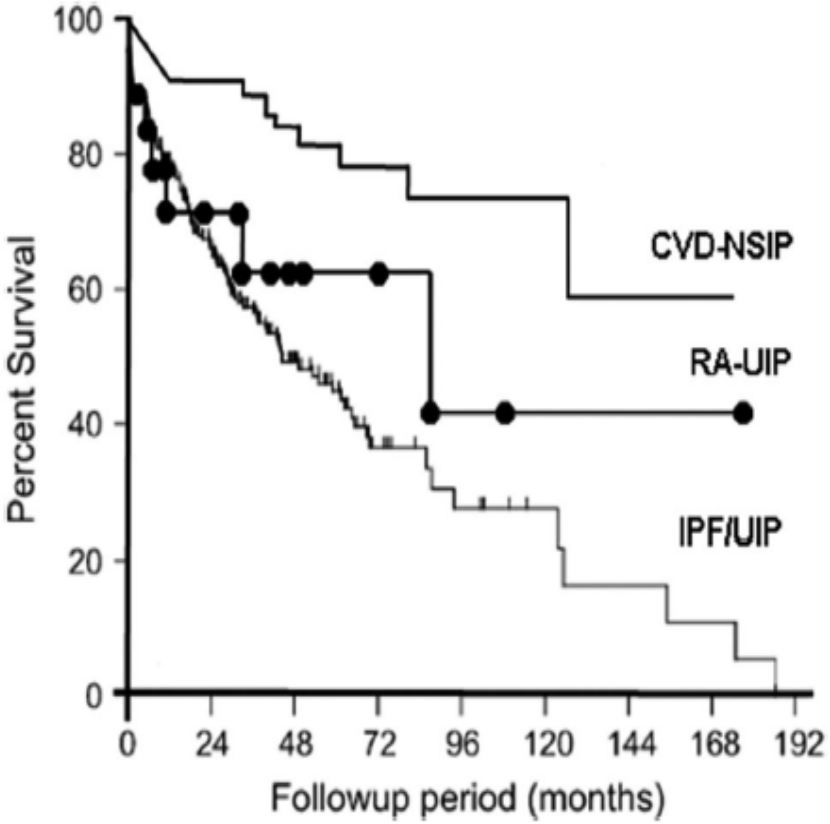
CHEST Commentary

Rheumatoid Arthritis-Associated Interstitial Lung Disease

The Relevance of Histopathologic and Radiographic Pattern

Eunice J. Kim, MD; Harold R. Collard, MD, FCCP; and Talmadge E. King Jr, MD, FCCP

(CHEST 2009; 136:1397–1405)



- Patients with RA-ILD and NSIP pattern should be treated aggressively with pharmacologic therapy.
- Patients with RA-ILD and UIP pattern should be counseled as to their worse prognosis and referred for lung transplantation evaluation if considered a reasonable candidate. The role of pharmacologic therapy in this setting is unknown and should be the focus of future study.

Are existing data sufficient to make such recommendations?

. Given the clinical impact of RA-ILD, and the absence of definitive data on its treatment, prospective, controlled studies are necessary to guide the field.

Brown KK, PATS 2007

Therapeutic options for systemic sclerosis related interstitial lung diseases

Luc Mouthon [a,*], Alice Bérezné [a], Loïc Guillevin [a], Dominique Valeyre [b]

It is important to mention that symptomatic treatments such as oxygenotherapy, rehabilitation and treatment of gastro–oesophagal reflux are very important in the management of SSc-ILD.

Thus, the current approach is to evaluate lung involvement in the early years of disease, in order to assess the patient's risk of progressive pulmonary fibrosis. We could

Patients with significant worsening of PFTs the last 6 to 12 months → CYC

Mycophenolate mofetil

Lung Transplantation

Respir Med 2010; 104 Suppl 1: S59-69

Conclusions

The importance of differentiating NSIP from IPF lies in the management of the individual patient

- Limited treatment options for both diseases
- Management beyond medication prescription:

→look for autoimmune rheumatic disease

→look for drug or organic dust exposure

→ discuss outcome

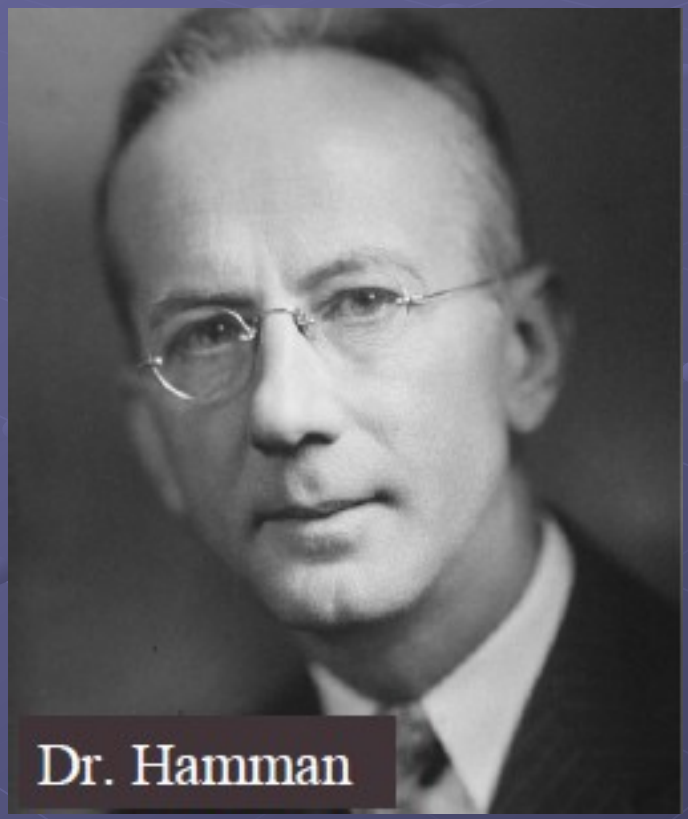
→monitor pace of change of severity of disease

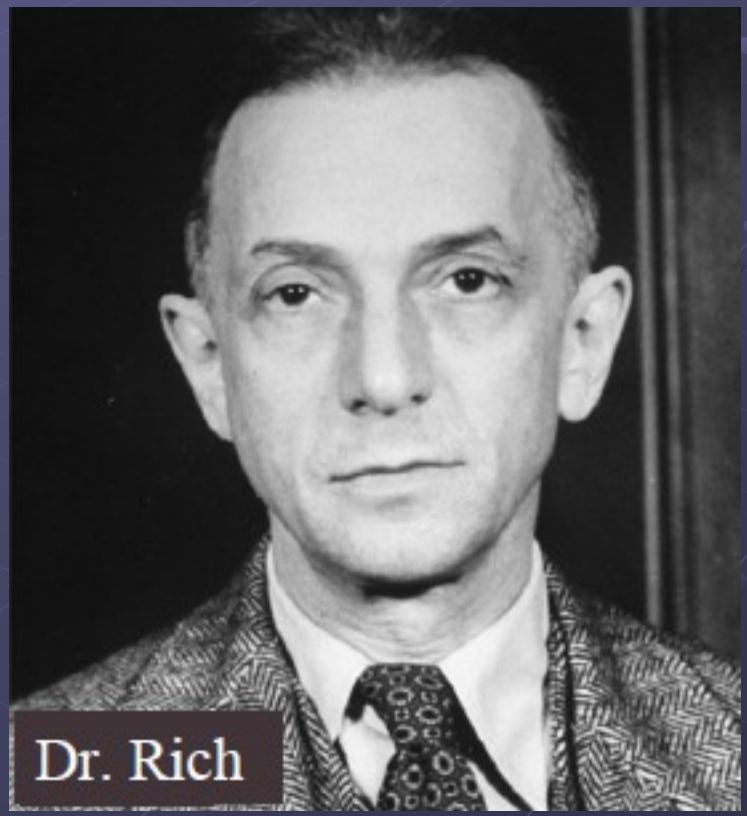
New guidelines…

new data and probably new hope…

FULMINATING DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS.

By LOUIS HAMMAN, M.D., and ARNOLD R. RICH, M.D.,
BALTIMORE, MD.





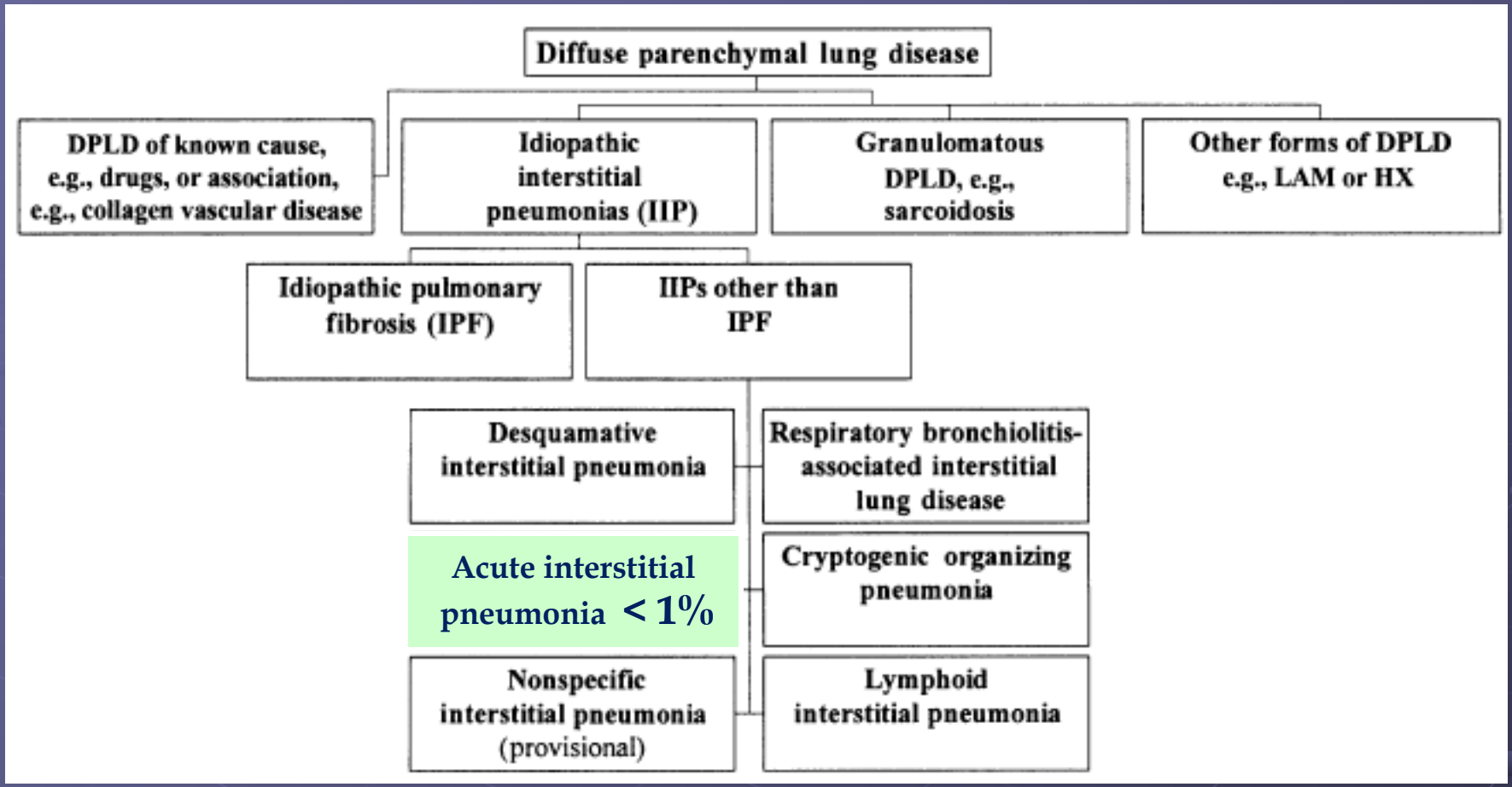
Trans Am Clin Climatol Assoc. **1935; 51: 154–163.**

The American Journal of Surgical Pathology *10(4): 256–267, 1986*

Acute Interstitial Pneumonia

A Clinicopathologic, Ultrastructural, and Cell Kinetic Study

Anna-Luise A. Katzenstein, M.D., Jeffrey L. Myers, M.D., and Michael T. Mazur, M.D.



American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

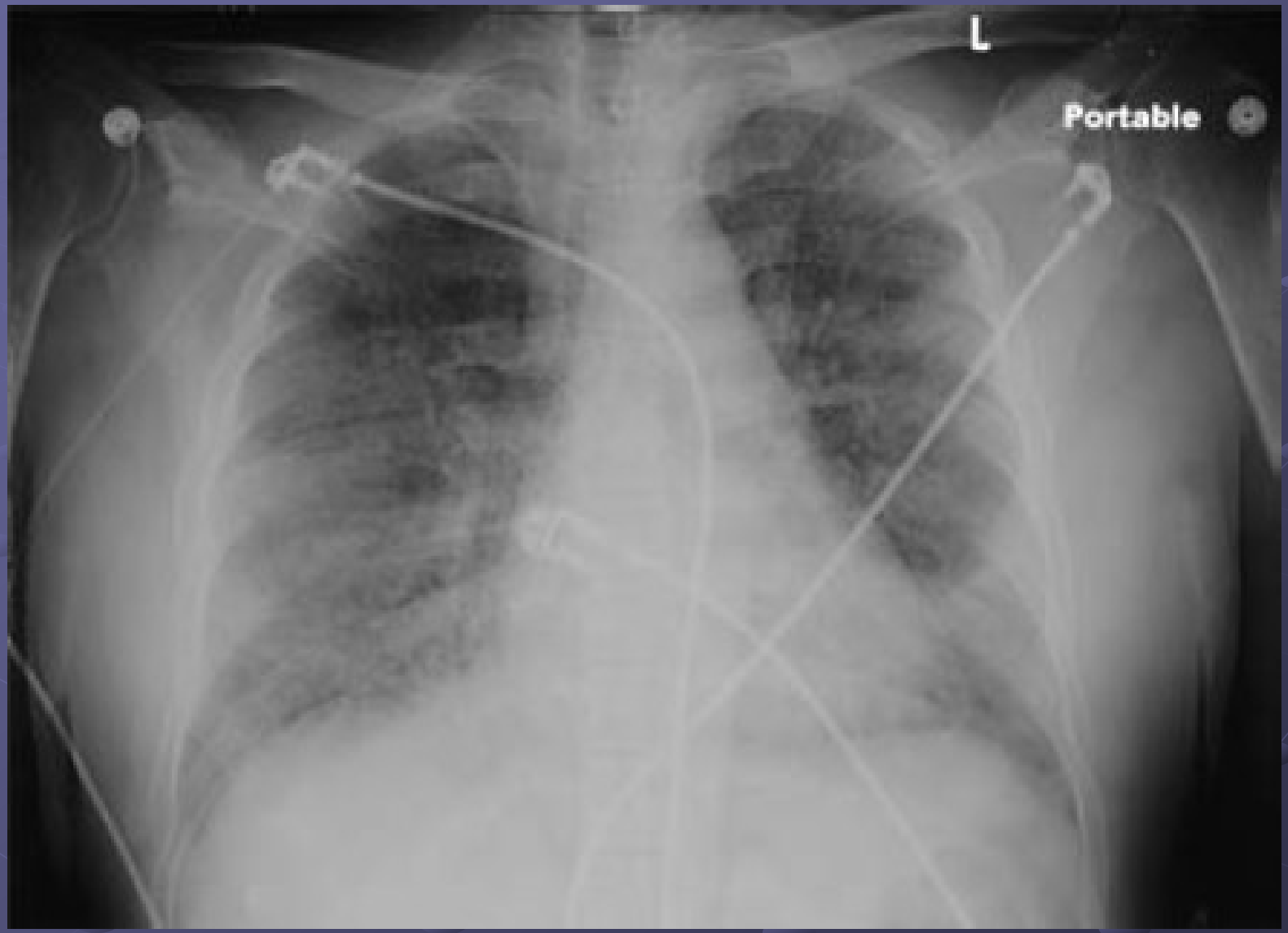
This Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, June 2001 and by The ERS Executive Committee, June 2001

AIP is a rapidly progressive
and histologically distinct form of interstitial pneumonia.

The pathology is described as an organizing form
of diffuse alveolar damage (DAD) indistinguishable from the
histologic pattern found
in acute respiratory distress syndrome (ARDS)
caused by sepsis and shock

The term AIP is reserved for cases of unknown cause

Acute Interstitial Pneumonia



Acute interstitial pneumonia

- ALI/ARDS of unknown cause
- Mean age=50 years
- M/F=1/1
- Not affected by smoking
- Severe respiratory failure necessitating mechanical ventilation in less than 3 weeks
- Diffuse crackles
- History of a viral like illness
- BAL: siderophages, ↑ neutrophils and lymphocytes
- Supportive treatment
- Prognosis poor (mortality >50%)
- In patients who survive, progression to fibrosis

