ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ ΕΚΠΑ

‘ΜΟΝΑΔΕΣ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ’

2018-2019

Διάχυτα διάμεσα νοσήματα των πνευμόνων (ΔΔΠ)

Interstitial lung diseases (ILD)

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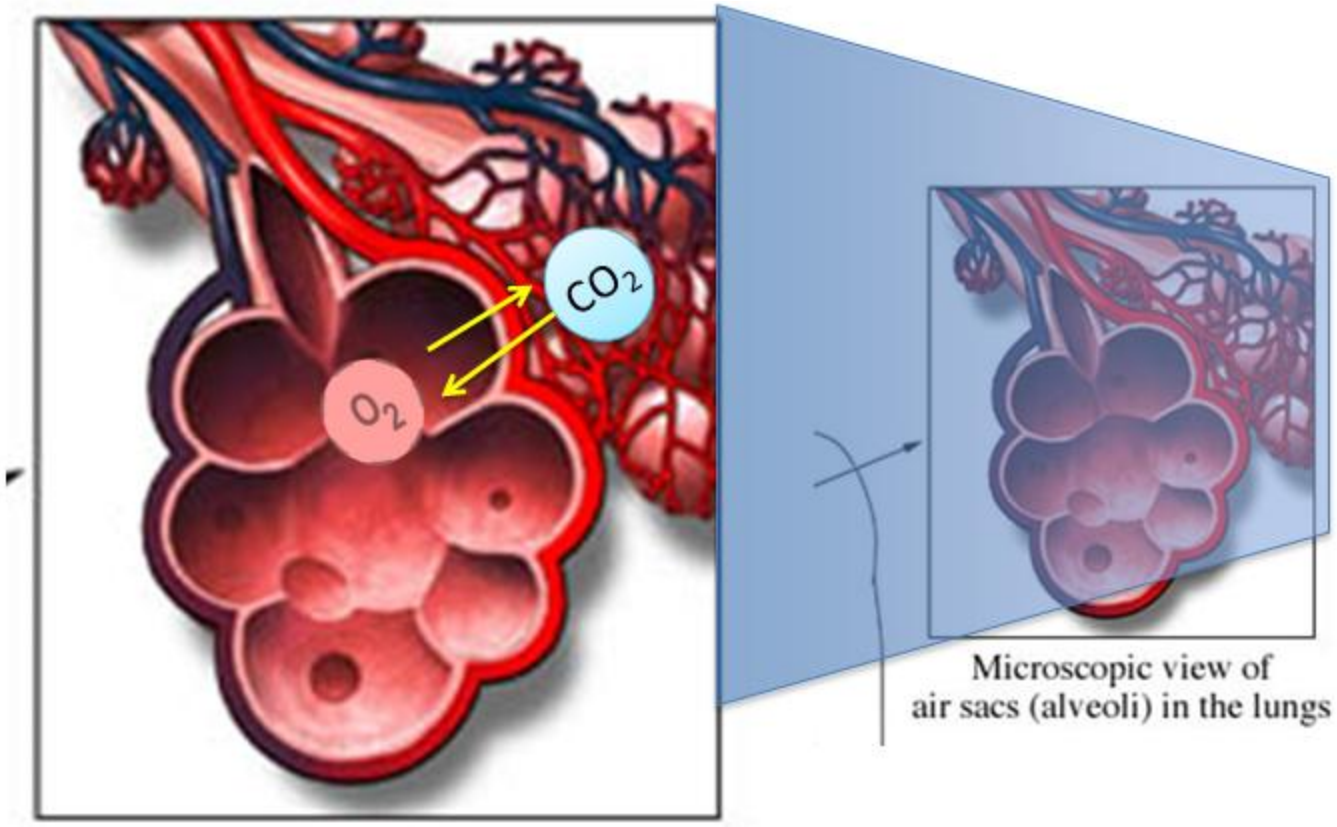
Επιμελητής Α’ ΕΣΥ
7η Πνευμονολογική Κλινική
ΝΝΘΑ ‘’ Η ΣΩΤΗΡΙΑ”

WHAT IS THE INTERSTITIUM?



The interstitial lung diseases (ILDs) are a group of diseases affecting the interstitium of the lungs. **Inflammation** and **scar tissue** are commonly seen.