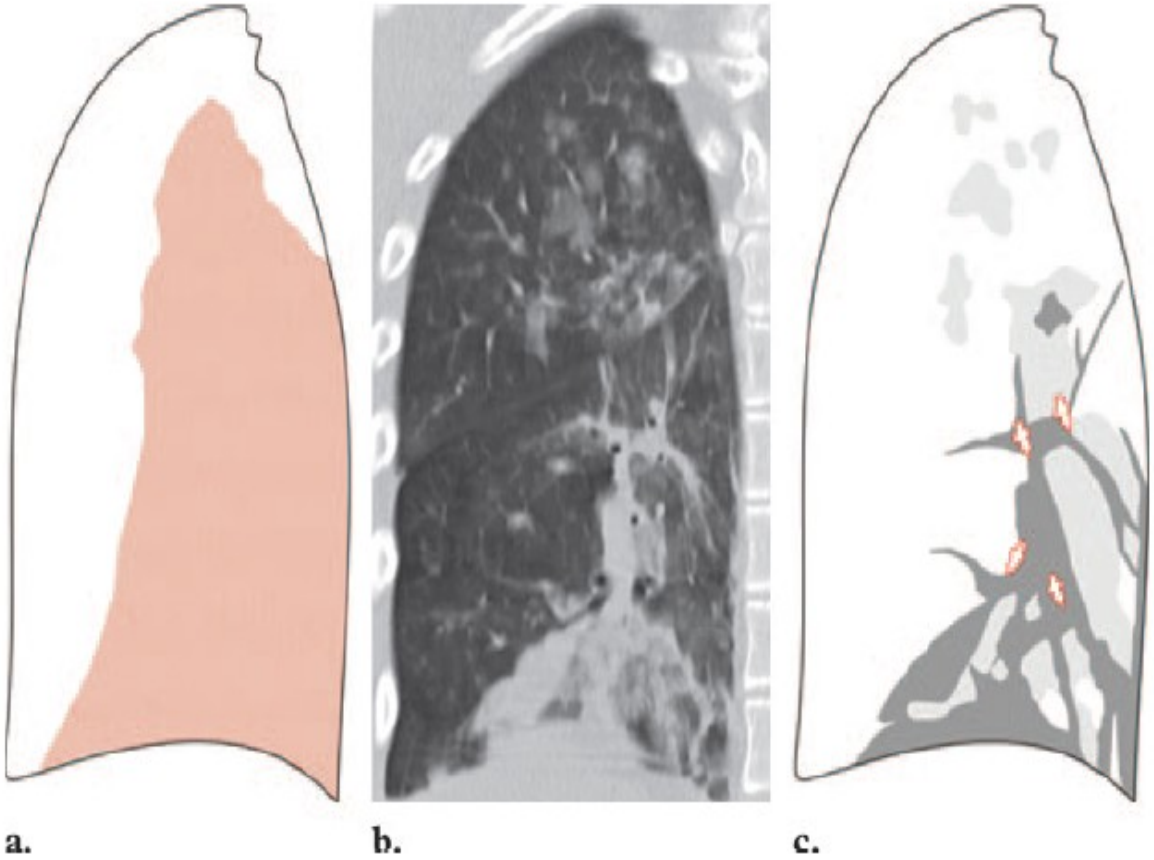
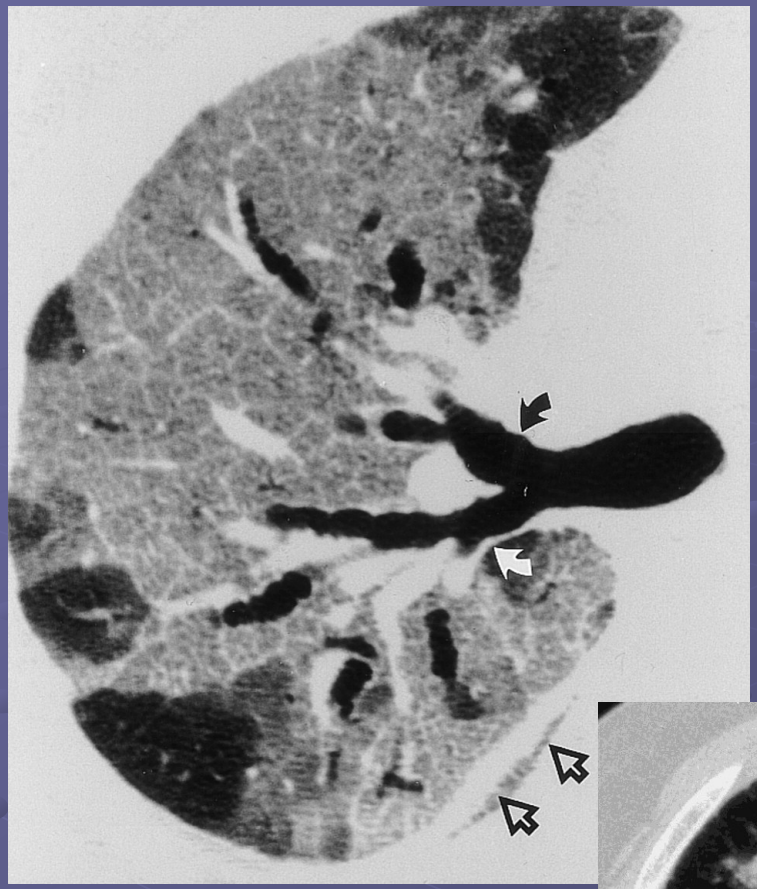
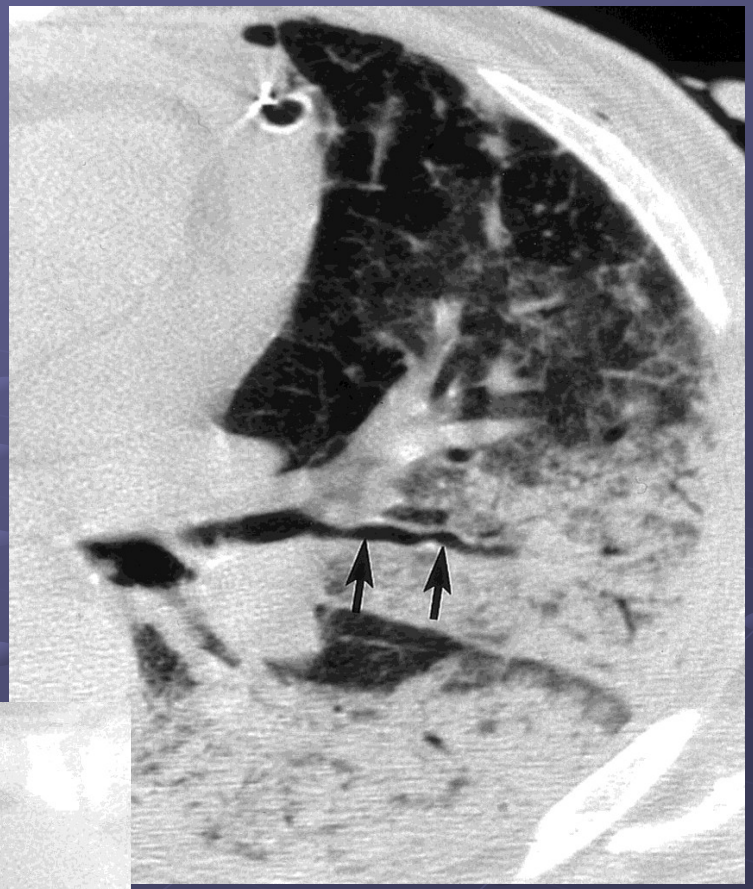
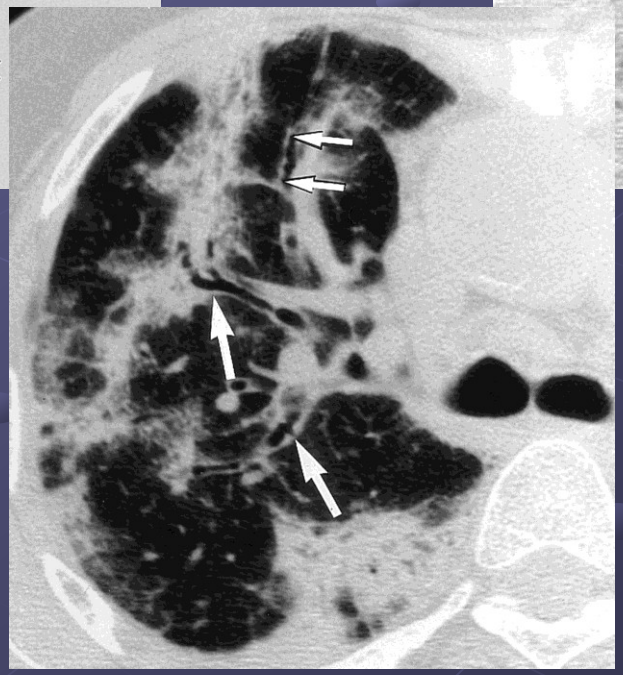


Figure 28. Distribution (**a**), CT image (**b**), and CT pattern (**c**) of AIP. AIP has a basal predominance (red area in **a**). CT shows airspace consolidation (dark gray areas in **c**), ground-glass opacities (light gray areas in **c**), and bronchial dilatation (red areas in **c**).

Mueller-Mang Ch. Et al. Radiographics 2007; 27:595-615







Acute Interstitial Pneumonia: Thin-Section CT Findings in 36 Patients[1]

Johkoh et al | Radiology · June 1999

Extent and Prevalence of CT Findings

Finding	Group A (*n* = 10) < 1week	Group B (*n* = 15) 1-3 weeks	Group C (*n* = 11) > 3 weeks
Ground-glass attenuation (%)			
Mean ± SD	44 ± 22 (10)	53 ± 16 (15)	62 ± 13 (11)
Range	19–75	. . .	. . .
Median	35		
Traction bronchiectasis (no. of segments or subsegments)			
Mean ± SD	9 ± 5 (10)	9.9 ± 5.4 (15)	13.2 ± 3.5 (11)
Range	2–14	1–18	. . .
Median	11	9	
Generations of bronchial divisions involved (score)*	2.6 ± 1.2	2.8 ± 0.89	3.6 ± 1.2
Mean ± SD	. . .	. . .	. . .
Range			
Median			
Airspace consolidation (%)			
Mean ± SD	34 ± 19 (9)	21 ± 12 (14)	22 ± 12 (10)
Range	0–56	0–44	0–44
Median	37	22	19
Emphysema (%)			
Mean ± SD	1.5 ± 1.3 (2)	5.2 ± 3.0 (6)	3.4 ± 3.2 (1)
Range	0–11	0–37	. . .
Median	0	0	
Honeycombing (%)			
Mean ± SD	0 (0)	1.7 ± 1.3 (3)	1.7 ± 1.4 (2)
Range	. . .	0–11	0–11
Median		0	0

Acute Interstitial Pneumonia

Comparison of High-Resolution Computed Tomography Findings between Survivors and Nonsurvivors

Kazuya Ichikado, Moritaka Suga, Nestor L. Müller, Hiroyuki Taniguchi, Yasuhiro Kondoh, Masanori Akira, Takeshi Johkoh, Naoki Mihara, Hironobu Nakamura, Mutsumasa Takahashi, and Masayuki Ando

Am J Respir Crit Care Med Vol 165. pp 1551–1556, 2002

TABLE 2. HIGH-RESOLUTION CT FINDINGS IN SURVIVORS AND NONSURVIVORS OF AIP

CT Findings	Survivors (*n* = 10)	Nonsurvivors (*n* = 21)
Architectural distortion	6 (60%)	21 (100%)*
Traction bronchiolectasis	7 (70%)	20 (95%)
Traction bronchiectasis	8 (80%)	20 (95%)
Intralobular septal thickening	3 (30%)	13 (62%)
Interlobular septal thickening	7 (70%)	19 (90%)
Honeycombing	0 (0%)	2 (10%)
Ground-glass attenuation	10 (100%)	21 (100%)
Air-space consolidation	10 (100%)	20 (9

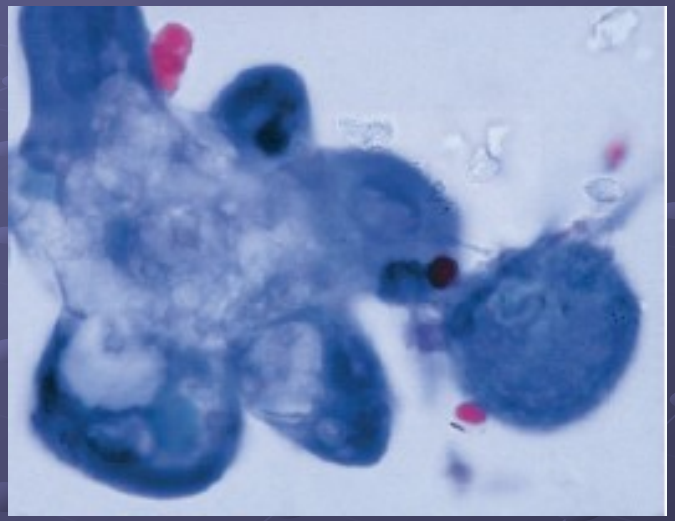
TABLE 3. EXTENT OF EACH CT FINDING IN SURVIVORS AND NONSURVIVORS OF AIP

CT Findings	Survivors (*n* = 10)	Nonsurvivors (*n* = 21)	p Value*
Spared area	34.0 ± 15.4	23.3 ± 18.6	NS
Ground-glass attenuation	32.0 ± 18.5	10.2 ± 13.4	0.002
Air-space consolidation	16.0 ± 15.0	3.7 ± 7.2	0.029
Ground-glass attenuation + traction bronchiolectasis or bronchiectasis	15.0 ± 25.0	43.0 ± 40.1	0.004
Air-space consolidation + traction bronchiolectasis or bronchiectasis	3.5 ± 6.5	19.4 ± 22.2	0.009
Honeycombing	0.0 ± 0.0	0.5 ± 1.2	NS

BAL

- exclusion of other diseases
- indications for DAD

Cluster of atypical epithelial cells with wide, vacuolated cytoplasm and amorphous extracellular and intracellular material (fragments of hyaline membranes)



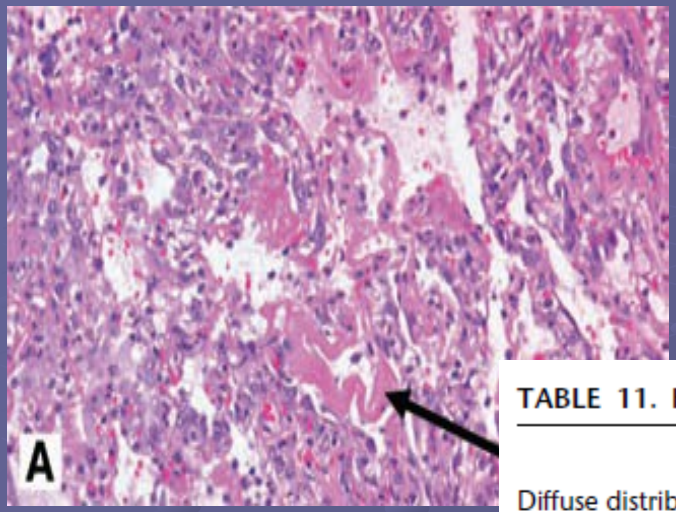
TBNB → Controversy

Open lung biopsy → 'Gold standard'

Bonnacorsi A, *ERJ* 2003

ATS/ERS *consensus, AJRCCM* 2002

Diffuse Alveolar Damage



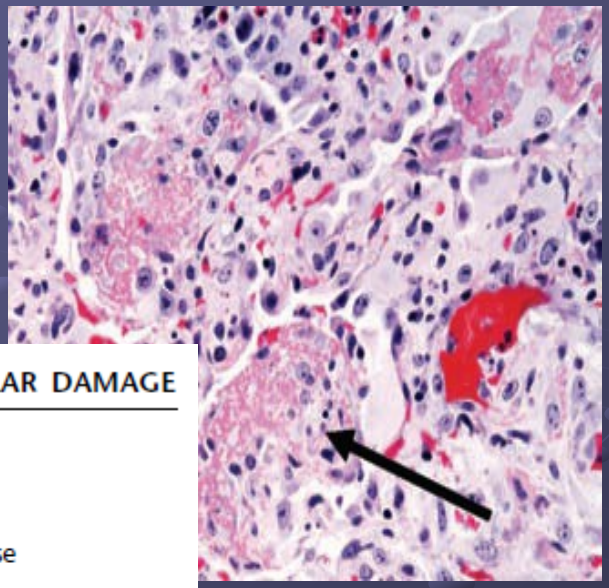


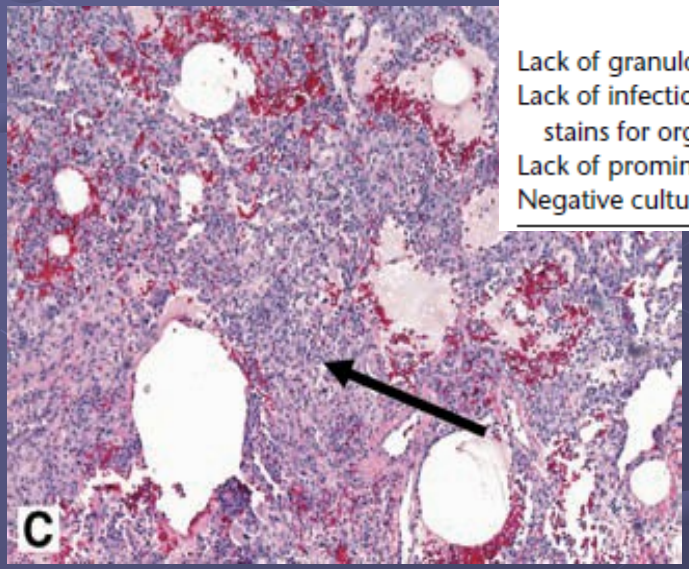
TABLE 11. HISTOLOGIC FEATURES OF DIFFUSE ALVEOLAR DAMAGE

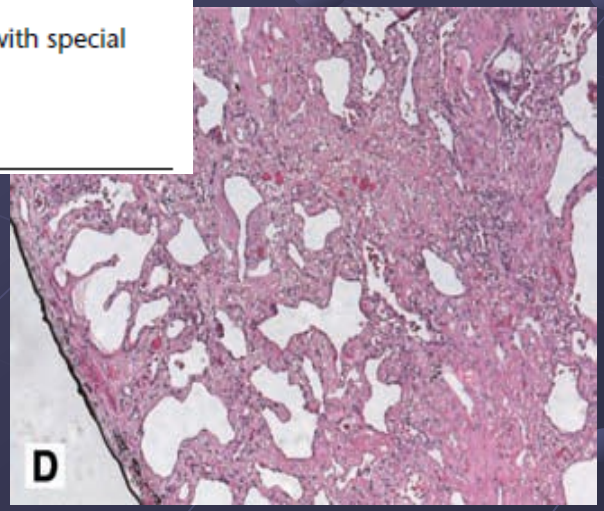
Key Histologic Features

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





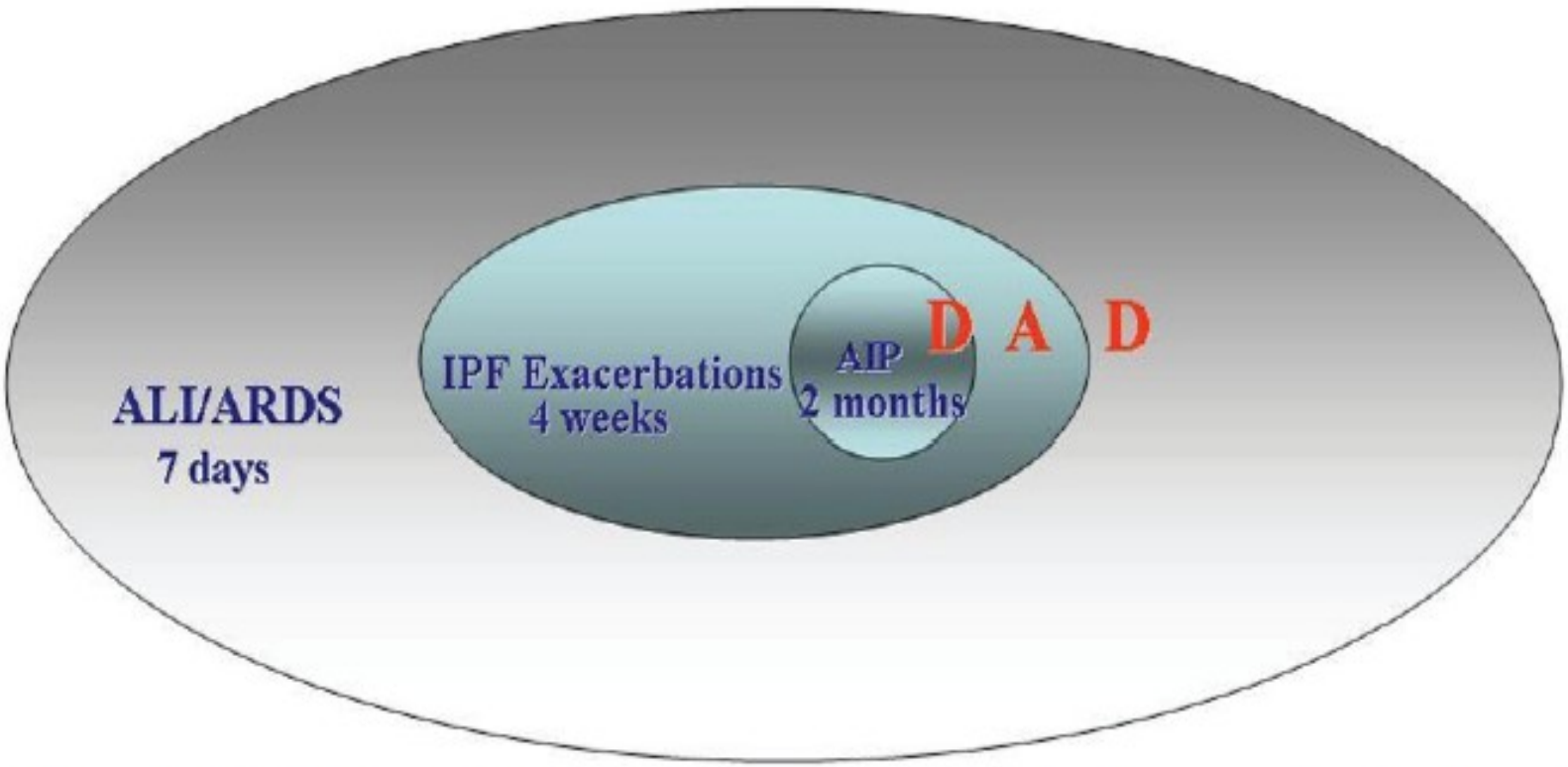


Figure 5. Different clinical settings characterized by diffuse alveolar damage (DAD) pathology. This non-proportional figure denotes the incoherence of the clinical significance of acute respiratory distress syndrome (ARDS), acute interstitial pneumonia (AIP), and idiopathic pulmonary fibrosis (IPF) exacerbations in which DAD, despite being the common denominator, develops upon different histology substrates (UIP in IPF exacerbations, normal lungs in AIP, and normal or diseased lungs in ARDS) and, according to current definitions, presents at different time intervals: 7 days for ARDS, 4 weeks for IPF exacerbations, and 2 months for AIP. This incoherence led also to a different pharmacologic approach, which proved to be unsuccessful at least in AIP and in IPF true exacerbations. ALI, acute lung injury.