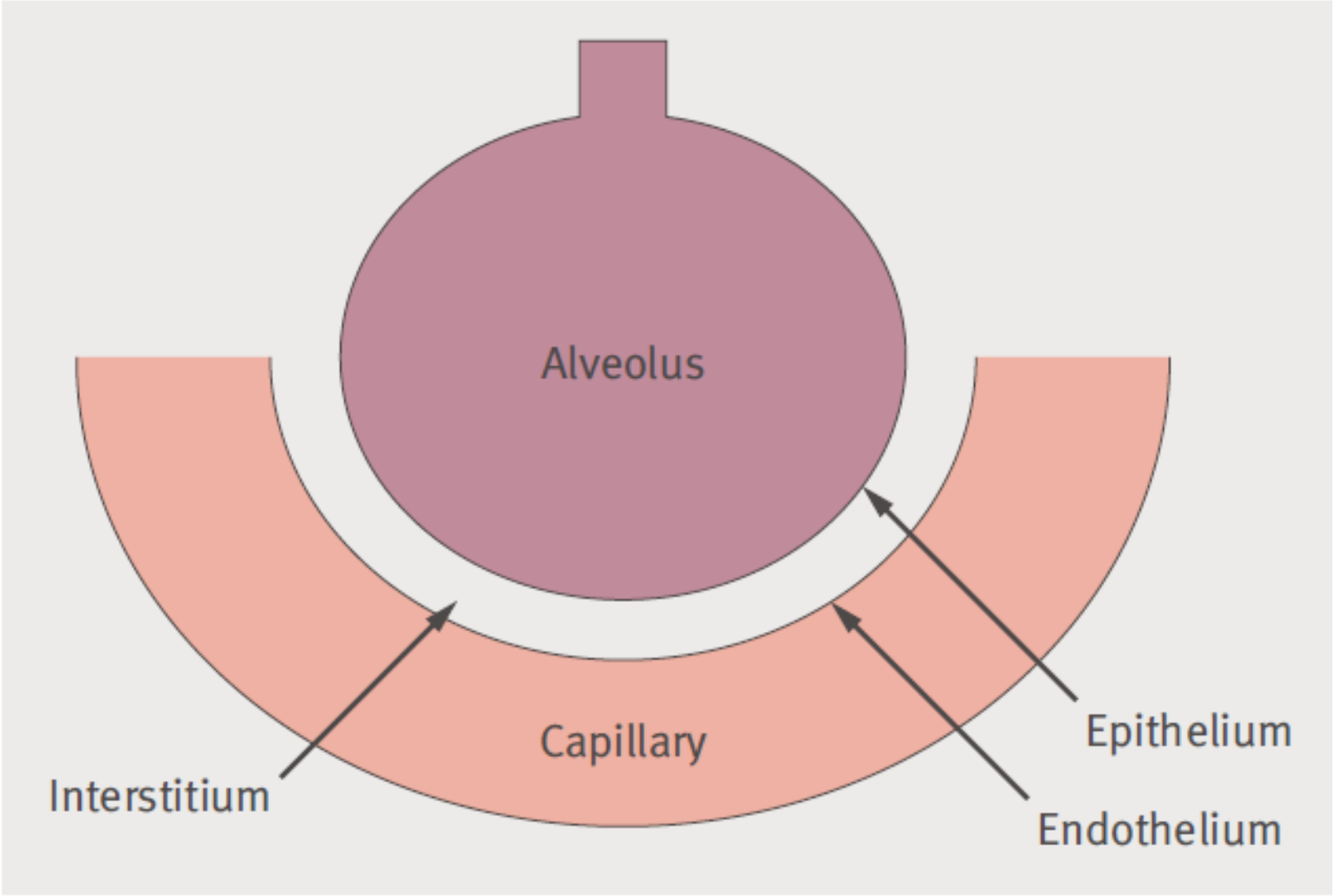
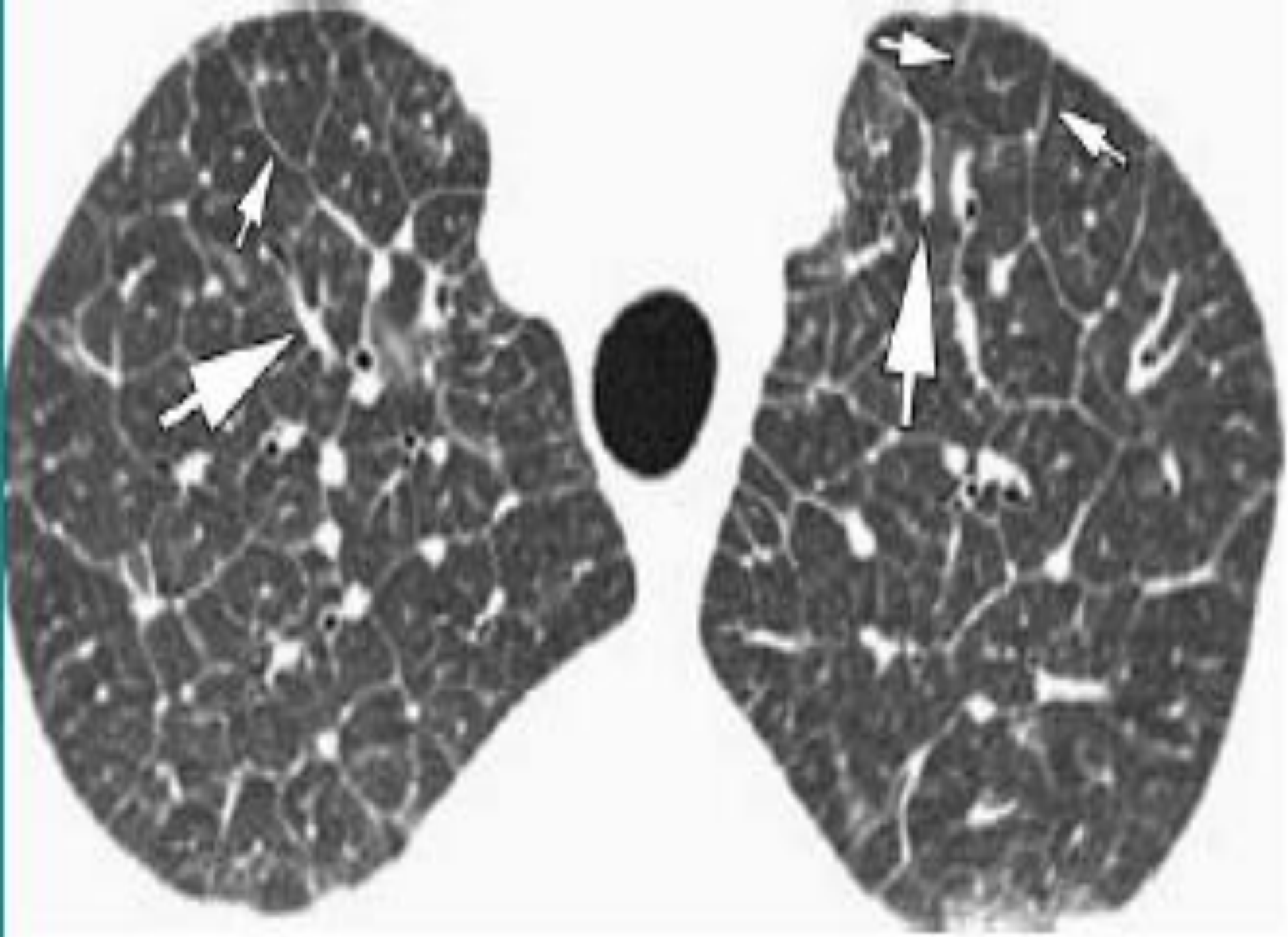


Fig 1 | The pulmonary interstitium is the microscopic space between the alveolar epithelium and capillary endothelium and is crucial for gas exchange



Key Pattern

Reticular pattern

Smooth
Nodular
Irregular

Nodular pattern

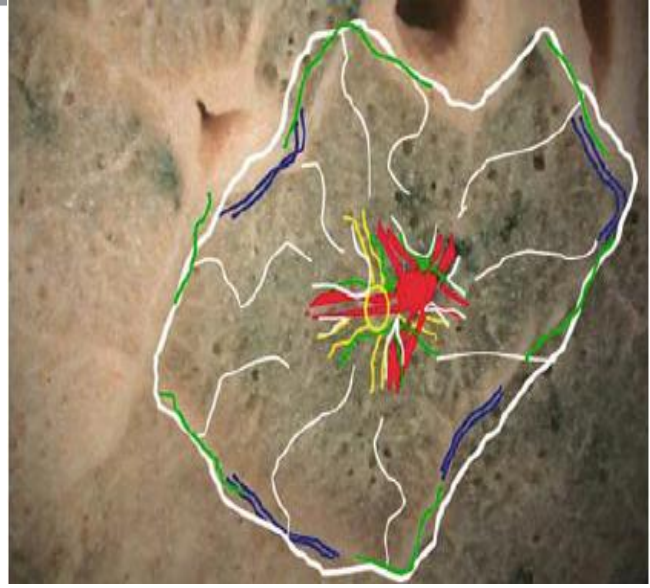
Centrilobular
Random
Perilymphatic

Alveolar pattern

Mixed-density, acute
Mixed-density, chronic
Mosaic oligemia with air-trapping
Tree-in-bud