Papiris SA, et al. Crit Care 2010; 14:246

TABLE 12. CLINICAL CONDITIONS ASSOCIATED WITH DIFFUSE ALVEOLAR DAMAGE PATTERN

Idiopathic (acute interstitial pneumonia)	Uremia
Infection	Sepsis
Collagen vascular disease	Transfusion-related acute lung injury
Drug toxicity	Shock
Toxic inhalation	Trauma

Acute Interstitial Pneumonia

Table 2 Differential Diagnosis of Acute Interstitial Pneumonitis

Acute eosinophilic pneumonia
Acute exacerbation of IPF or other chronic fibrosing ILDs
Acute hypersensitivity pneumonitis
ARDS
Acute respiratory failure in collagen-vascular disease (e.g., dermatomyositis/ polymyositis, rheumatoid arthritis, systemic lupus erythematosus)
COP (acute variant)
Diffuse alveolar hemorrhage
Drug-induced lung disease
Infection
Inhalational/toxic exposures

Treatment of AIP

- No proven treatment
- Best supportive care (as for ARDS)
- Lack of controlled treatment trials
- Transplantation?

Early Intervention Can Improve Clinical Outcome of Acute Interstitial Pneumonia *

Gee Young Suh, Eun Hae Kang, Man Pyo Chung, Kyung Soo Lee, Joungho Han, Masanori Kitaichi and O Jung Kwon

Chest 2006;129;753-761

Smoking related Interstitial Pneumonias

Cigarette smoking and interstitial lung disease

Cigarette smoking may

- **be the *primary cause* (RB-ILD, DIP, PLCH)**
- ***influence* the risk and the clinical course (IPF, RA-ILD)**
- ***precipitate* the acute course (AEP, pulmonary hemorrhage syndromes)**
- ***confer protection* (sarcoidosis, HP)**

Patel RR, et al. Drugs 2008; 68: 1511-1527

Cigarette smoking and diffuse lung disease
Respiratory bronchiolitis-interstitial lung disease

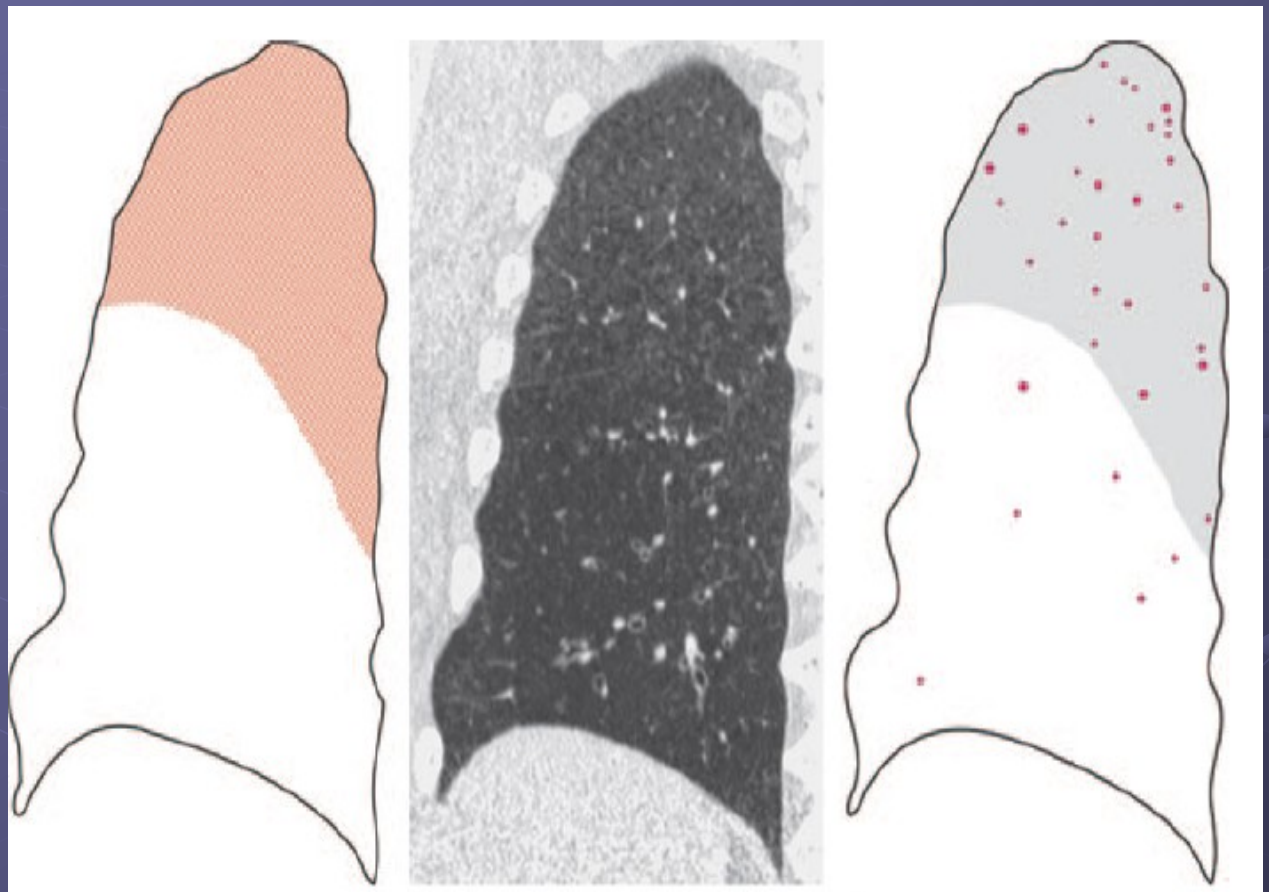
	RBILD
Smoking	100%
Age	3rd–5th decades
Sex M:F	Slight male dominance
Occurrence in children	No
Onset	Insidious
Presenting symptoms	Dyspnoea, cough
Crackles	~50%
Clubbing	Rare
Chest radiograph	Interstitial or normal
HRCT	Patchy ground glass
Pulmonary function	Mixed defect or normal
Treatment	Smoking cessation
Response to steroids	Good
Prognosis	Good
Complete recovery possible	Yes

Unknown

RBILD is a clinicopathological entity characterized by the presence of pigmented macrophages and mild interstitial inflammatory changes centering on respiratory bronchioles and neighbouring alveoli. Alveolar septa in the peribronchiolar region may be mildly thickened but without fibrosis.

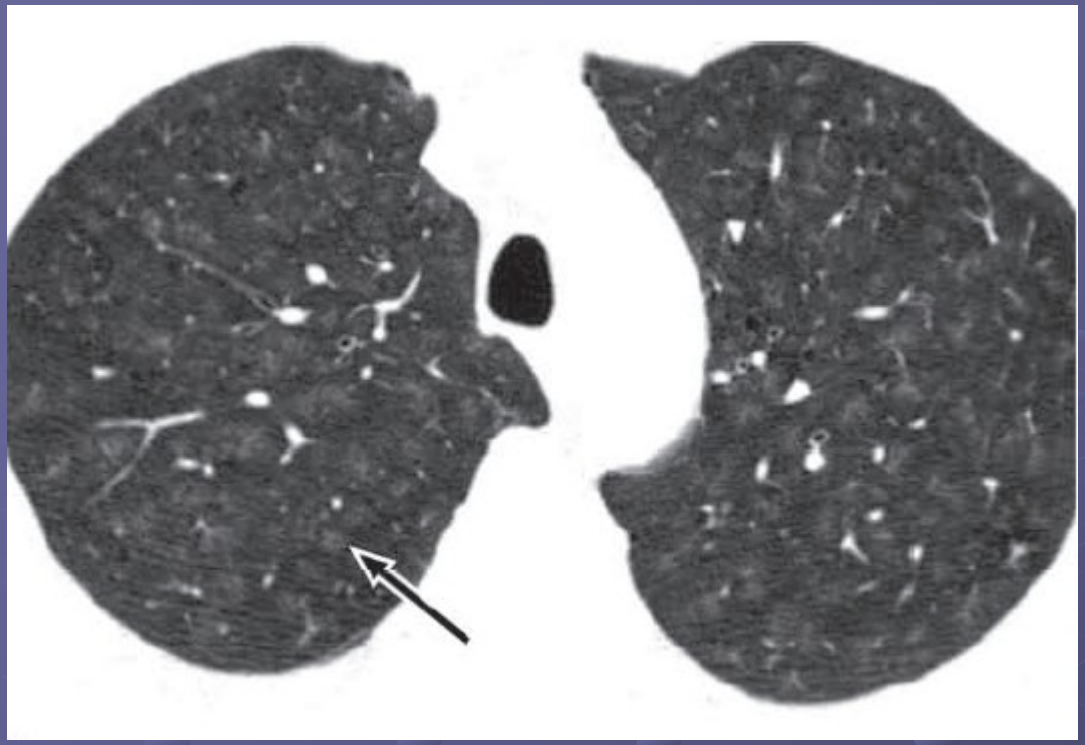
Ryu JH, et al. Eur Respir J 2001; 17: 122-132

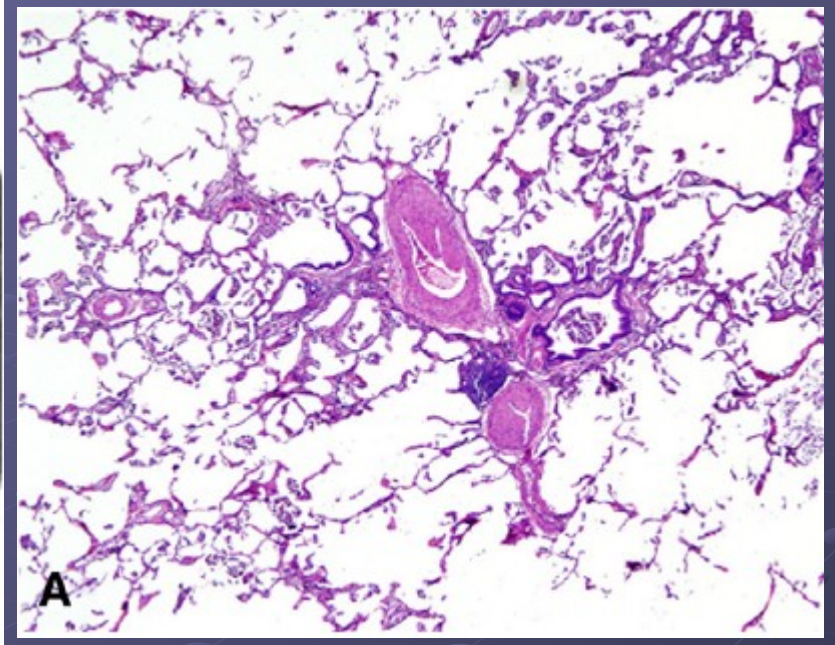
Respiratory Bronchiolitis-ILD



a. b. c.

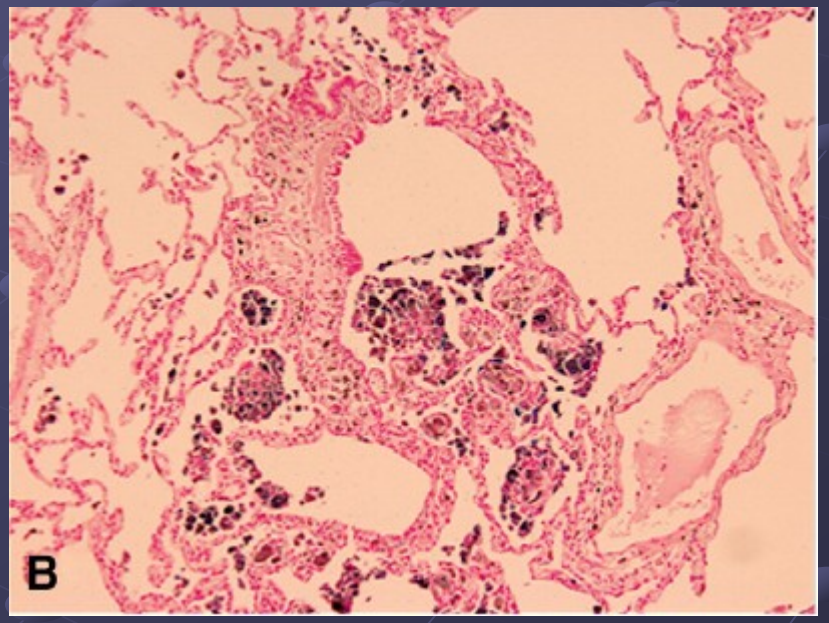
Figure 18. Distribution (**a**), CT image (**b**), and CT pattern (**c**) of RB-ILD. RB-ILD has an upper lung predominance (red area in **a**). CT shows ground-glass opacity (gray area in **c**) and centrilobular nodules (red areas in **c**).





High-Resolution CT Findings of RB-ILD

Centrilobular nodular opacities
Patchy ground-glass opacity
Bronchial wall thickening
Upper lobe predominance
Associated centrilobular emphysema
Air trapping at expiration
Findings of fibrosis absent



Attili AK, et al. Radiographics 2008

Cigarette smoking and diffuse lung disease
Desquamative Interstitial Pneumonia

	DIP
Smoking	90%
Age	3rd–5th decades
Sex M:F	Nearly 2:1
Occurrence in children	Rare
Onset	Insidious
Presenting symptoms	Dyspnoea, cough
Crackles	60%
Clubbing	Nearly 50%
Chest radiograph	Interstitial, patchy ground-glass
HRCT	Ground glass with lower lung predominance
Pulmonary function	Restrictive
Treatment	Smoking cessation, steroids
Response to steroids	Good
Prognosis	Good
Complete recovery possible	Yes

60%-90%

30%-50%

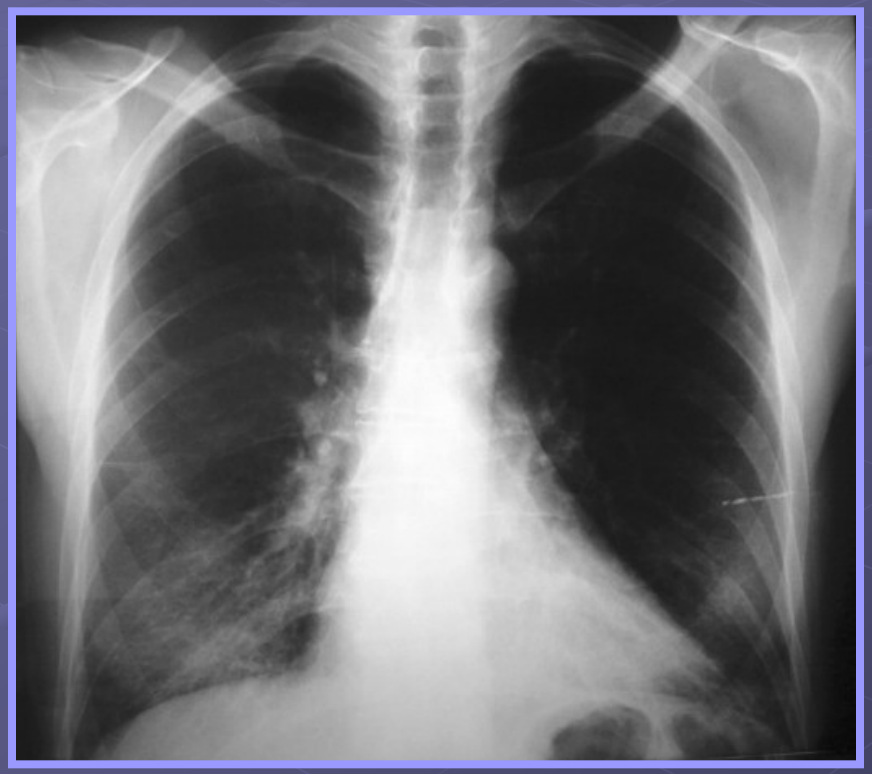
Moderate

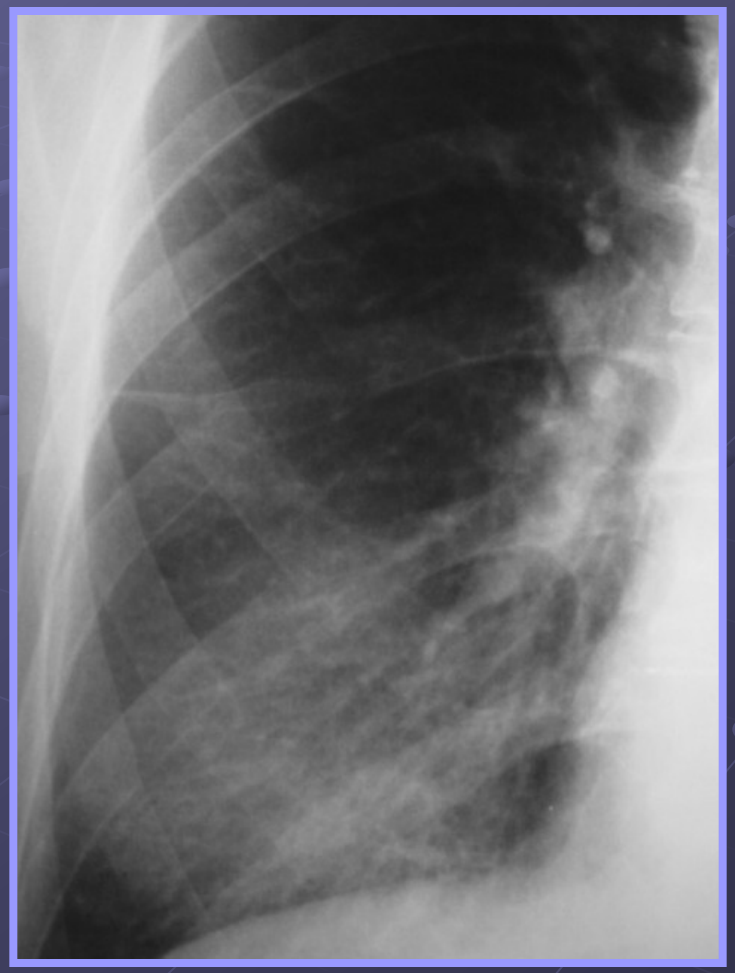
Desquamative interstitial pneumonia is characterized histologically by the diffuse exudation of pigmented macrophages within alveolar spaces