Cystic pattern

Clusters of grapes
String of pearls
Honeycombing
Random cysts

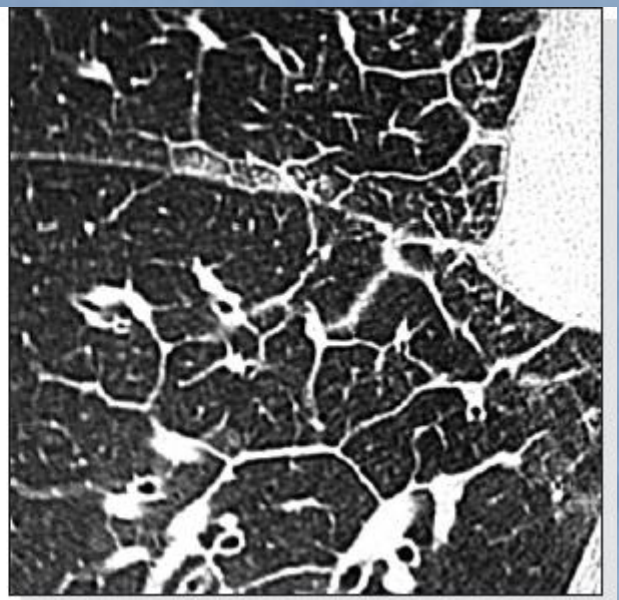


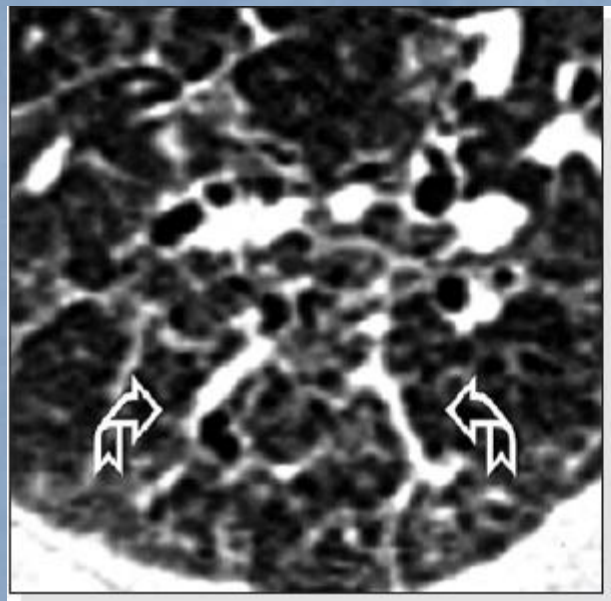
Reticular pattern

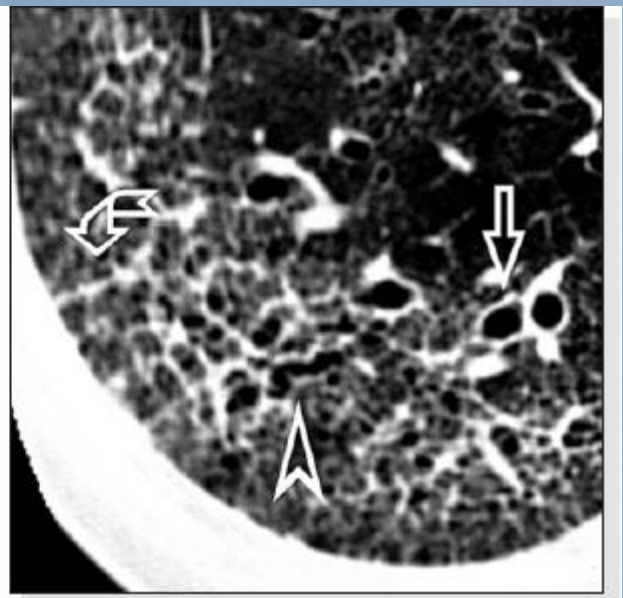
Nodular pattern

Alveolar pattern

Cystic pattern





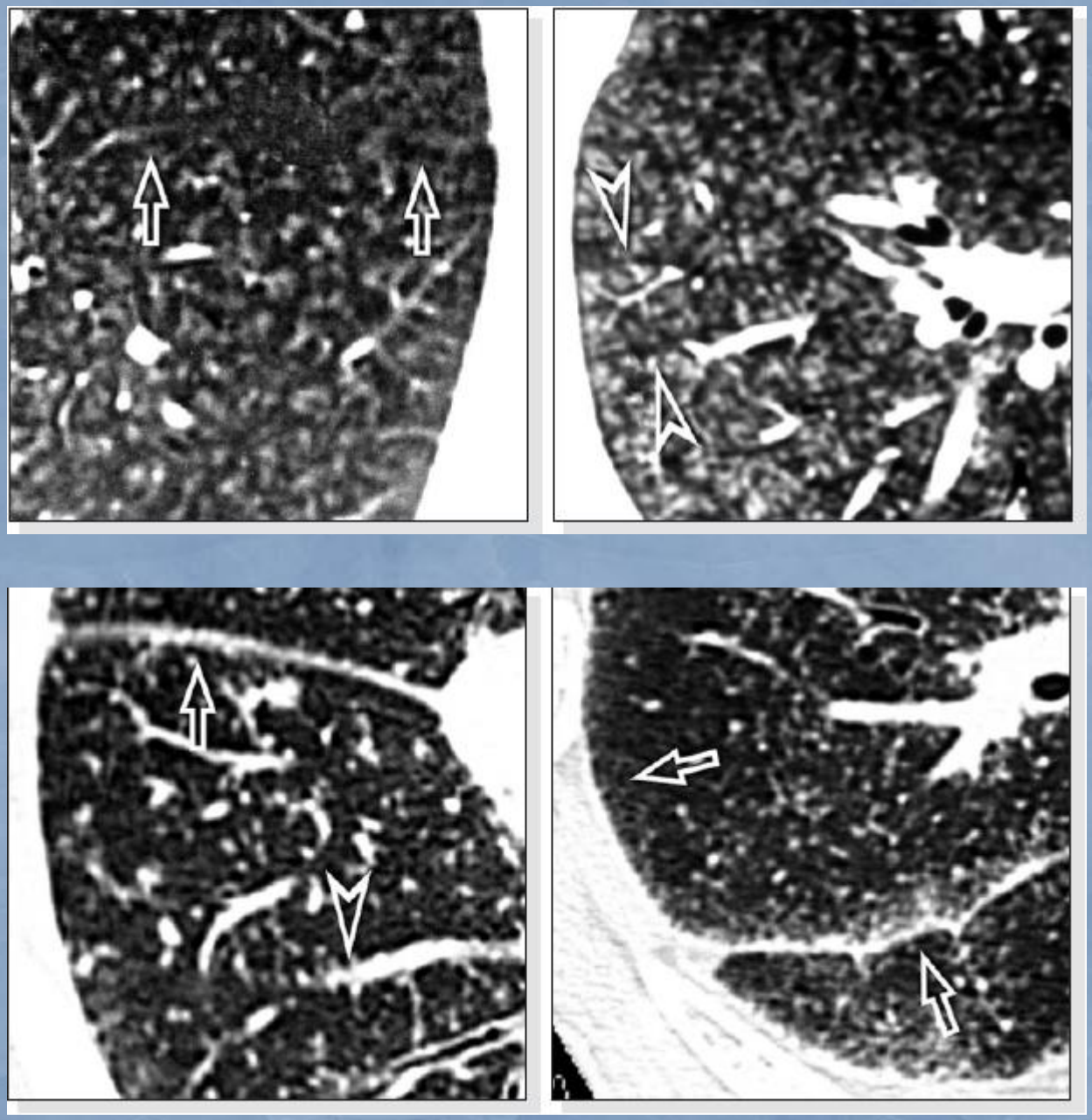


Reticular pattern

Nodular pattern

Alveolar pattern

Cystic pattern

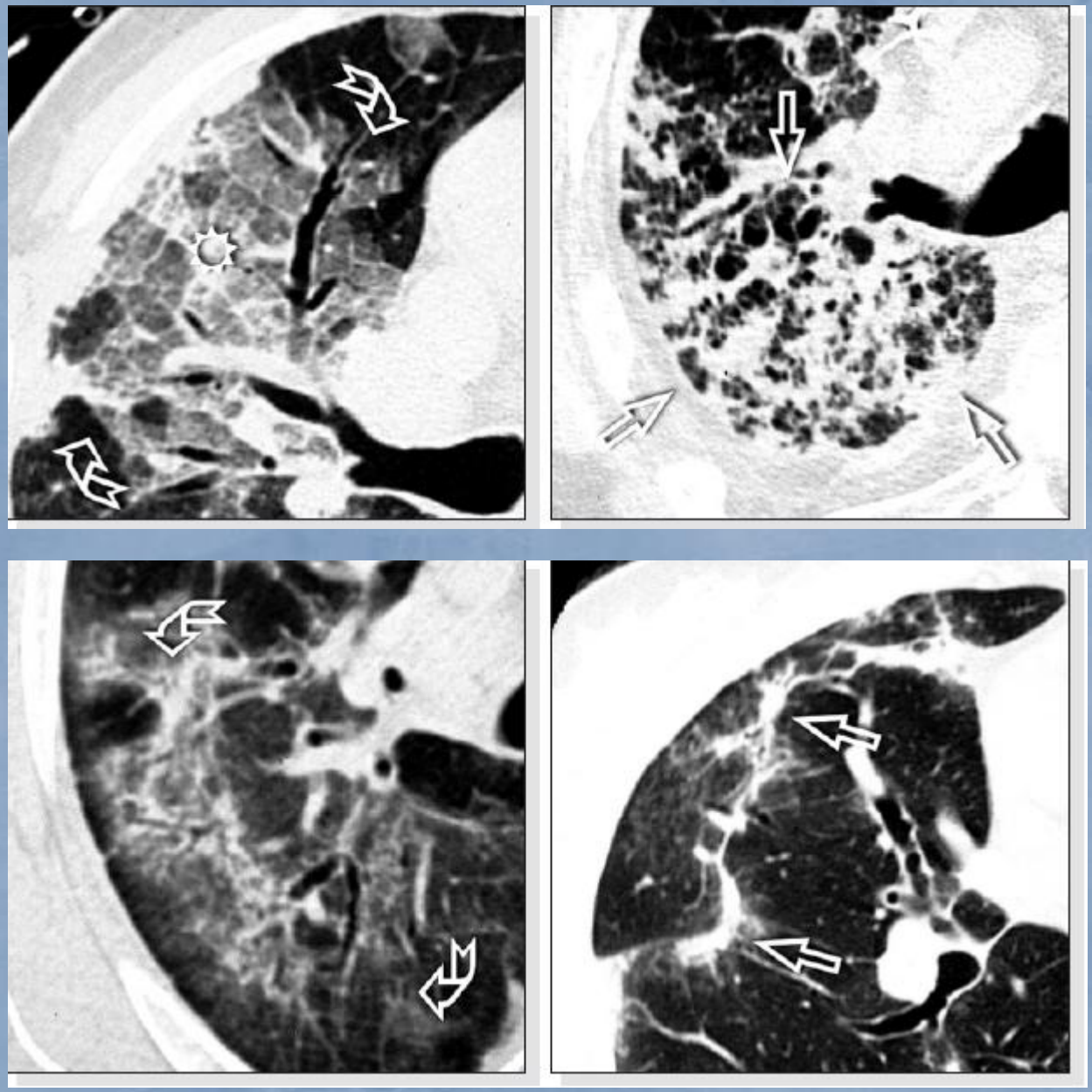


Reticular pattern

Nodular pattern

Alveolar pattern

Cystic pattern

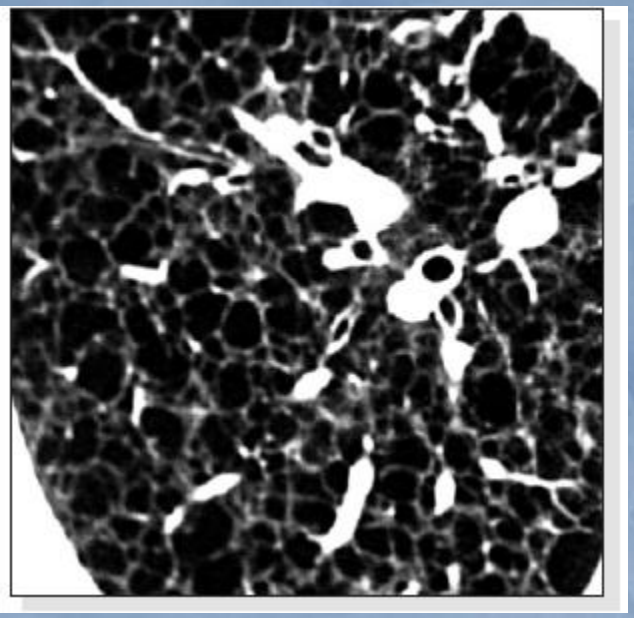


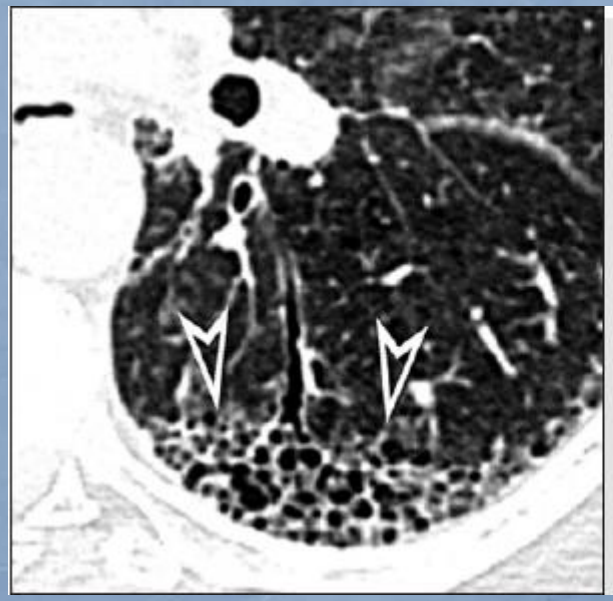
Reticular pattern

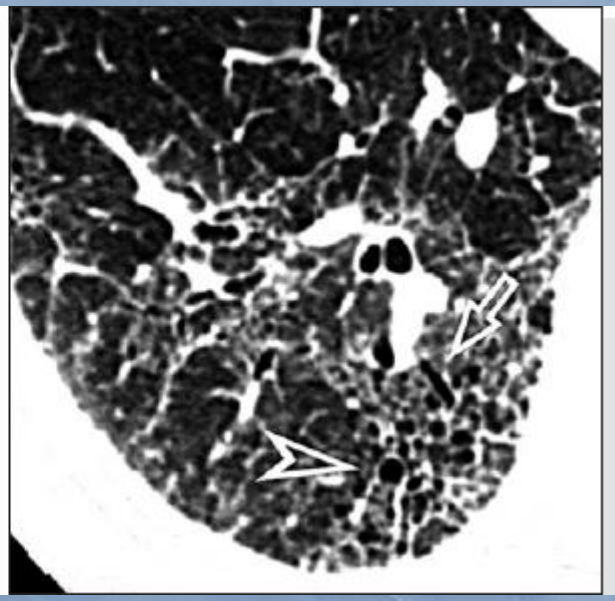
Nodular pattern

Alveolar pattern

Cystic pattern







ΔΙΑΜΕΣΕΣ ΠΝΕΥΜΟΝΟΠΑΘΕΙΕΣ

ΓΕΝΙΚΑ

- Ανομοιογενής ομάδα μη λοιμωδών, μη νεοπλασματικών παρεγχυματικών παθήσεων του πνεύμονος, χαρακτηριζόμενες από αποδιοργάνωση των κυψελιδικών τοιχωμάτων και απώλεια των λειτουργικών τριχοειδοκυψελιδικών μονάδων.

ILD
> 500

- Ταξινομούνται μαζί λόγω πολλών κοινών κλινικών, παθοφυσιολογικών, απεικονιστικών και παθολογοανατομικών χαρακτηριστικών.

- Χαρακτηρίζονται από χρονία φλεγμονή και προοδευτική ίνωση του διαμέσου ιστού.