Nagarjun Rao R et al. Ann Diagn Pathol 2008

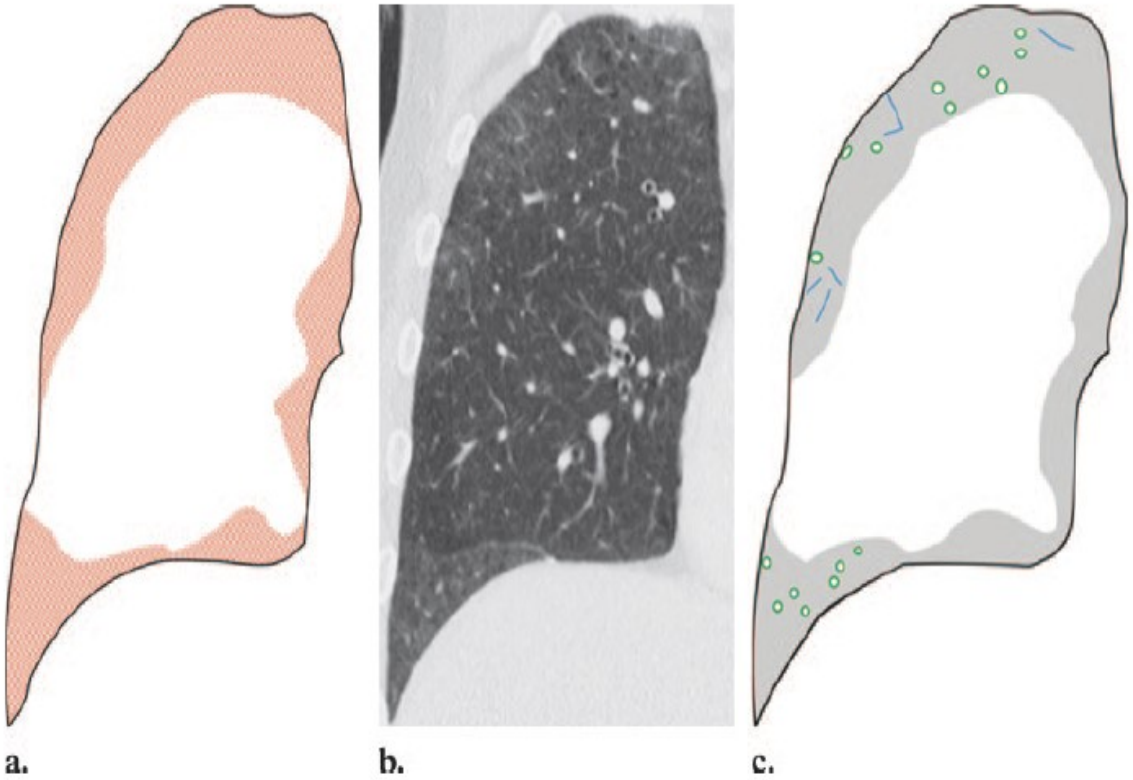
Ryu JH, et al. Eur Respir J 2001
Patel RR, et al. Drugs 2008

DIP Ακτινογραφία θώρακος



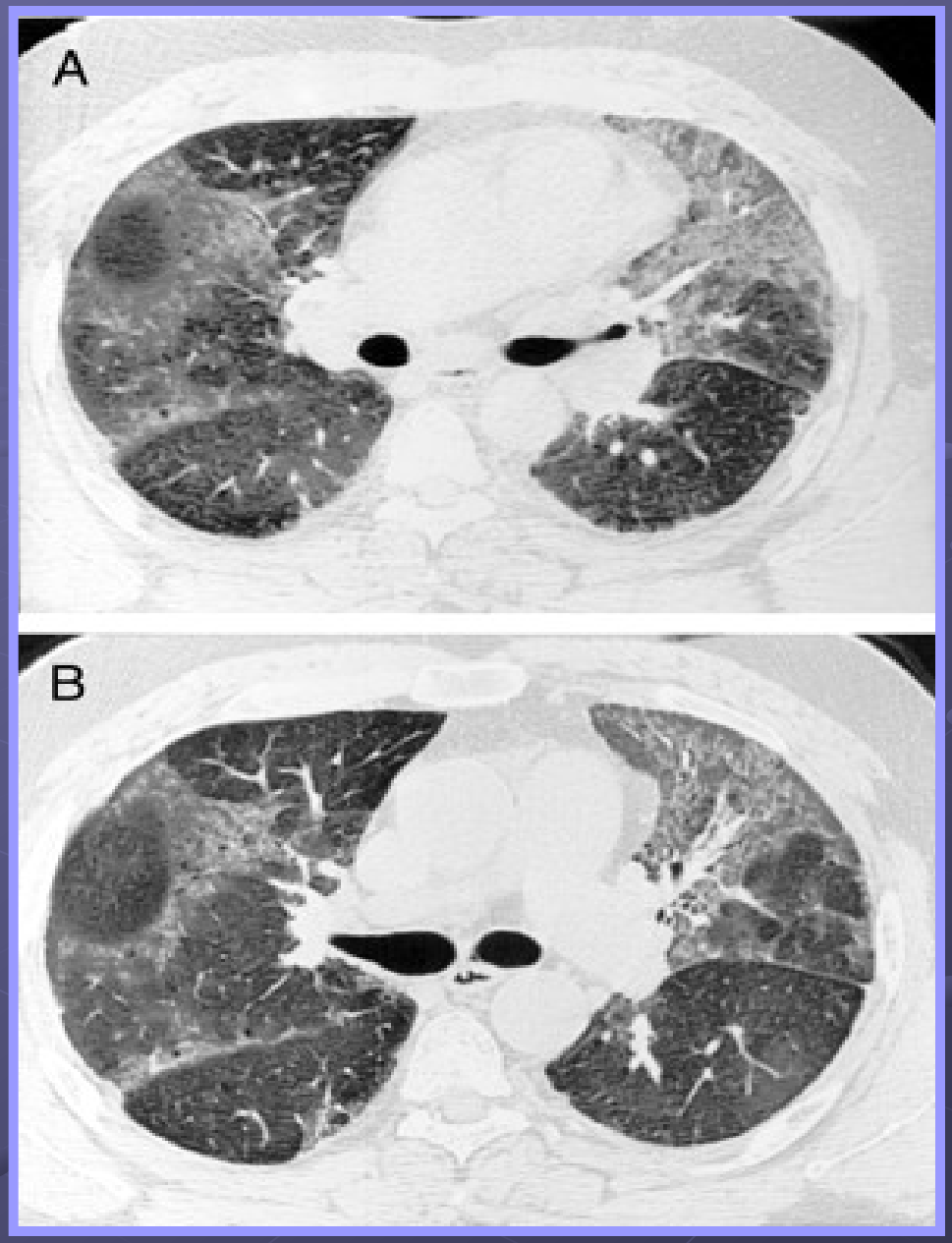


Desquamative interstitial pneumonia



a. b. c.

Figure 21. Distribution (**a**), CT image (**b**), and CT pattern (**c**) of DIP. DIP has a peripheral predominance (red areas in **a**). CT shows ground-glass opacity (gray area in **c**), irregular linear opacities (blue areas in **c**), and cysts (green areas in **c**).



Mastora I, et al. Radiology 2001; 218: 695-702

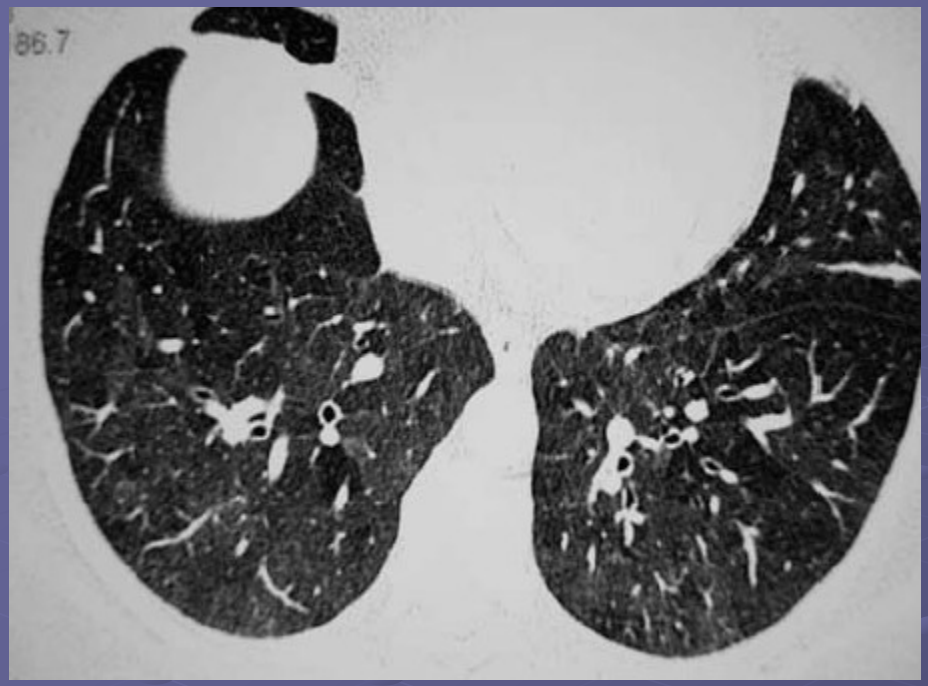
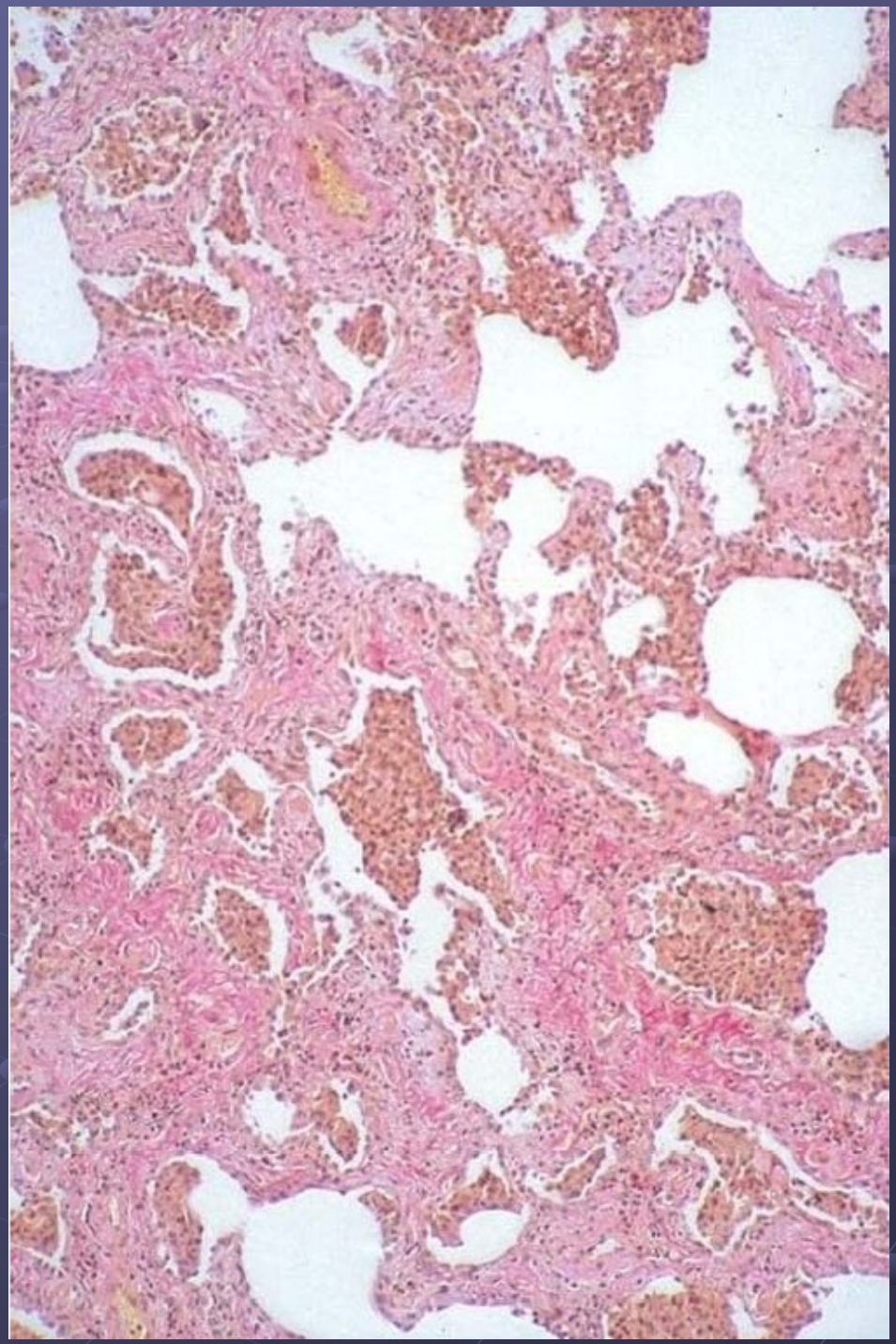


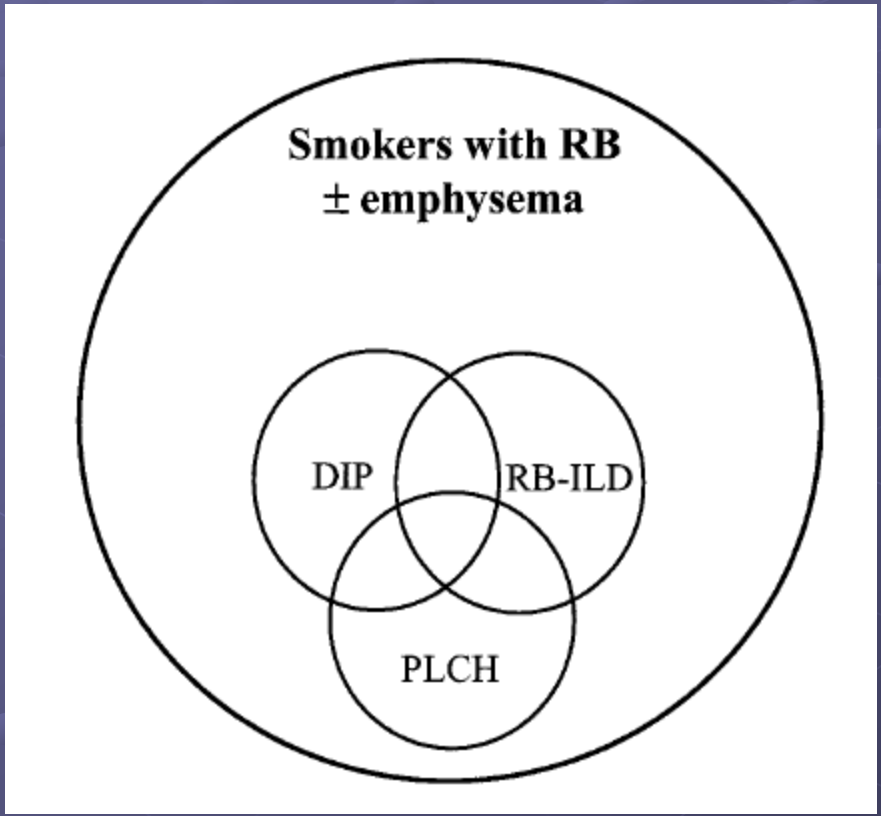
Table 3
High-Resolution CT Findings of DIP

Bilateral patchy ground-glass opacity
Reticular opacities
Subpleural and basal predominance
Honeycombing uncommon
Associated centrilobular emphysema



Attili AK, et al. Radiographics 2008
Caminati A, et al. Proc Am Thor Soc 2006

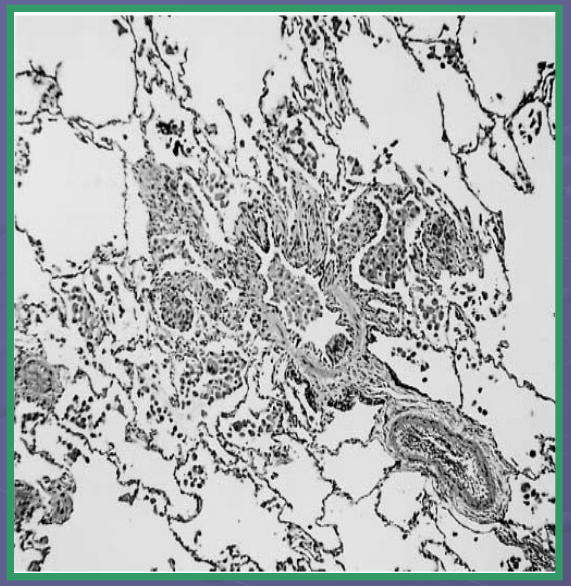
The Overlap Between Respiratory Bronchiolitis and Desquamative Interstitial Pneumonia in Pulmonary Langerhans Cell Histiocytosis High-Resolution CT, Histologic, and Functional Correlations



14 patients with PLCH, RB/DIP-like changes are exceedingly common may be sufficiently severe to cause the appearance of ground-glass attenuation on HRCT, and correlate with the cumulative exposure to cigarettes smoked.

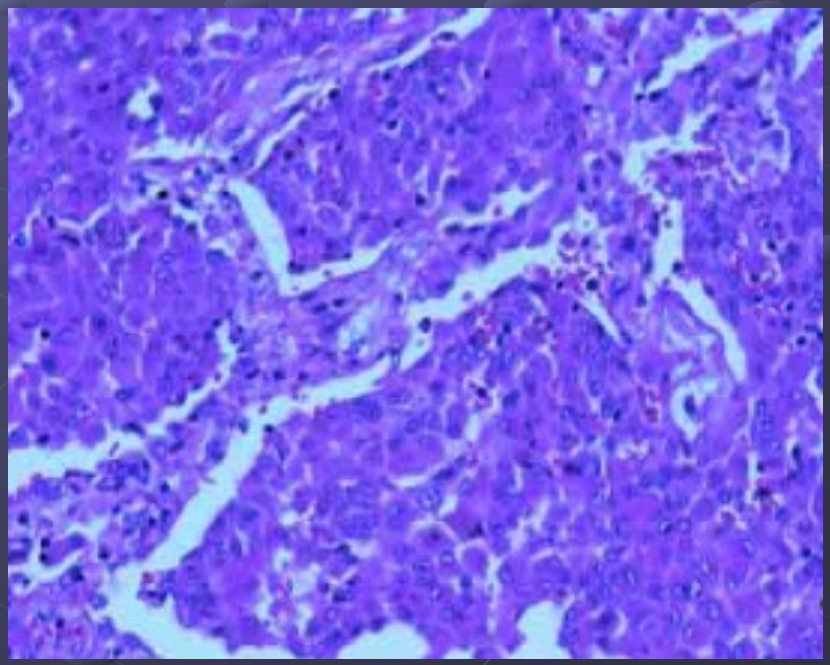
Vassalo R, et al Chest 2003

RB-ILD / DIP



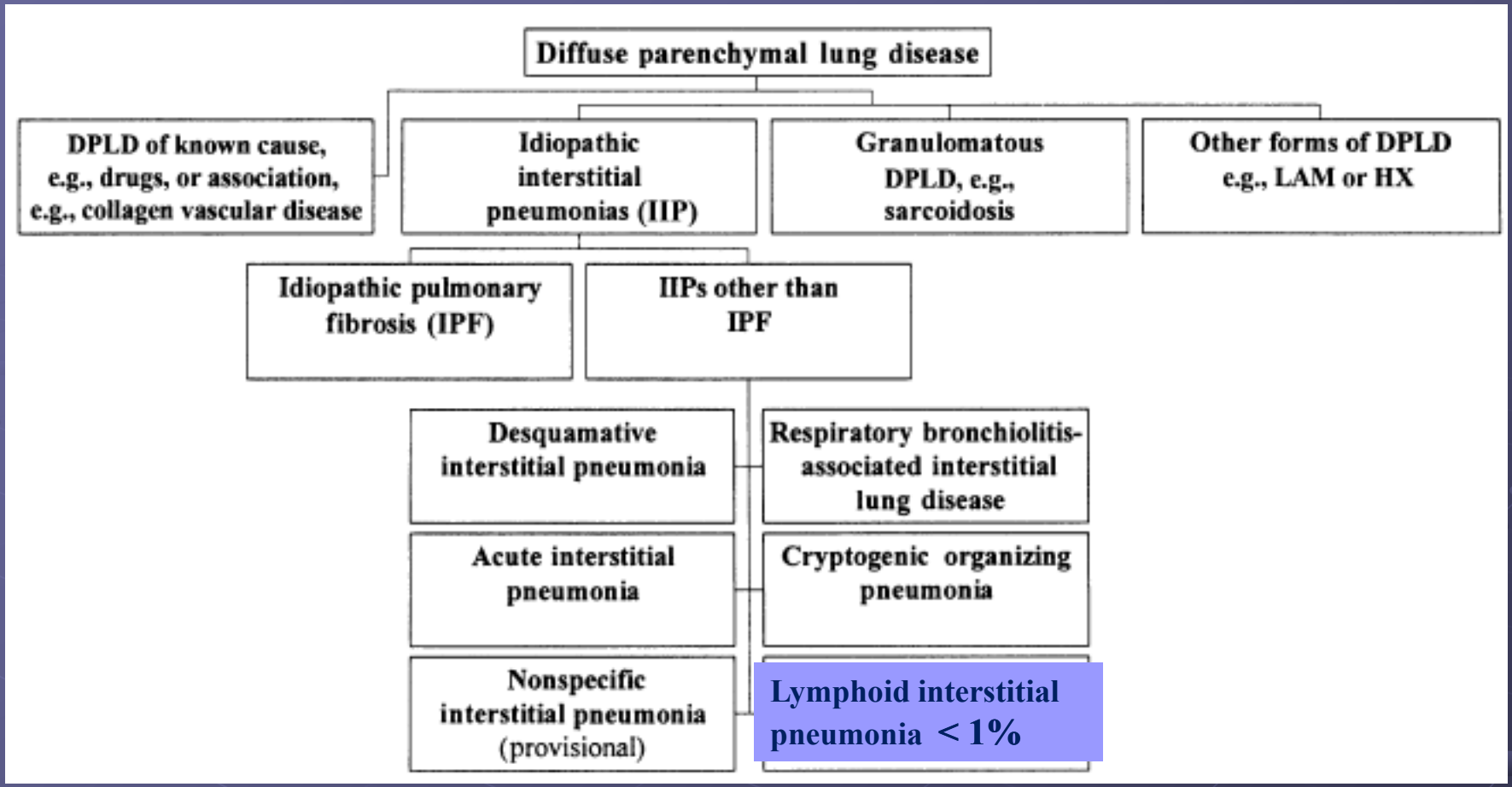
RB occurs as an incidental finding in smokers, so it is impossible to know whether it is the main problem or there is some other lesion not been sampled

A surgical lung biopsy is required to make a confident diagnosis of DIP. TBB is usually non-diagnostic.