Interstitial Lung Diseases

- ILD of Known Cause or Association
  - Medications
  - Radiation
  - Connective Tissue Disease
  - Vasculitis & DAH
  - Hypersensitivity Pneumonitis
  - Pneumoconioses
- Idiopathic Interstitial Pneumonias
- Sarcoidosis & Other Granulomatous Diseases
- Other
  - LAM
  - Pulmonary LCH
  - Eosinophilic Pneumonias
  - Alveolar Proteinosis
  - Genetic Syndromes

Adapted from: ATS/ERS Guidelines for IIP. *Am J Respir Crit Care Med* 2002

Reason for a specific diagnosis in IIPs

- Pathogenesis varies
- Prognosis varies
- Treatment varies
- Clinical trial eligibility requirements

Reversible and self-limiting (RB-ILD)

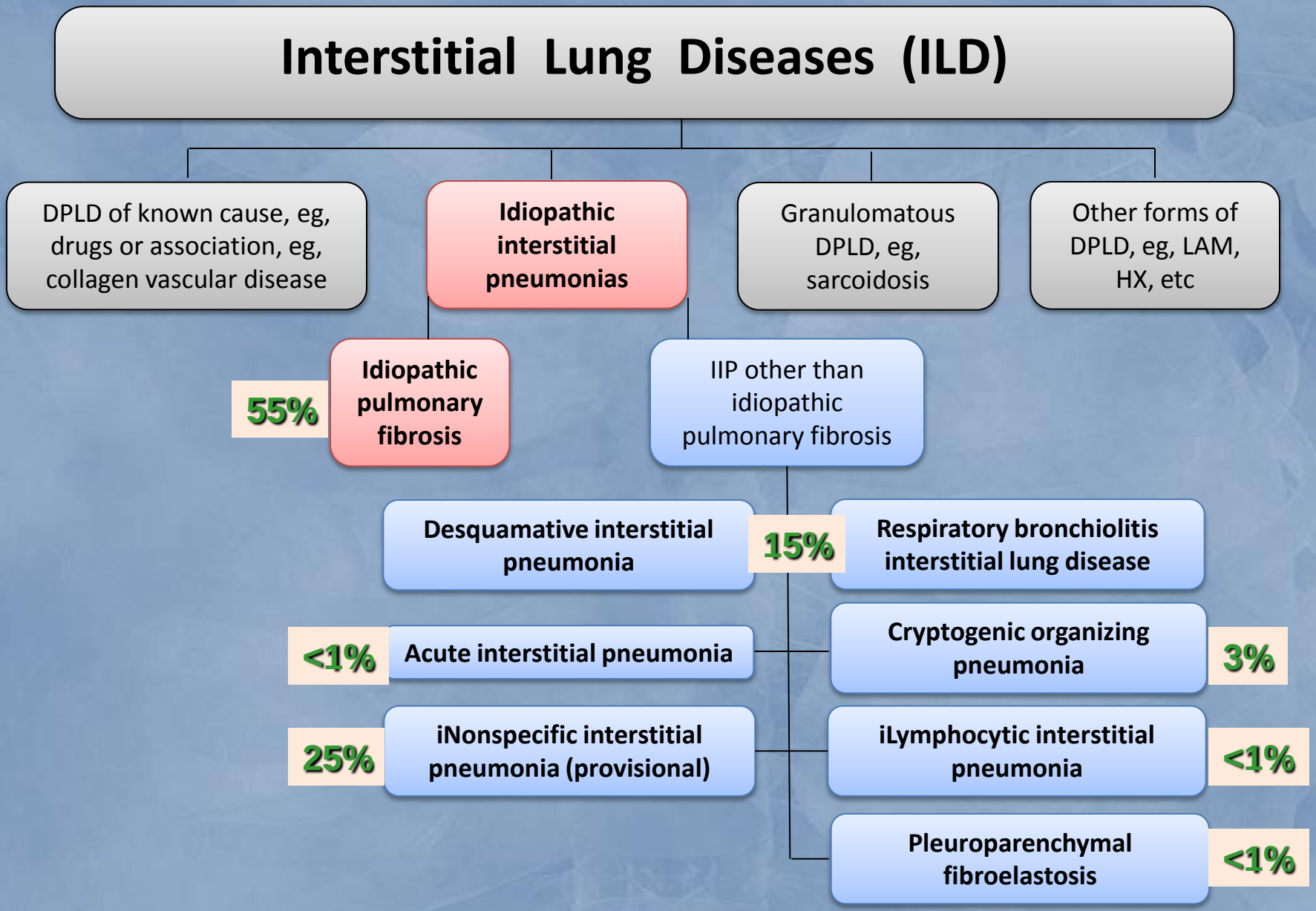
Reversible but risk of progression (cellular NSIP, DIP, COP)

Stable with residual disease (some fibrotic NSIP)

Progressive, irreversible disease with potential stabilization (fibrotic NSIP)

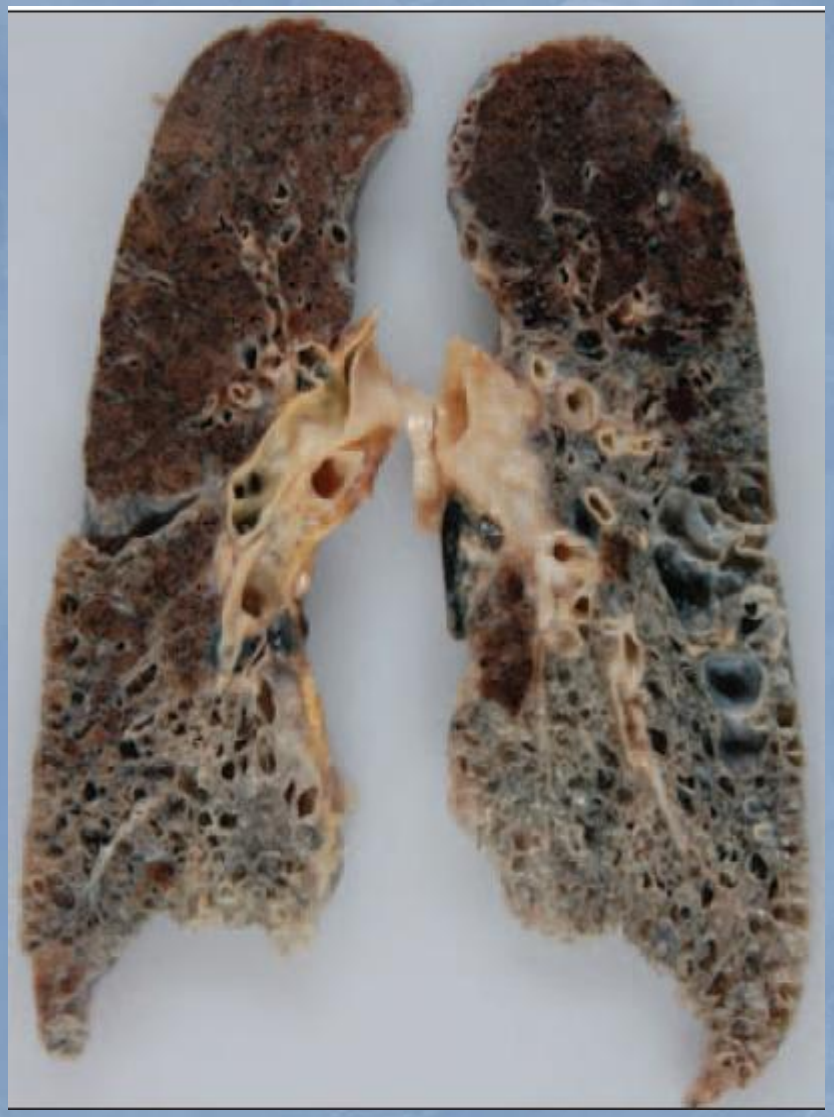
Progressive, irreversible disease despite treatment (e.g. IPF)

Interstitial Lung Diseases (ILD)



Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

Idiopathic Pulmonary Fibrosis (IPF)



Η ιδιοπαθής πνευμονική ίνωση (IPF) είναι μια μορφή χρόνιας, προοδευτικά εξελισσόμενης, ινωτικού τύπου διάμεσης πνευμονοπάθειας, άγνωστης αιτιολογίας, που προσβάλλει κυρίως ηλικιωμένα άτομα, περιορίζεται στο αναπνευστικό σύστημα και χαρακτηρίζεται από το ιστολογικό/ακτινολογικό πρότυπο της συνήθους διάμεσης πνευμονίας (UIP).

Η διάγνωση απαιτεί τον αποκλεισμό άλλου τύπου διάμεσων πνευμονοπαθειών που σχετίζονται με περιβαλλοντική έκθεση, φάρμακα ή συστηματικά νοσήματα.

Raghu G *et al*, AJRCCM 2011

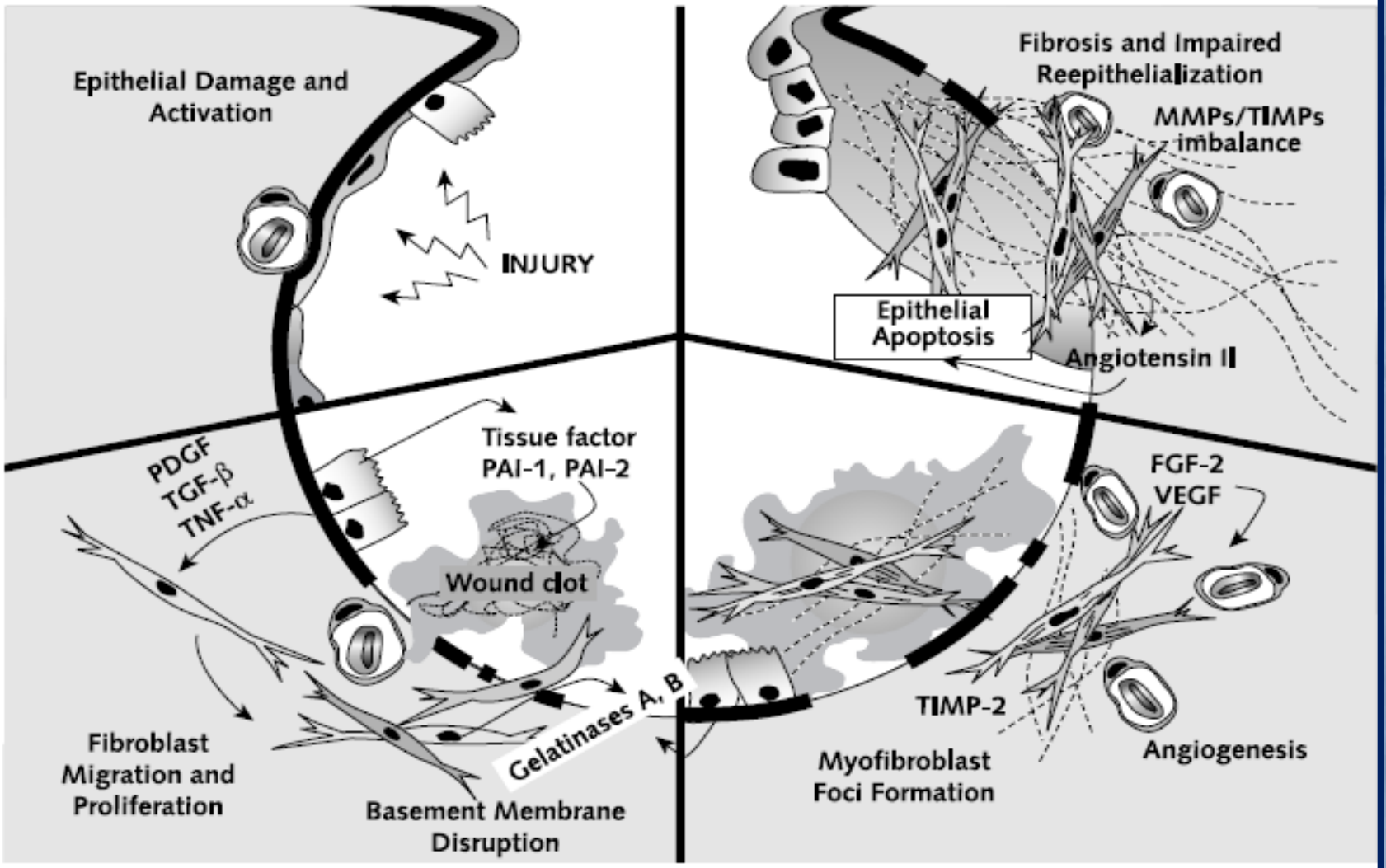
Idiopathic pulmonary fibrosis
Risk factors