Therapeutic management

Characteristic	DIP (n = 23)	RB-ILD (n = 12)
Treatment		
None	2 (9)	1 (8)
Corticosteroids	21 (91)	11 (92)
Smoking cessation†		
Yes	4 (27)	4 (40)
No	11 (73)	6 (60)
Response to corticosteroid therapy		
Subjective improvement	5 (24)	6 (55)
Objective improvement	7 (33)	7 (64)
Final clinical outcome‡		
Improved	1 (5)	3 (25)
Stable	12 (63)	8 (67)
Worsened	1 (5)	1 (8)
Dead	5 (26)	0 (0)



American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

This Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, June 2001 and by The ERS Executive Committee, June 2001

Lymphoid interstitial pneumonia: clinical features, associations and prognosis

S-I. Cha*, M.B. Fessler#, C.D. Cool¶, M.I. Schwarz# and K.K. Brown#

Eur Respir J 2006; 28: 364–369

Lymphoid interstitial pneumonia (LIP) is rare and
its clinical course incompletely described
LIP was originally described
by LIEBOW and CARRINGTON
as a benign lymphoproliferative disorder limited to the lungs and
characterized by diffuse infiltration of the alveolar septa
by dense collections of lymphocytes
admixed with plasma cells and other cellular elements

TABLE 1 Clinical characteristics of subjects

Characteristic	
Subjects	15
Sex	
Males	4
Females	11
Age yrs	47.1±18.9
Caucasians	13 (86.7)
Smoking status	
Never-smoker	11 (73.3)
Former smoker	4 (26.7)
Constitutional symptoms	
Fatigue	13 (86.7)
Fever	5 (33.3)
Unintentional weight loss	5 (33.3)
Arthralgia	6 (40.0)
Respiratory symptoms	
Duration yrs	2.8±3.2
Cough	8 (53.3)
Sputum	5 (33.3)
Dyspnoea	11 (100)
Grade	3–10
Duration yrs	2.7±3.2
Physical findings	
Basilar crackles	11 (73.3)
Wheezing	1 (7.7)
Clubbing	2 (13.3)

Lymphoid interstitial pneumonia

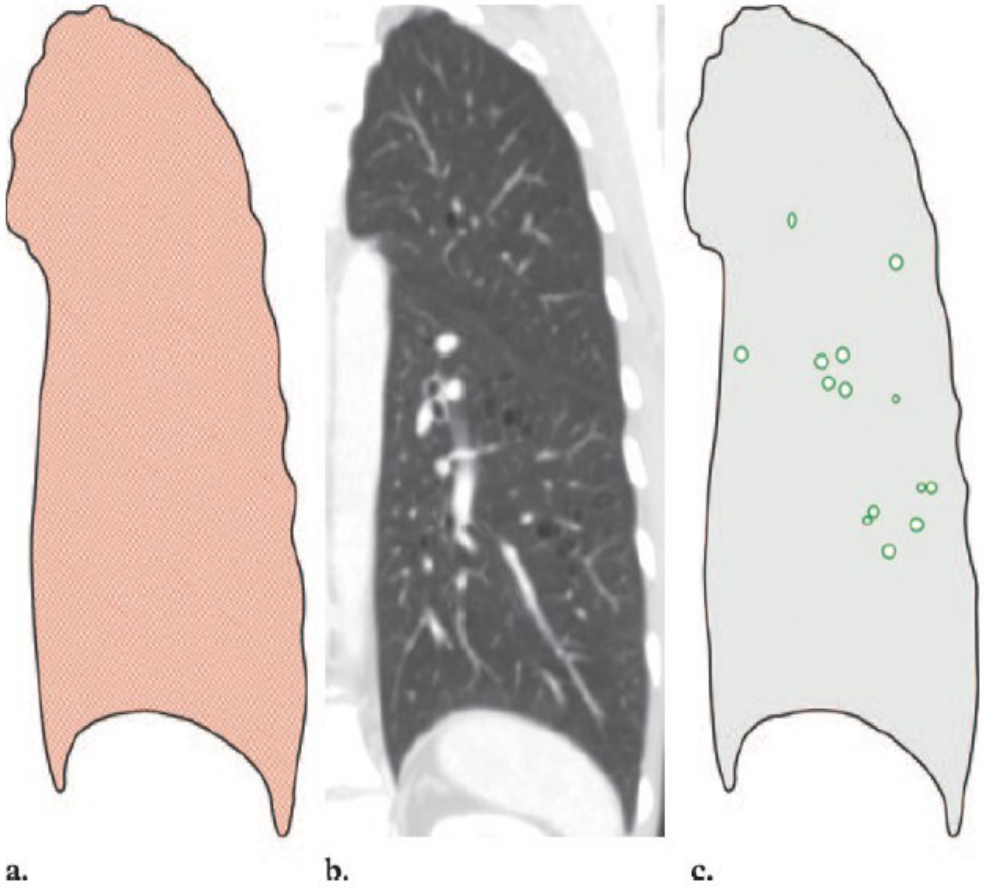
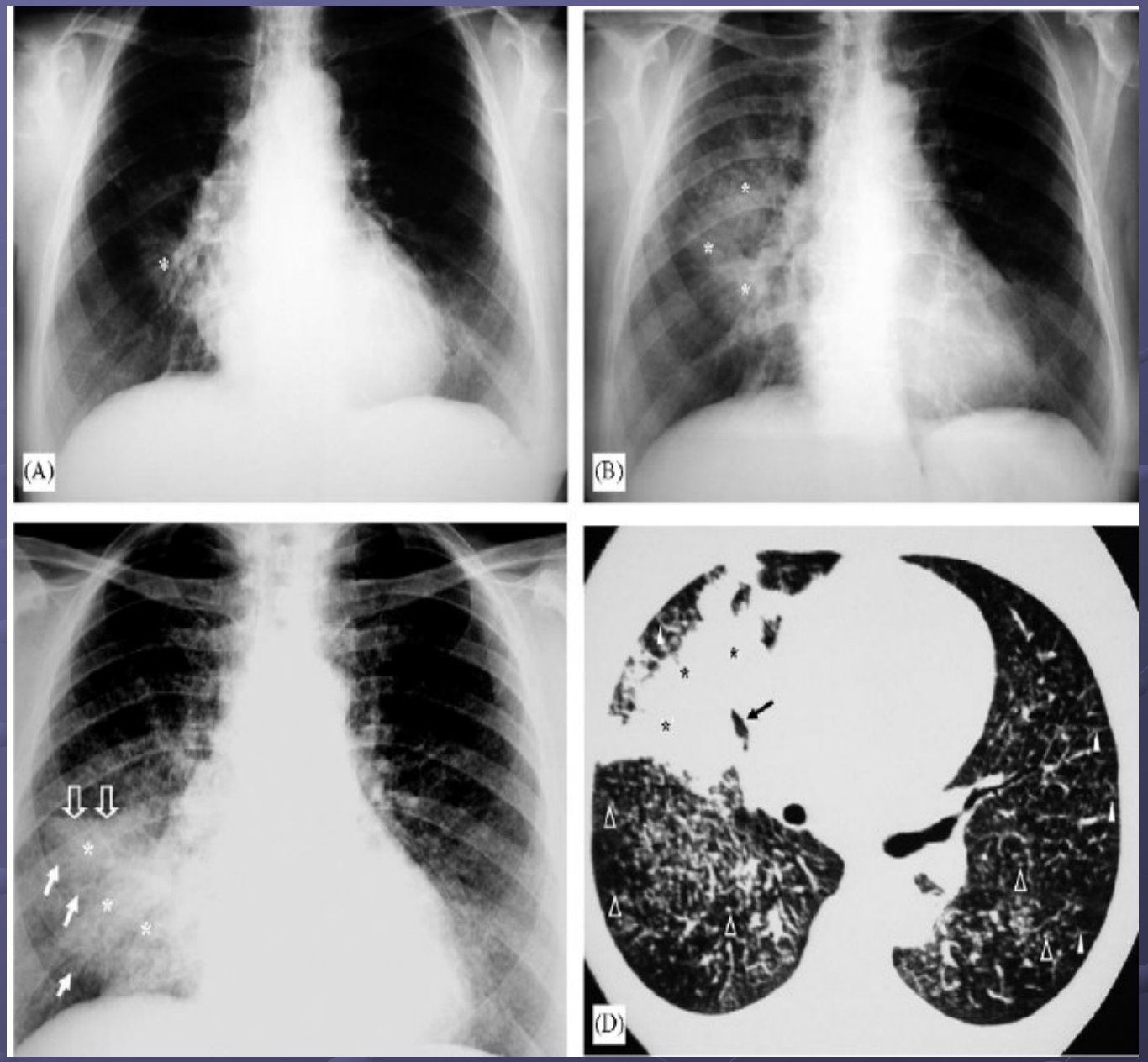
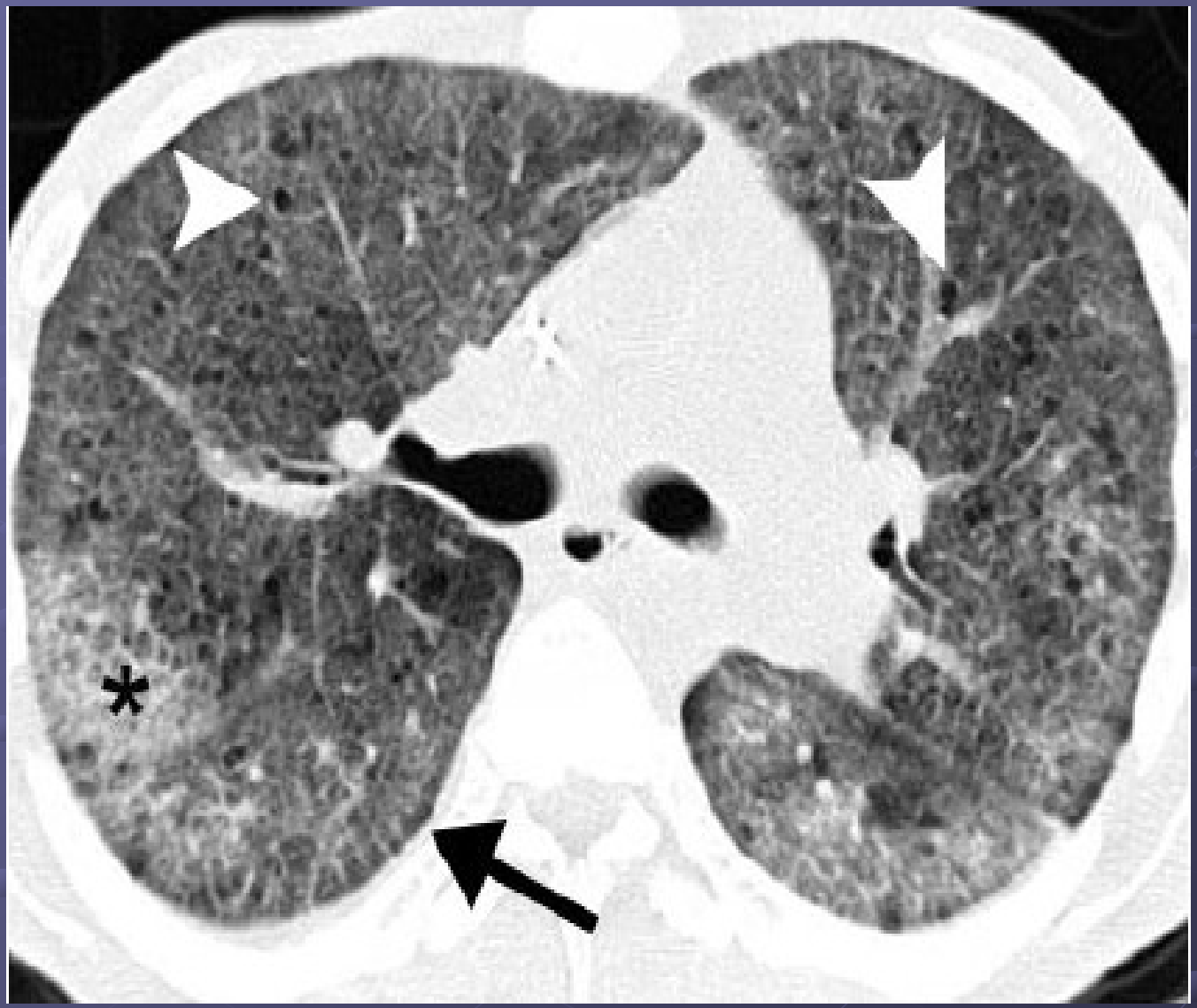


Figure 25. Distribution (**a**), CT image (**b**), and CT pattern (**c**) of LIP. The distribution is diffuse (red area in **a**). CT shows ground-glass opacity (gray area in **c**) and perivascular cysts (green areas in **c**).


(A)
(B)
(D)



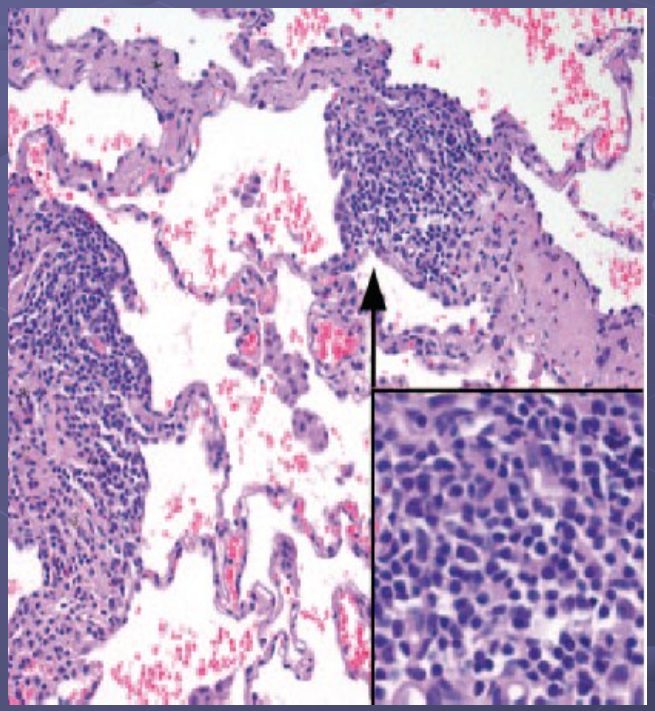


TABLE 15. HISTOLOGIC FEATURES OF LYMPHOID INTERSTITIAL PNEUMONIA

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

TABLE 3 Lung function testing

Parameters	LIP	Subjects n
FEV_1 % pred	67.3±18.4	15
FVC % pred	65.0±15.0	15
FEV_1/FVC %	80.3±5.0	15
TLC % pred	78.2±16.1	13
V_{tg} % pred	77.5±16.8	13
RV % pred	120.5±36.3	13
R_{aw} % pred	135.1±56.8	13
$D_{L,CO}$ % pred	62.5±18.4	13
$D_{L,CO}/V_A$ % pred	93.6±22.2	13
P_{A-a,O_2}		
Resting mmHg	17.2±8.6	12
Peak exercise mmHg	42.9±10.5	

TABLE 4 Analysis of bronchoalveolar lavage fluid

Parameter	Values	Subjects n
WBC count $\times 10^6$	60.6±40.5	6
Differential count %		
Alveolar macrophages	44.5±28.6	6
Neutrophils	17.5±17.3	6
Eosinophils	7.5±7.0	6
Lymphocytes	30.5±29.1	6
T-cells (CD3)	75.7±27.7	3
T-helper (CD4)	30.3±33.5	3
T-suppressor (CD8)	37.3±33.7	3
B-cells (CD21)	0.8±1.1	6

TABLE 5 Response to treatment in subjects in whom follow-up was available

Patient No.	Treatment[#]	Clinical response	Radiological response	Physiological response	
				TLC and/or FVC	$D_{L,CO}$
1	Steroid	↑	→	→	→
	Colchicine				
3	Steroid	↑	↑	↑	↑
4[¶]	Steroid	↑	↑	↑	↑
5[¶]	Steroid	→	↓	→	↓
6	Steroid	NA	↑	↑	↑
7	Steroid	→	↓	→	→
	Cyclophosphamide	↓	↓	→	→
	Colchicine	↑	→	→	→
8	Steroid	↑	→	↓	→
13	Steroid				
	Cyclophosphamide				
	Azathioprine	→	→	↓	→
14	Steroid	→	↑	→	→
	Cyclosporin A	↑	↑	↑	→
15	Steroid+MTX	↑	↑	↓	→
	Cyclophosphamide	↑	↑	→	→

TABLE 16. CLINICAL CONDITIONS ASSOCIATED WITH LYMPHOID INTERSTITIAL PNEUMONIA PATTERN

Idiopathic
Infection (especially *Pneumocystis carinii*, hepatitis B, Epstein–Barr virus)
Collagen vascular disease, especially Sjögren's syndrome, rheumatoid arthritis, or systemic lupus erythematosus
Immunodeficiency (HIV, SCID)
Other immunologic disorders
Autoimmune hemolytic anemia, myasthenia gravis, pernicious anemia, Hashimoto's thyroiditis, chronic active hepatitis, primary biliary cirrhosis
Drug-induced/toxic exposure