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

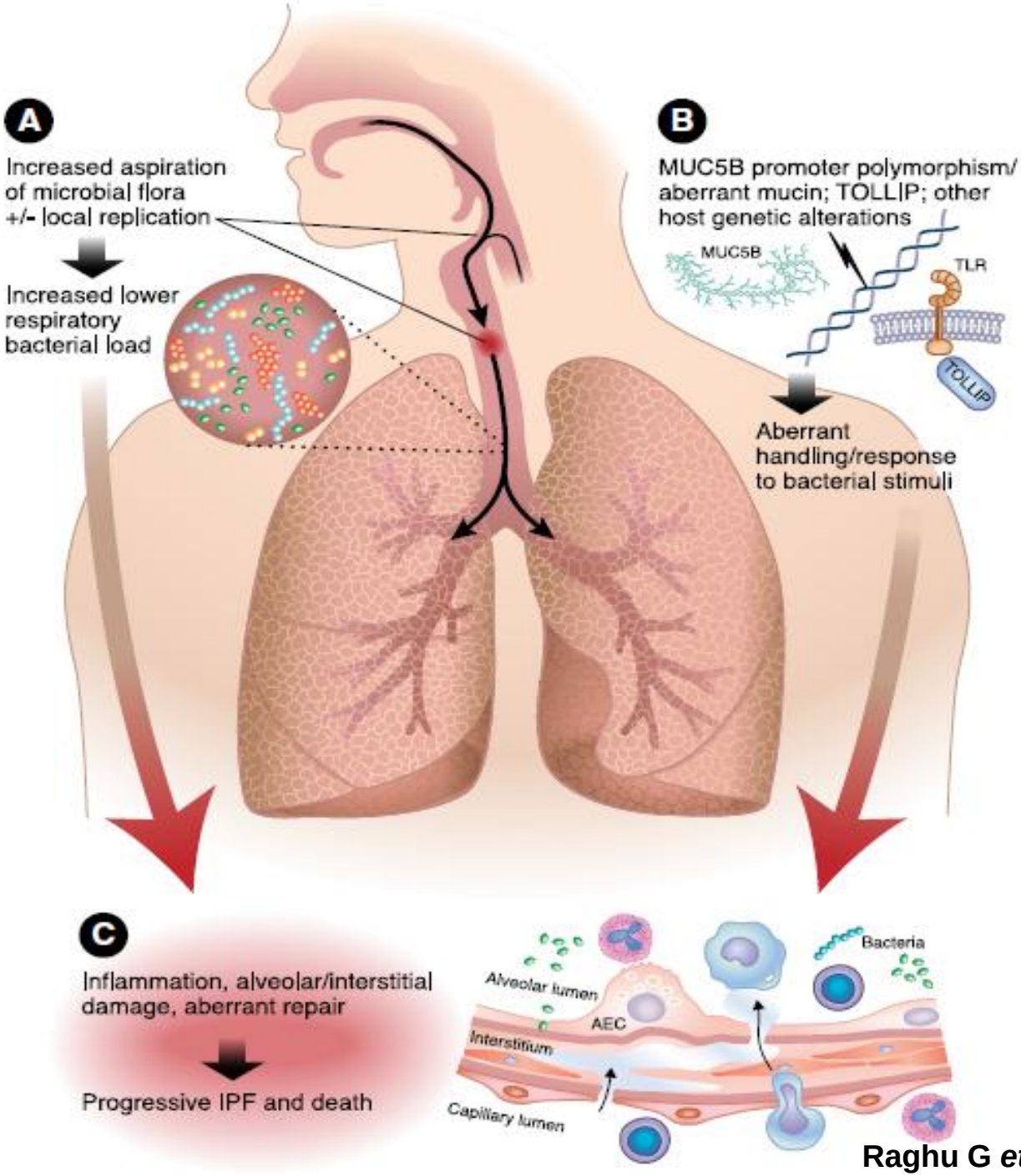
Raghu G *et al*, AJRCCM 2011

Idiopathic pulmonary fibrosis

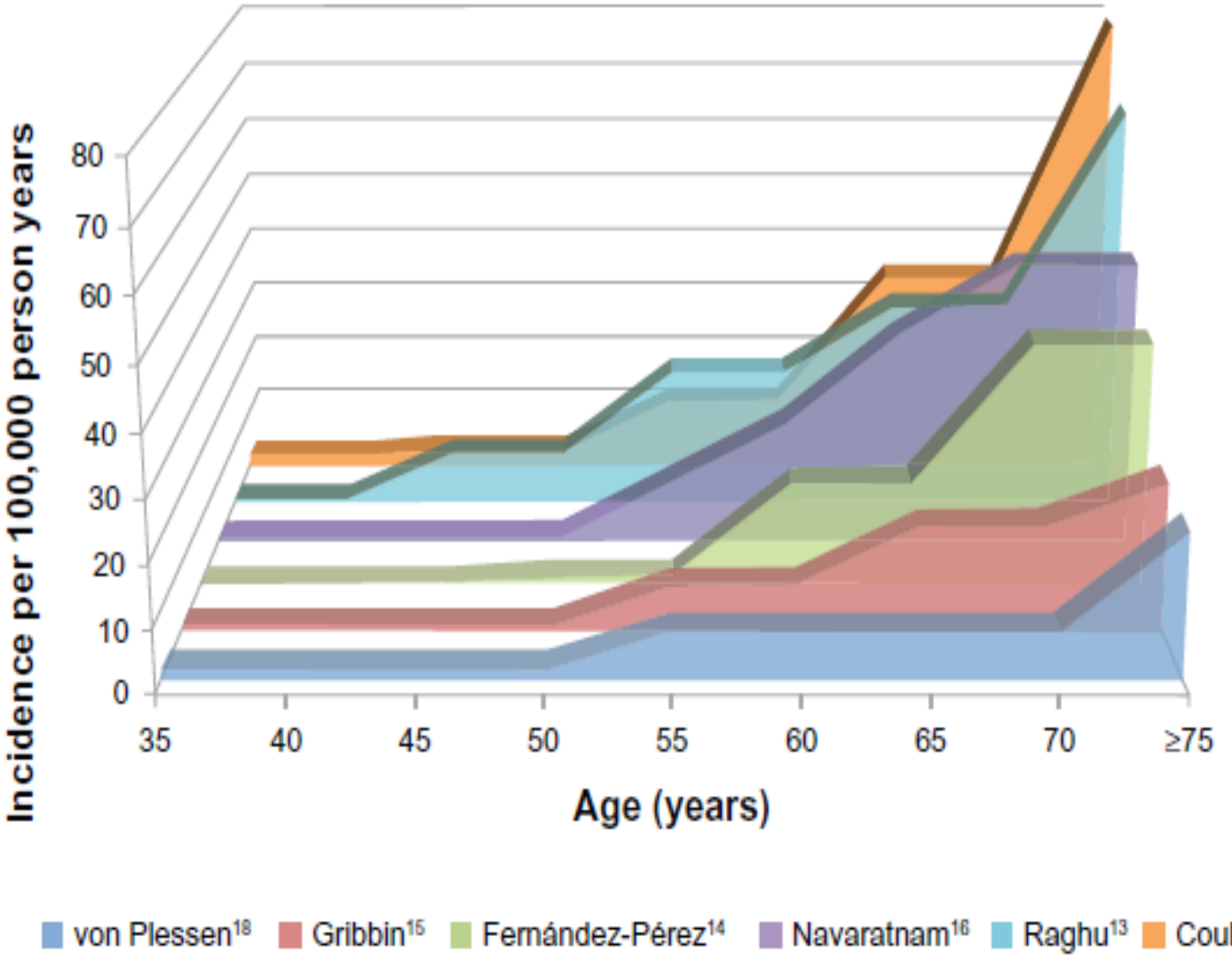
Pathogenesis



Raghu G *et al*, AJRCCM 2011



Raghu G *et al*, AJRCCM 2011



Ley B *et al*, Clinical Epidemiology 2013

Prevalence – Incidence IPF

Geography	Study year(s)	Prevalence (per 100,000)	Incidence (per 100,000/y
United States			
New Mexico[12] (Bernalillo County)	1988–1990	13.2–20.2[a]	7.4–10.7[a]
Twenty states[13]	2000	14.0–42.7[b]	6.8–16.3[b]
Minnesota[14] (Olmsted County)	1997–2005	27.9–63.0[b]	8.8–17.4[b]
Europe			
Czech Republic[17]	1981–1990	6.5–12.1[c]	0.74–1.28[c]
Norway[18]	1984–1998	23.4	4.3
Finland[19]	1997–1998	16–18	–
Greece[8]	2004	3.4	0.9
UK[15]	1991–2003	–	4.6
UK[16]	2000–2009	–	7.4
Turkey[9]	2007–2009	–	4.9[d]
Asia			
Taiwan[20]	1997–2007	0.7–6.4[e]	0.6–1.4[e]
Japan[11]	2005	2.9[f]	–

Ley B *et al*, Clinical Epidemiology 2013

Respiratory Medicine (2009) 103, 1122–1129

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

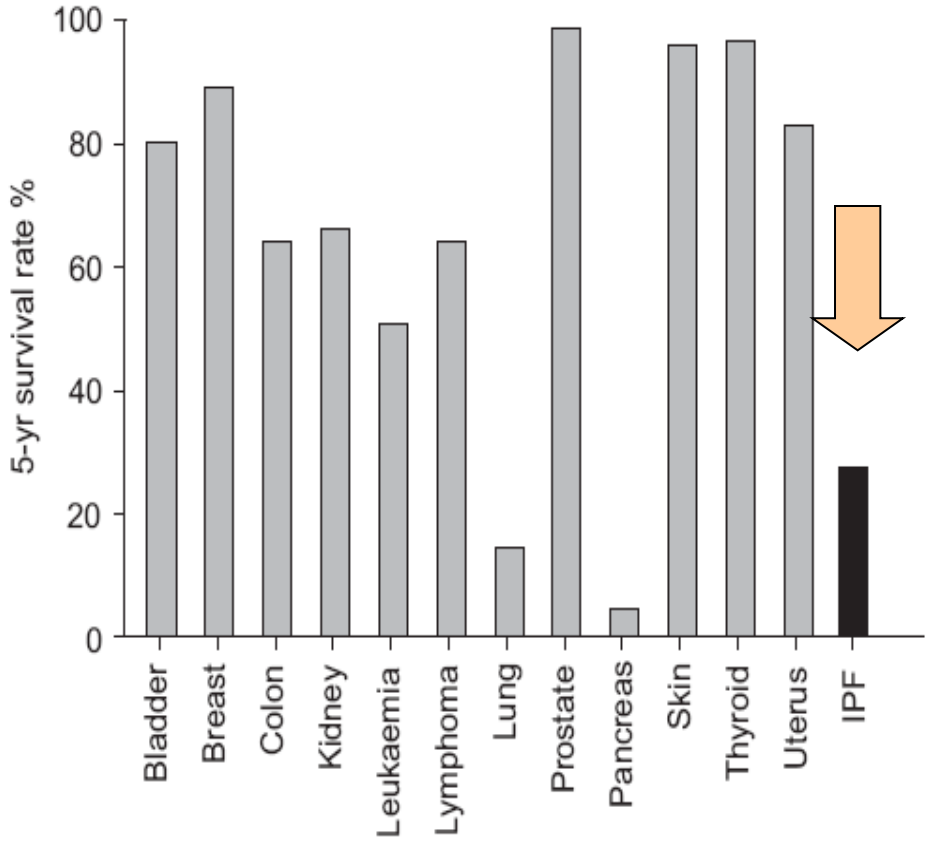
Epidemiology of interstitial lung diseases in Greece ☆