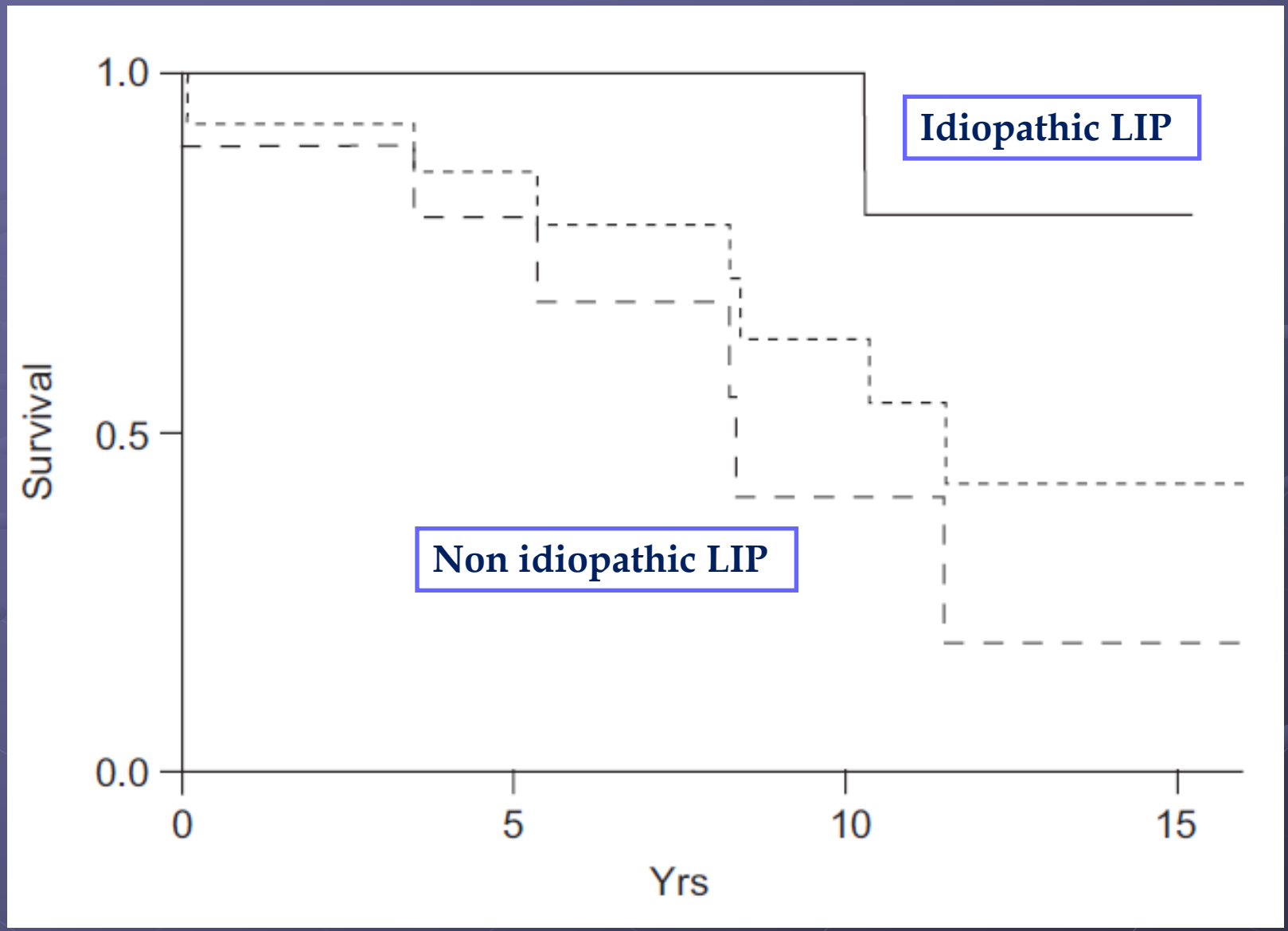
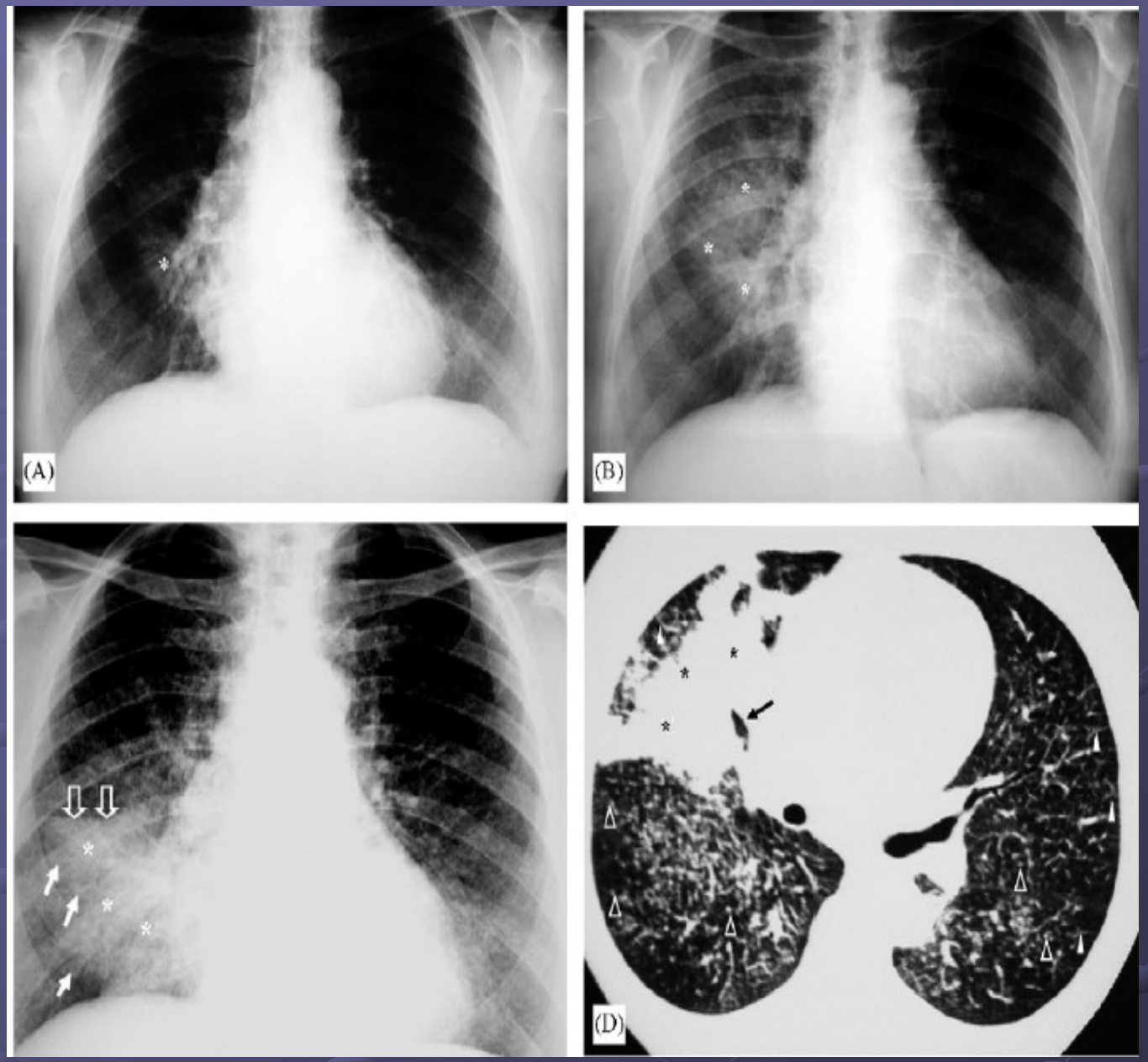

1.0
0.5
0.0
Survival
0
5
10
15
Yrs
Idiopathic LIP
Non idiopathic LIP

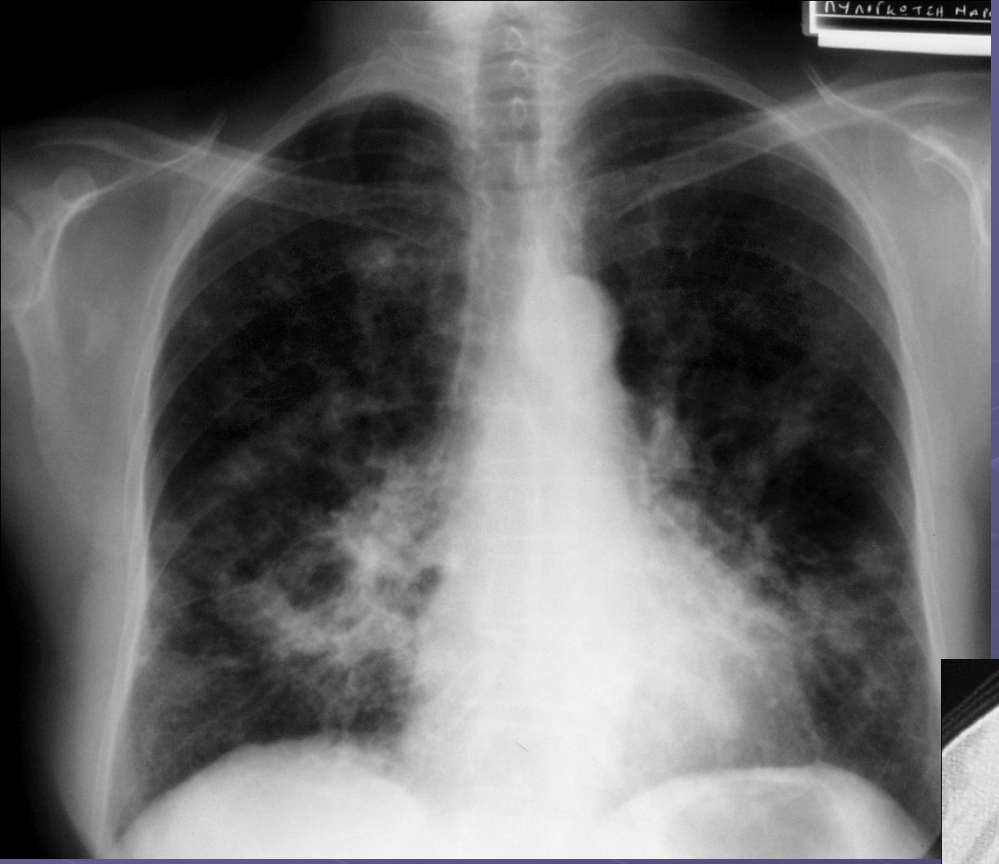
Table 2—*Histopathologic Features That Distinguish LIP, HP, and Small Lymphocytic/Lymphocytoplasmic Lymphoma/Extranodal Marginal Zone Lymphoma (MALToma)**

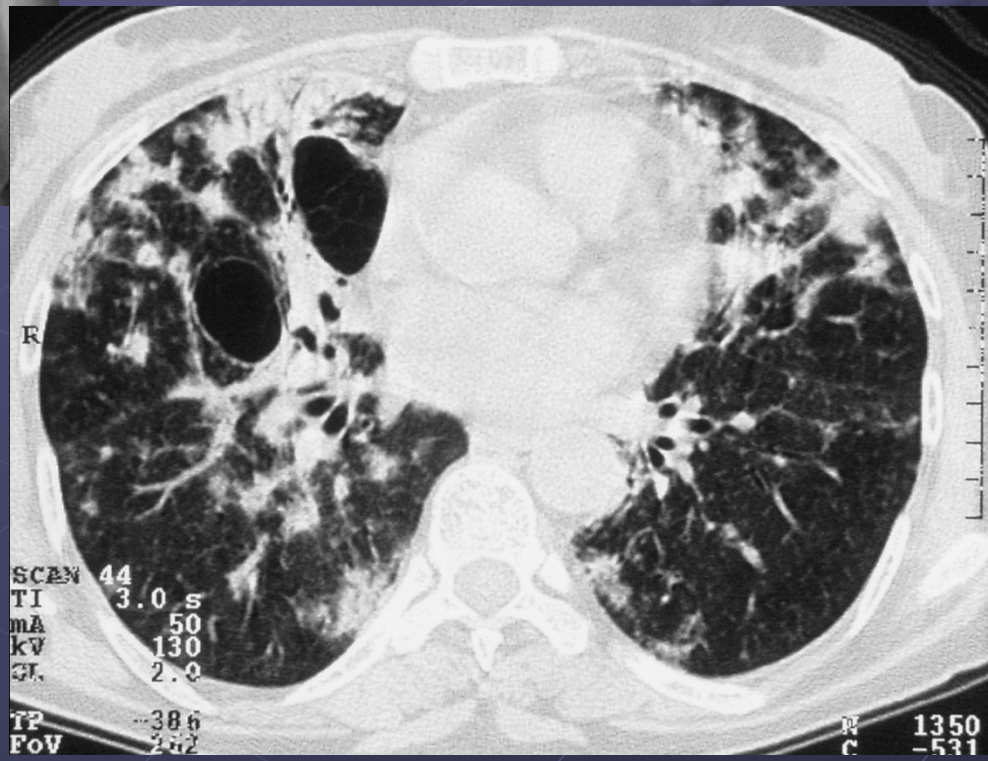
Features	LIP	HP	WDL/MALToma
Distribution	Diffuse, interstitial	Patchy, bronchiolocentric	Diffuse, lymphangitic
Alteration of airspace architecture	Compression by interstitial infiltrates	Absent	Compression by nodular infiltrates
Composition of cellular infiltrates	Polymorphous	Polymorphous	Monomorphous
Clonality studies	Polyclonal	Polyclonal	Monoclonal
Reactive lymphoid follicles	Present	Absent	Occasional
Epithelioid histiocytes/granulomas	Present	Present	Occasional in WDL

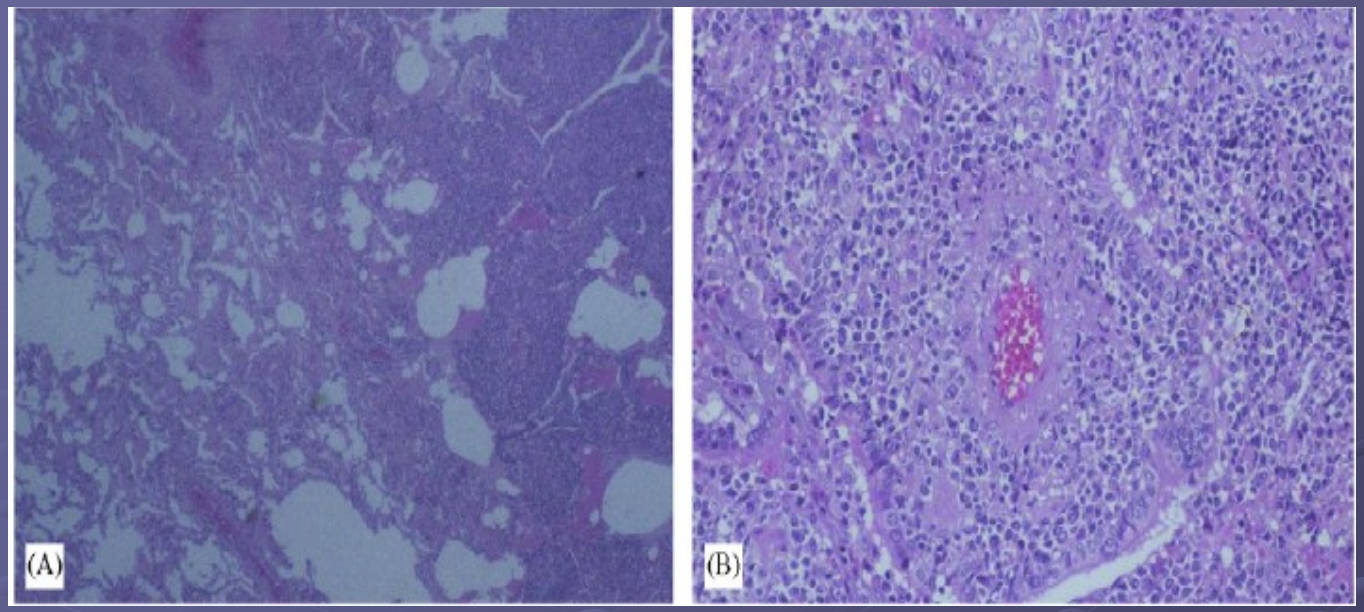
*WDL = small lymphocytic/lymphocytoplasmic lymphoma.

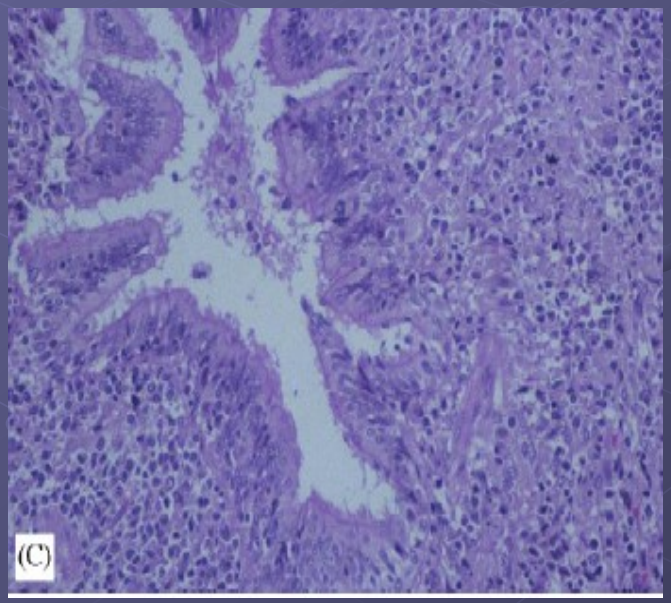
Swigris J, et al. Chest 2002; 122:2150-2164

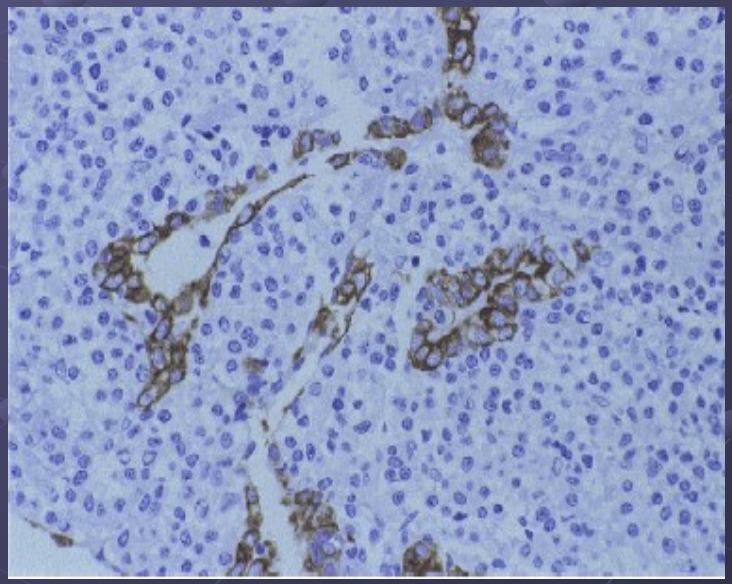

(A)
(B)
(D)




R
SCAN 44
TI 3.0 s
mA 50
kV 130
FoV







Papiris S, et al. Res Med 2007; 101:84-92

Extranodal marginal zone B-cell lymphoma of the lung in Sjögren's syndrome patients: Reappraisal of clinical, radiological, and pathology findings

Spyros A. Papiris[a,*], Ioannis Kalomenidis[b], Katerina Malagari[c], George E. Kapotsis[b], Nikolaos Harhalakis[d], Effrosyni D. Manali[e], Dimitra Rontogianni[f], Charis Roussos[b], Haralampos M. Moutsopoulos[g]

In conclusion, lung MZCL associated with pSs is characterized by an important dissociation between clinical expression and radiological pattern

A surgical lung biopsy is required to confidently distinguish LIP from pulmonary lymphoma, diffuse or nodular lymphoid hyperplasia and other interstitial diseases such as HP and NSIP.

Res Med 2007; 101:84-92

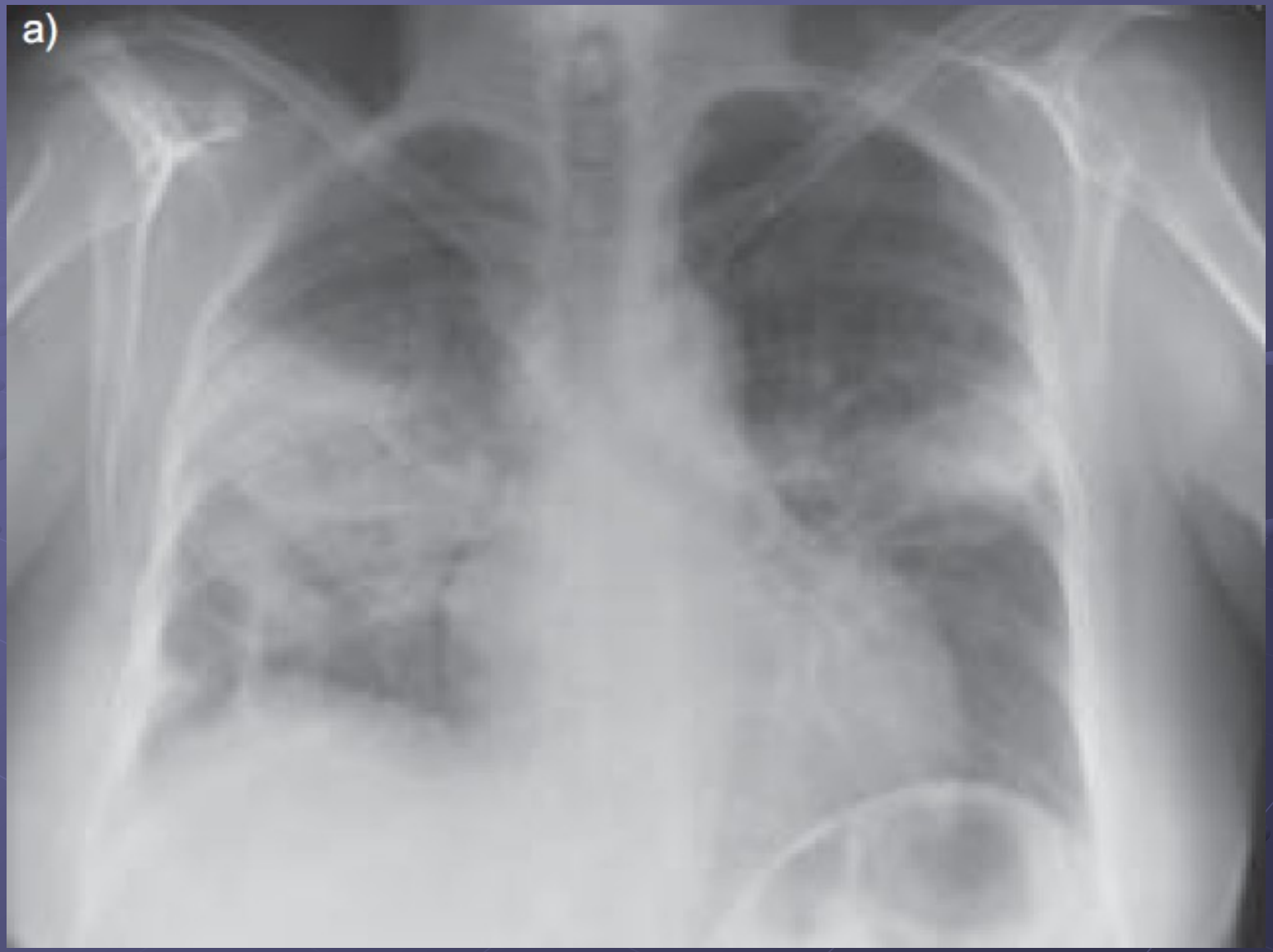
Eur Respir J 2006; 28: 422–446
DOI: 10.1183/09031936.06.00013505

SERIES "RARE INTERSTITIAL LUNG DISEASES"
Edited by C. Vogelmeier and U. Costabel
Number 3 in this Series

Cryptogenic organising pneumonia

J-F. Cordier

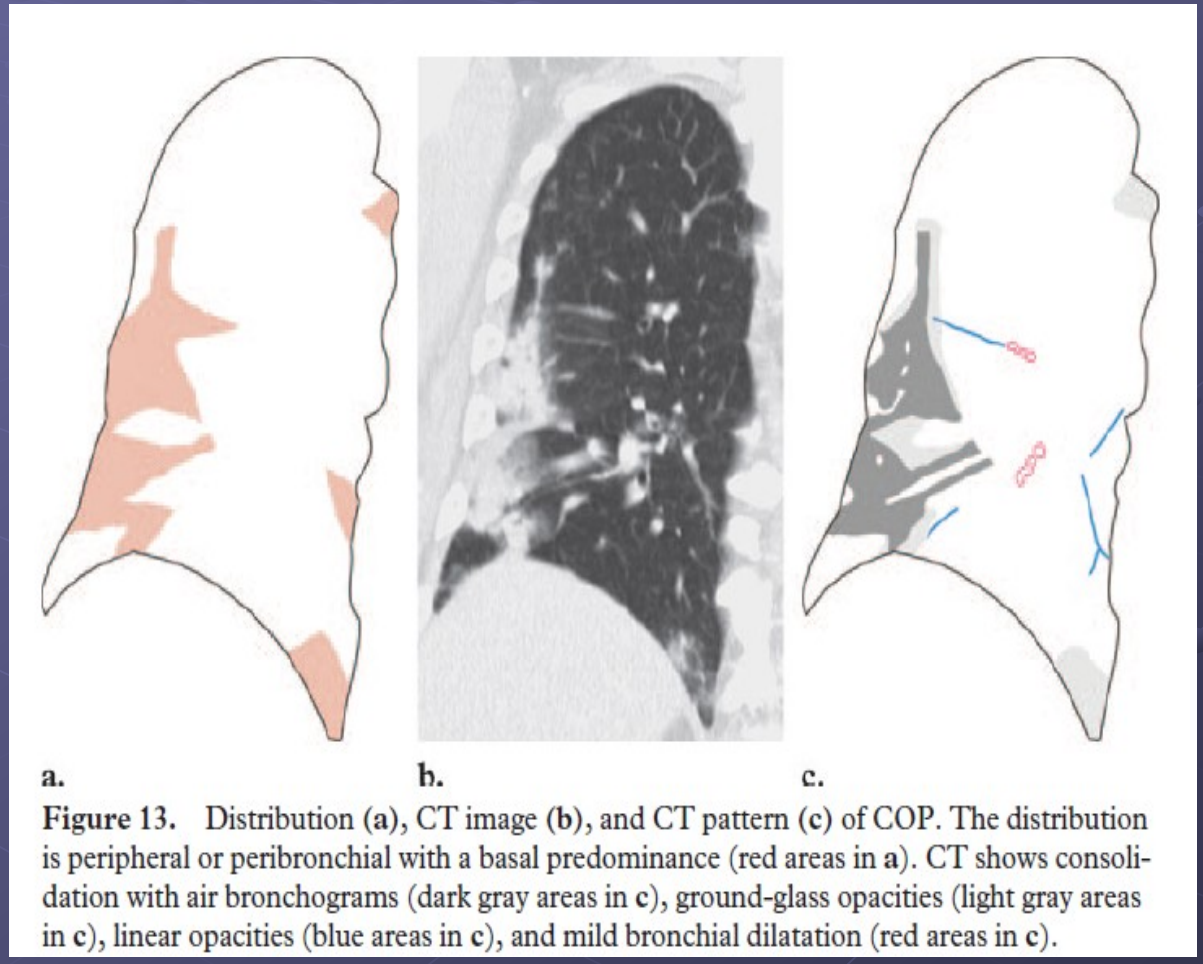
A DISTINCT ENTITY AMONG THE IDIOPATHIC INTERSTITIAL PNEUMONIAS


a)

Cryptogenic organizing pneumonia

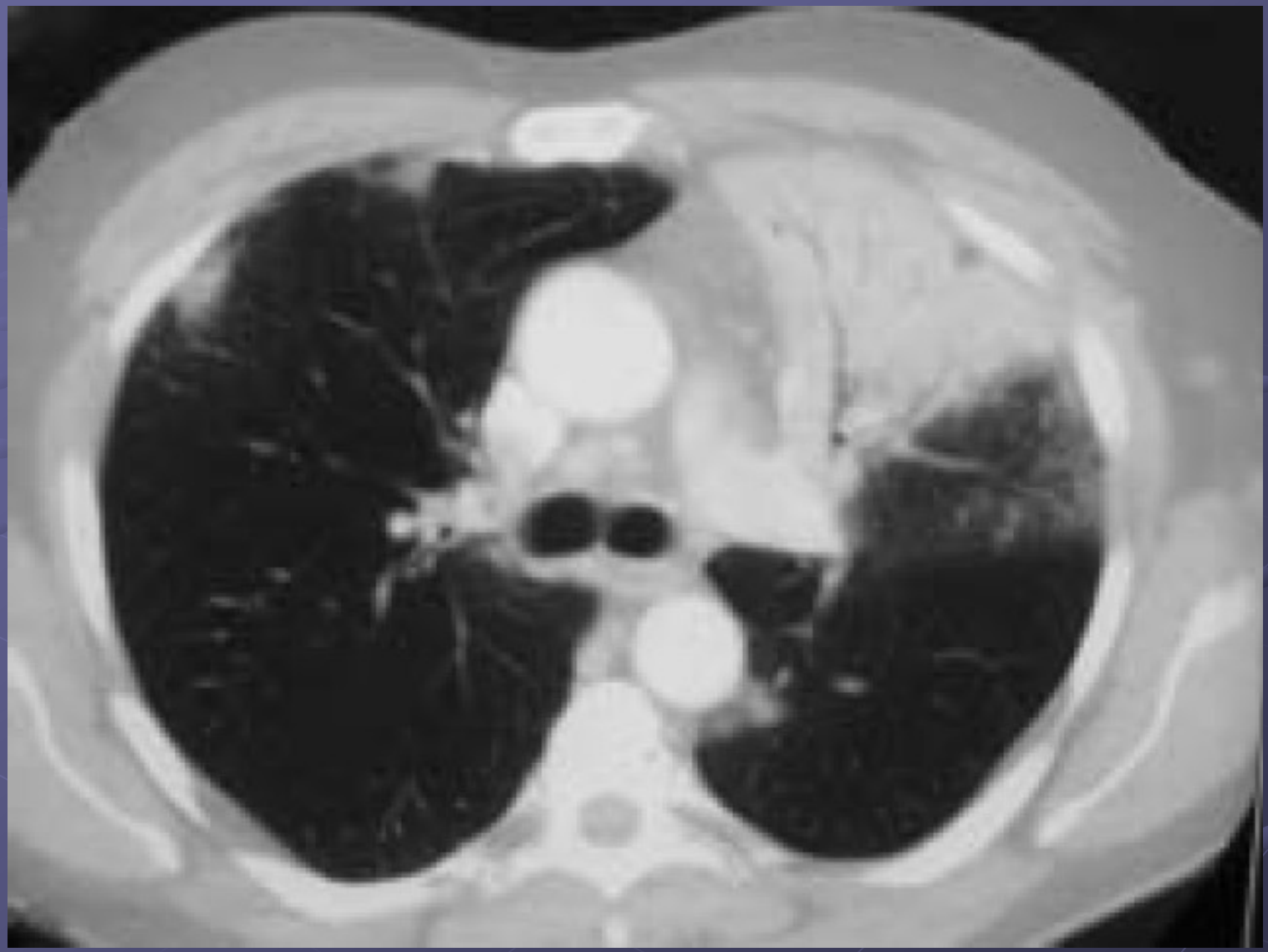
- A non infectious “pneumonia”
- Equal sex distribution
- Mean age of onset 50-60 years
- Non/ex smokers: smokers =2:1
- Short duration of symptoms (<3 mo)
- Cough, dyspnea, fever, weight loss, chills, myalgias
- Crackles
- No finger clubbing
- ↑ESR, CRP, neutrophils
- BAL: mixed pattern ↑ lymphocytes, ↑ neutrophils and eosinophils

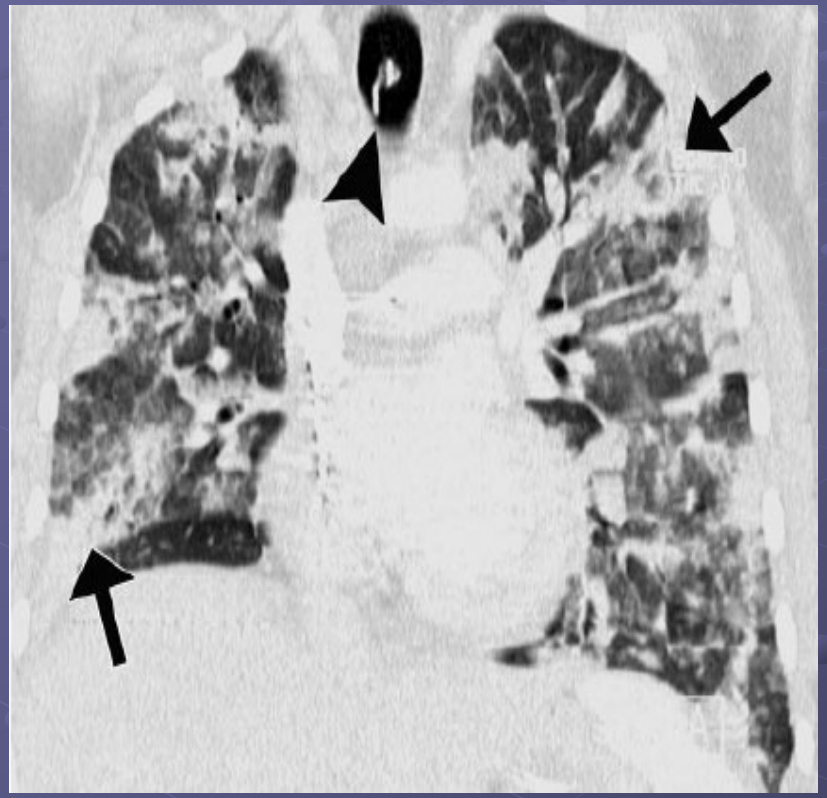
Cryptogenic organizing pneumonia

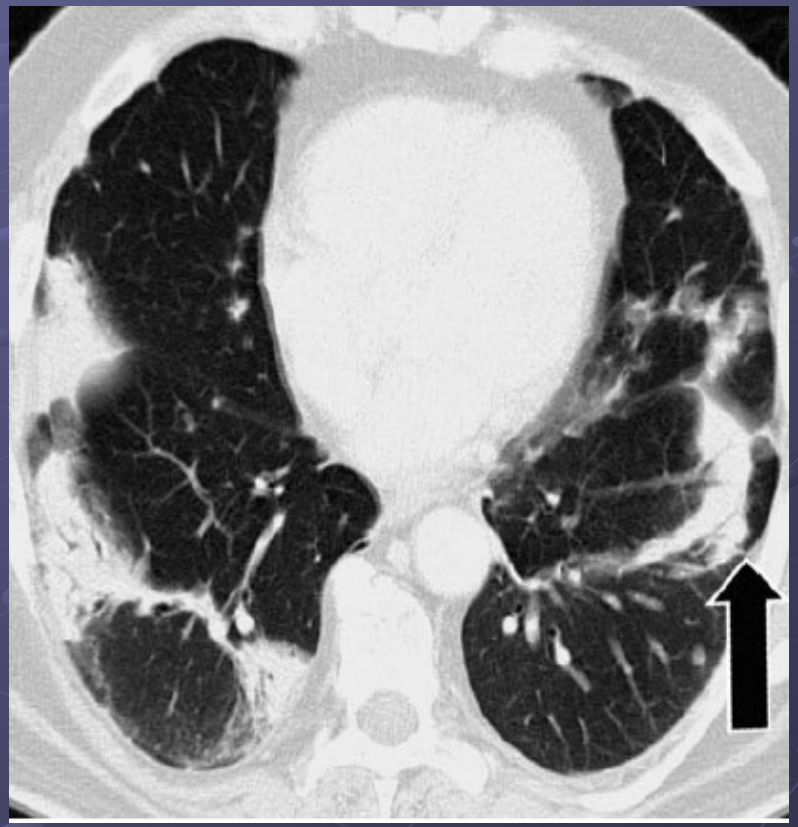


a. b. c.

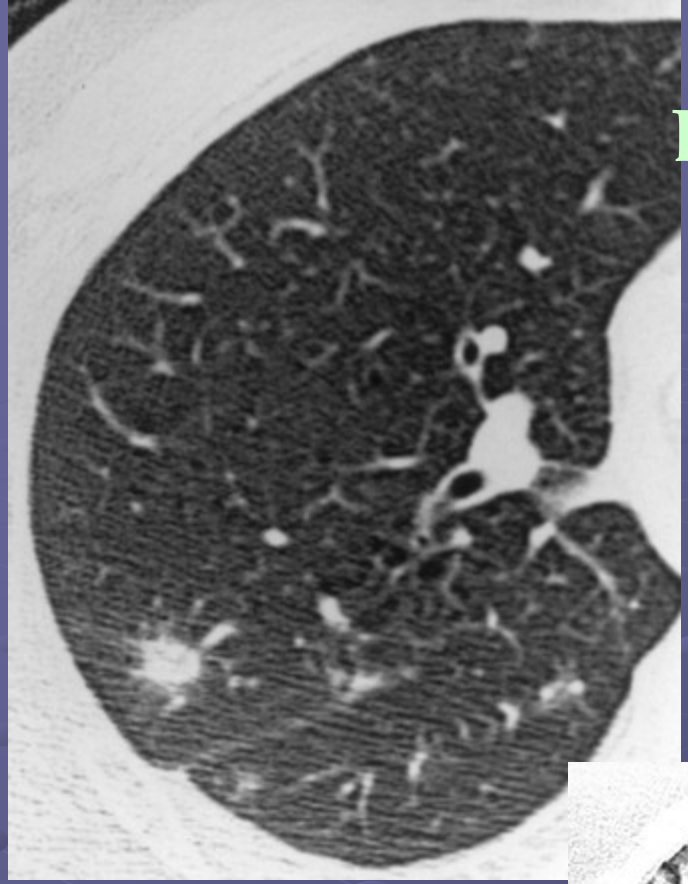
Figure 13. Distribution (**a**), CT image (**b**), and CT pattern (**c**) of COP. The distribution is peripheral or peribronchial with a basal predominance (red areas in **a**). CT shows consolidation with air bronchograms (dark gray areas in **c**), ground-glass opacities (light gray areas in **c**), linear opacities (blue areas in **c**), and mild bronchial dilatation (red areas in **c**).

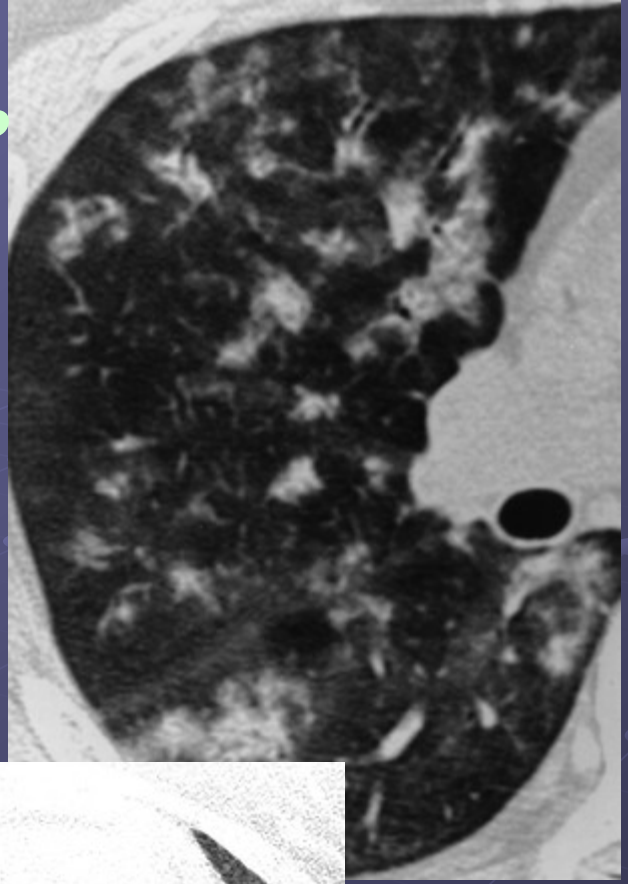






BOOP - COP





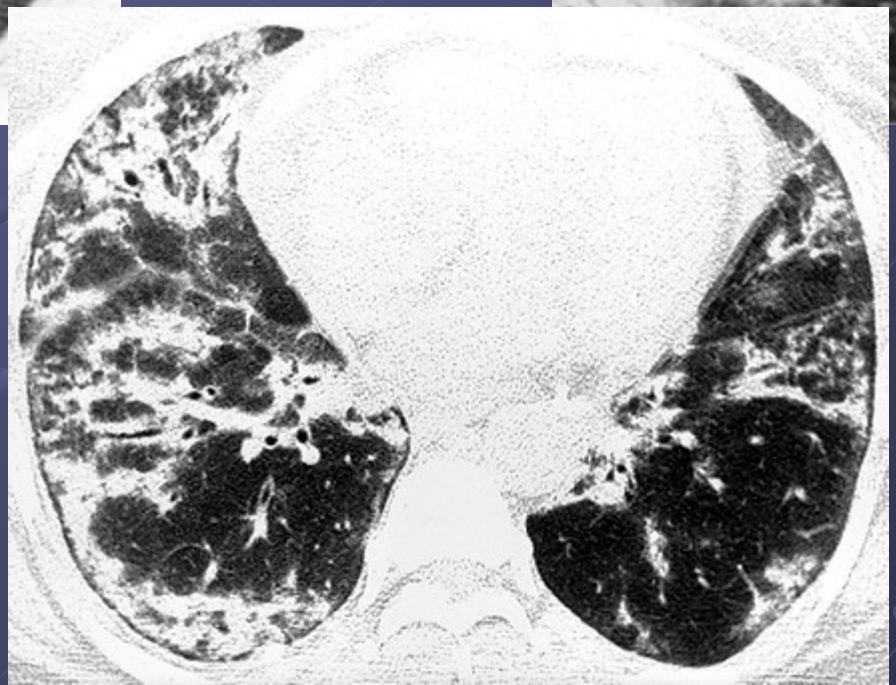


TABLE 3 Drugs identified as a cause of organising pneumonia

Drug	Reference
5-Aminosalicylic acid	[231, 232]
Acebutolol	[233]
Amiodarone	[90, 230, 233–240]
Amphotericin B	[241]
Bleomycin	[18, 242–252]
Busulfan	[230, 253, 254]
Busulfan and cyclophosphamide	[230]
Carbamazepine	[255, 256]; in association with carbamazepine induced lupus [257]
Cephalosporin (cefradin)	[258]
Chlorambucil	[259]
Doxorubicin	Possible recall after radiation to the breast [260]
Fluvastatin	[261]
Gold salts	[262, 263]
Hexamethonium	[264]
Interferon-α	[264, 265]
Interferon-α2b, pegylated interferon α2b	[266]
Interferon-α + cytosine arabinoside	[267]
Interferon + ribavirin	[266]
Interferon-β1a	[268, 269]
L-tryptophan	[270]
Mesalazine	[271]; in patients with ulcerative colitis [272]
Methotrexate	[230]
Minocycline	[273]
Nilutamide	[274]
Nitrofurantoin	[230, 275, 276]
Phenytoin	[277]
Sirolimus	In renal [278] and cardiac [279] transplant recipients
Sotalol	[280]
Sulfasalazine	[231]; in a patient with Crohn's disease [281]; in a patient with rheumatoid arthritis [282]; in patients with ulcerative colitis [283, 284]
Tacrolimus	[285]
Ticlopidine	In a patient with giant-cell temporal arteritis [286]
Trastuzumab	[287]
Vinbarbital-aprobarbital	[288]

ERJ 2006; 28:422-446

TABLE 2 Infectious causes of organising pneumonia

Organism	Reference
Bacteria	
Burkholderia cepacia	[183]
Chlamydia pneumoniae	[184, 185]
Coxiella burnetii	[186, 187]
Legionella pneumophila	[95, 188–194]
Mycoplasma pneumoniae	[95, 189, 195–197]
Nocardia asteroides	[198, 199]
Pseudomonas aeruginosa	[200]
Serratia marcescens	[201]; in lung transplant recipient [200]
Staphylococcus aureus	In lung transplant recipient [200]
Streptococcus pneumoniae	[5, 6, 202]
Viruses	
Adenovirus	[203]
Cytomegalovirus	[203, 204]
Herpes virus	In lung transplant recipient [200]
HIV	[205–210]; in a pregnant patient using cocaine [205]; following highly active antiretroviral therapy introduction [211]
Influenza virus	[189, 212–214]
Parainfluenza virus	[215]
Human herpes virus-7	[216] after lung transplantation
Respiratory syncytial virus	Overlap of organising pneumonia and eosinophilic pneumonia [136]
Parasites	
Plasmodium vivax	[217]
Dirofilaria immitis	[218]
Fungi	
Cryptococcus neoformans	[219]
Penicillium janthinellum	[220]
Pneumocystis jiroveci	In patients with HIV infection [207, 221, 222]; in a lung transplant recipient [200]; in a liver transplant patient [223]; following highly active antiretroviral therapy introduction [211]

TABLE 9. CLINICAL SETTINGS ASSOCIATED WITH ORGANIZING PNEUMONIA PATTERN

As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
Organizing diffuse alveolar damage
Organizing infections
Organization distal to obstruction
Organizing aspiration pneumonia
Organizing drug reactions, fume, and toxic exposures
Collagen vascular disease
Extrinsic allergic alveolitis/hypersensitivity pneumonitis
Eosinophilic lung disease
Inflammatory bowel disease
As a secondary reaction in chronic bronchiolitis
As a reparative reaction around other processes (including abscesses, Wegener's granulomatosis, neoplasms, and others)

Definition of abbreviation: COP = crytogenic organizing pneumonia.

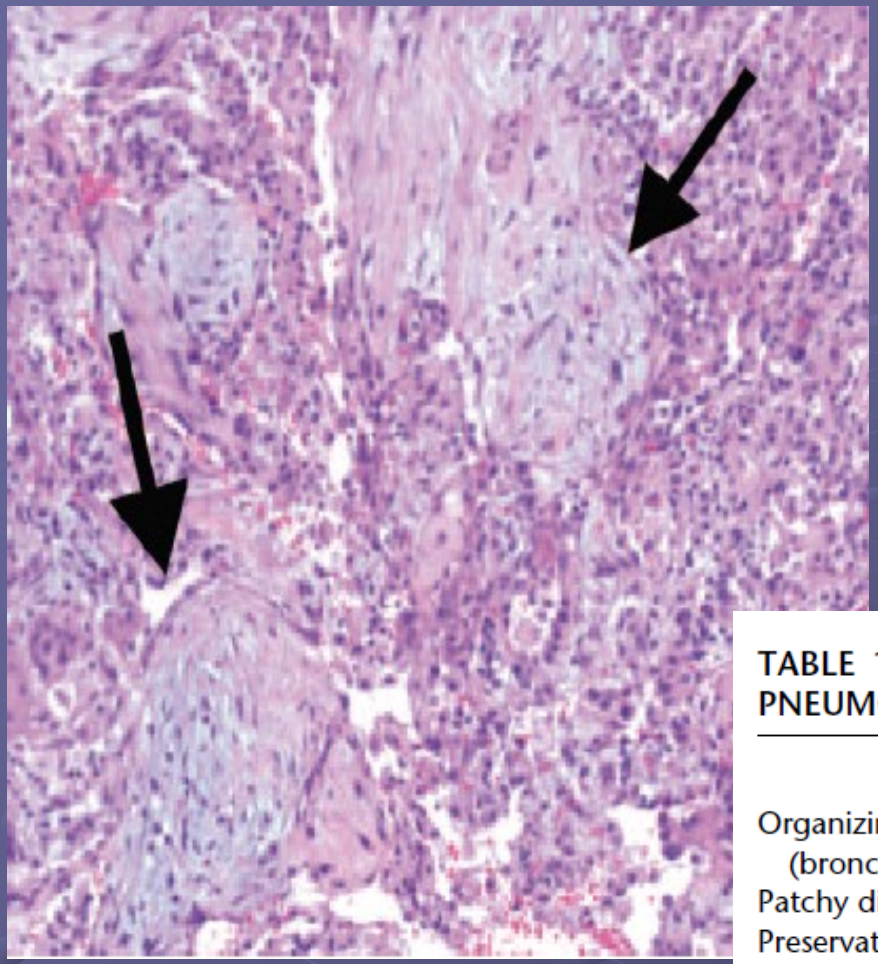


TABLE 10. HISTOLOGIC FEATURES OF ORGANIZING PNEUMONIA PATTERN

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

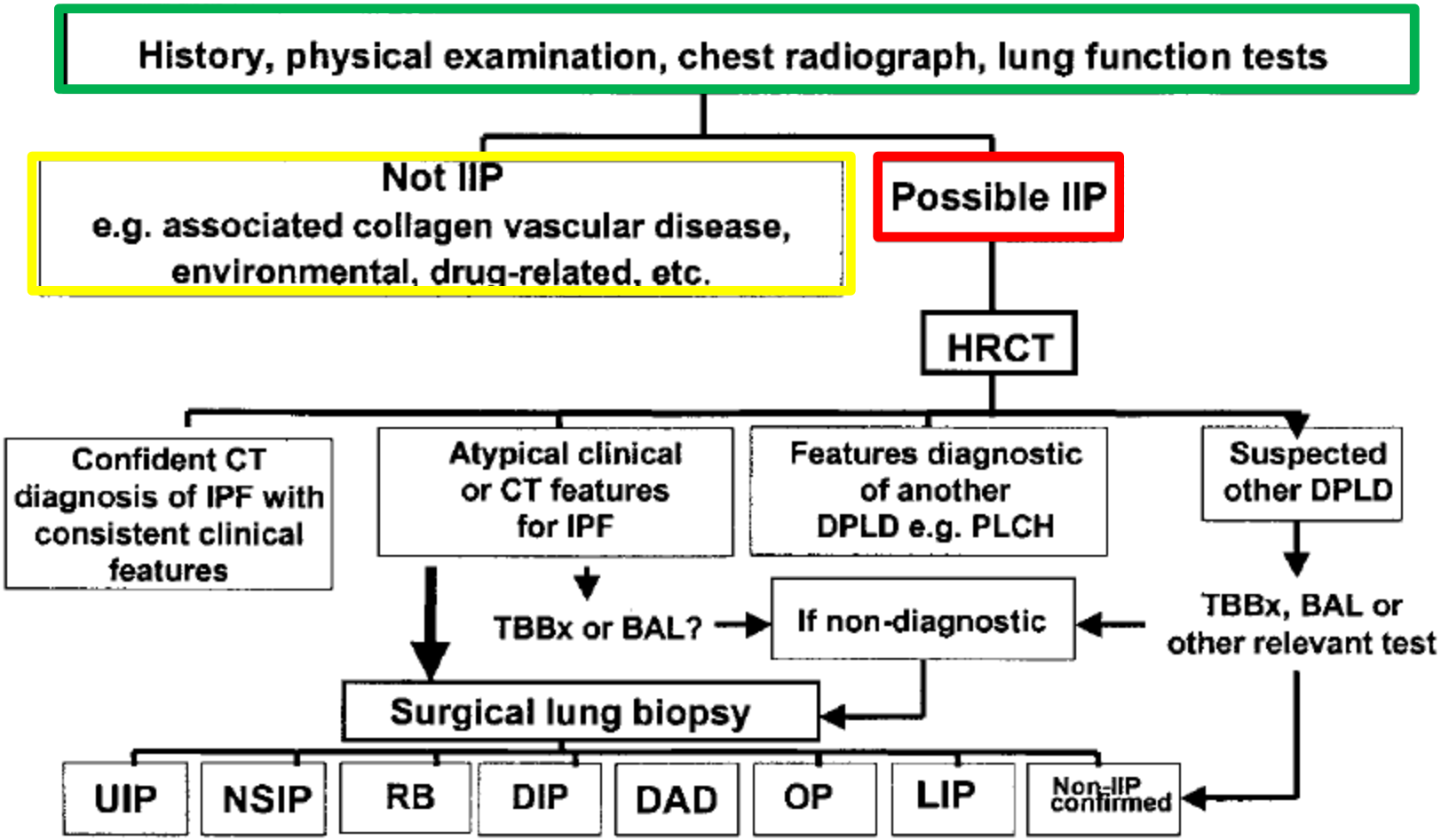
Cryptogenic organizing pneumonia: clinical course

- The majority: excellent response to corticosteroid treatment
- Frequent relapses at treatment tapering
- Spontaneous recovery in a minority
- Some cases progress to respiratory failure refractory to tx and death

Table 1
Clinical Features of Patients with IIPs according to the ATS-ERS Consensus Statement

Type of IIP	Mean Age at Onset (y)	Gender Distribution	Most Prominent Symptoms	Type of Onset	Association with Smoking	Prognosis	Response to Corticosteroids
IPF	>50	More common in men	Dyspnea, cough	Gradual	Currently under discussion	Poor (median survival, 2.5–3.5 y)	Poor, if any
NSIP	40–50	Equal	Dyspnea, cough, fatigue	Gradual or subacute	None	Variable, better than in UIP	Good
COP	55	Equal	Cough, mild dyspnea, fever	Subacute	More common in nonsmokers	Complete recovery in most patients	Excellent
RB-ILD	30–40	More common in men	Mild dyspnea, cough	Gradual	Required for diagnosis	Good after smoking cessation	Good
DIP	30–40	More common in men	Dyspnea, cough	Insidious	In most cases	Generally good after smoking cessation	Good
LIP	40–50	More common in women	Cough, dyspnea	Slow	None	Variable	Variable
AIP	50	Equal	Dyspnea	Acute	None	High mortality rate (≥50%)	Not proved

Diagnostic Process in DPLD



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REVIEW

Beyond a consensus classification for idiopathic interstitial pneumonias: progress and controversies

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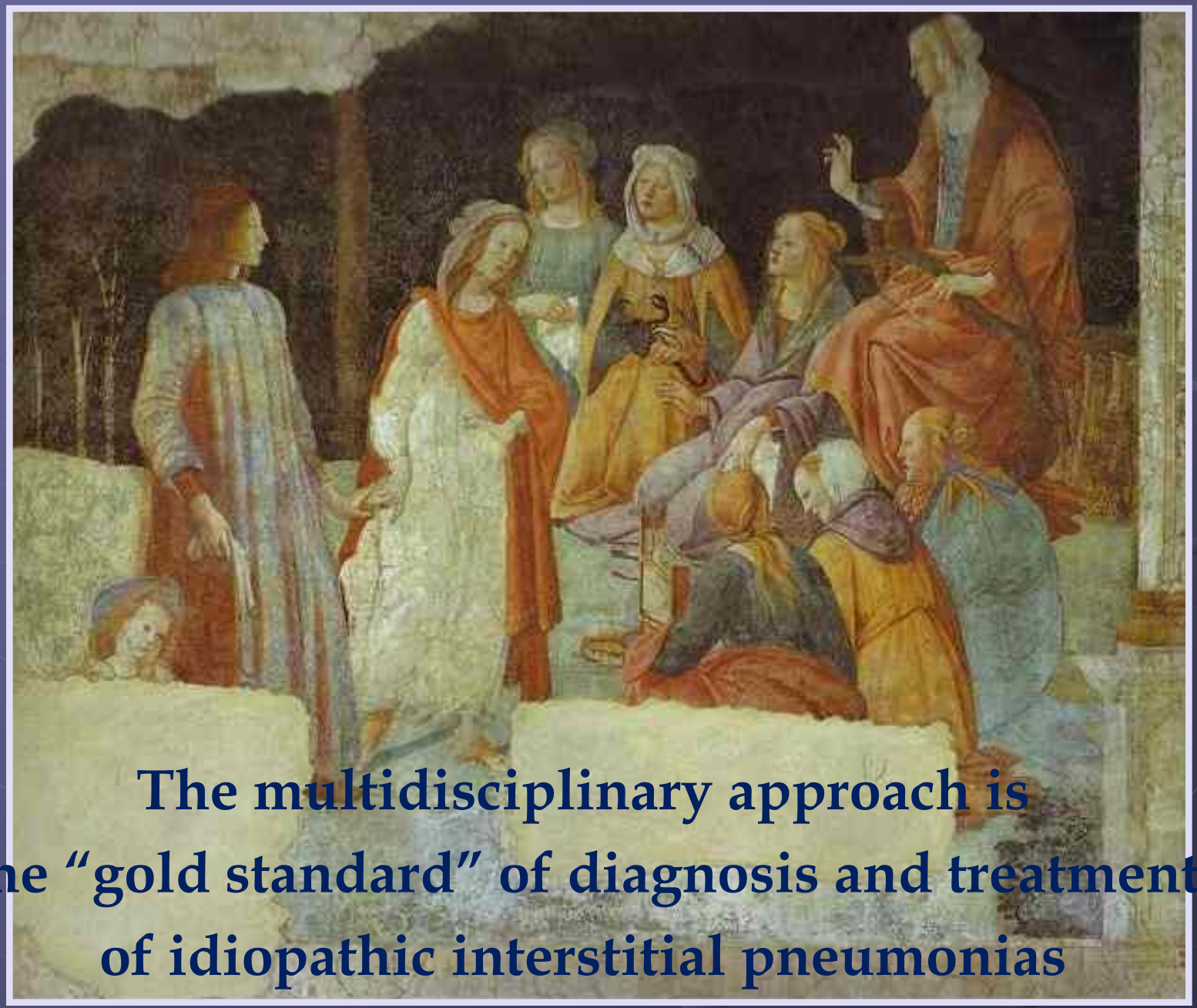
Histopathological classification schemes provide the underpinning for separating idiopathic interstitial pneumonias

Into clinically meaningful groups

Take home messages

- The new classification of IIPs is in progress
- IIPs are rare conditions
- Not all patients should undergo surgical lung biopsy
- When typical radiologic features do no not exist,
  a surgical biopsy is invaluable
- It is particularly important to re-evaluate the patient in search of a specific etiology when
  NSIP, DAD, and LIP are found on biopsy
- It is recommended that all patients be considered for recruitment to high quality clinical trials



The multidisciplinary approach is the "gold standard" of diagnosis and treatment of idiopathic interstitial pneumonias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