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

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

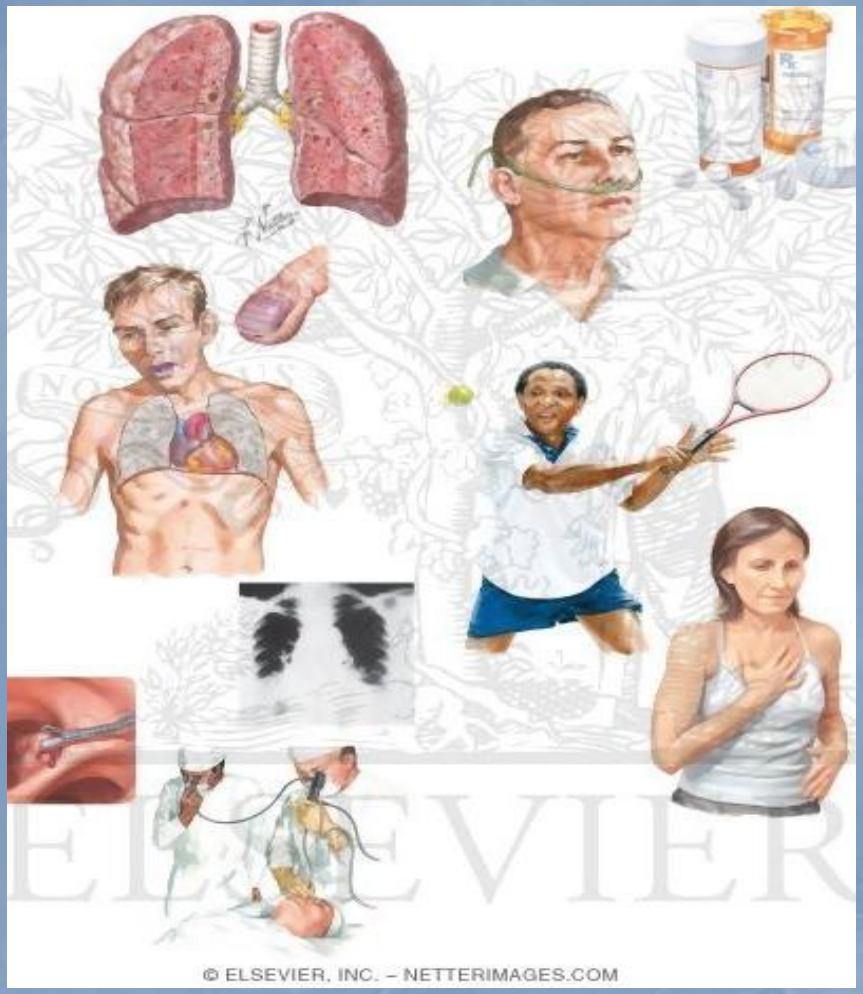


IPF is a dreadful, chronic and irreversibly progressive fibrosing interstitial pneumonia leading to death in all patients affected

Vancheri C, et al. Eur Respir J 2010
Papiris SA, et al. Crit Care 2010

Idiopathic pulmonary fibrosis
Clinical presentation

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



- Older age (6th – 7th decades of life)
- Men > women

- Exertional dyspnea,

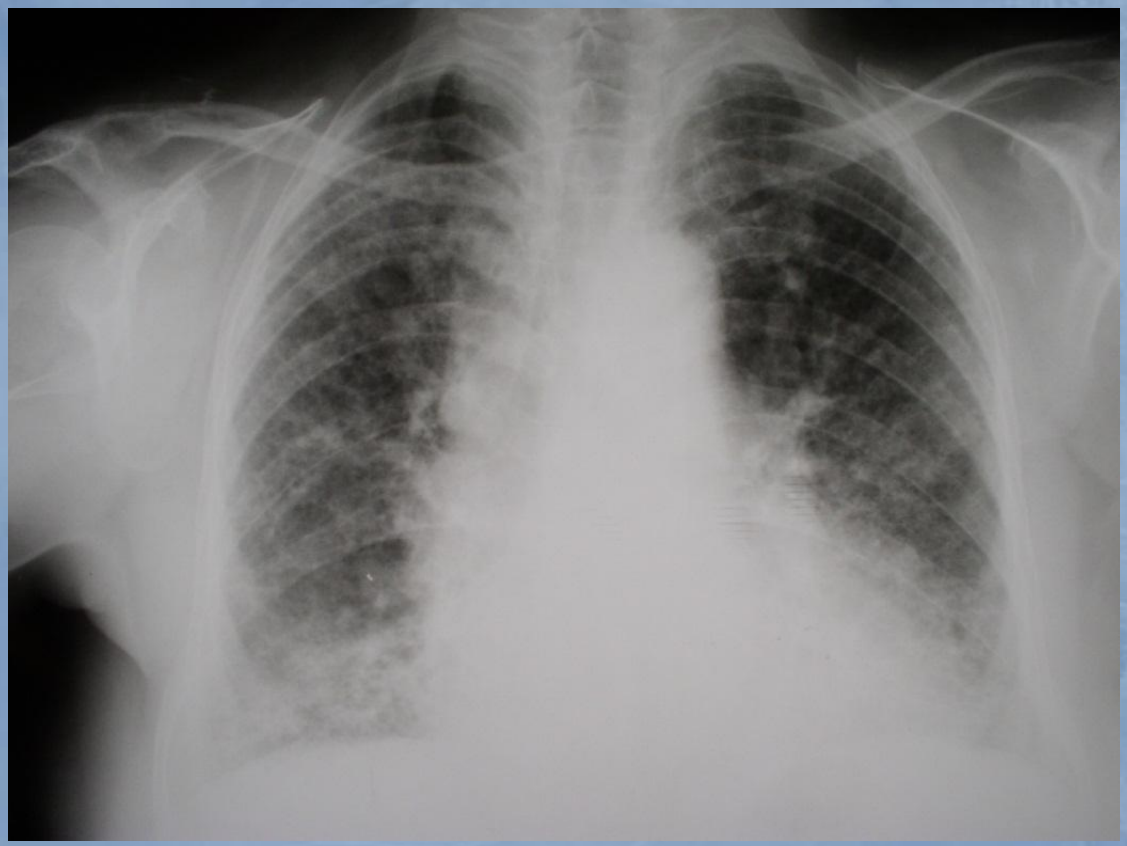
the most prominent and disabling symptom in these patients

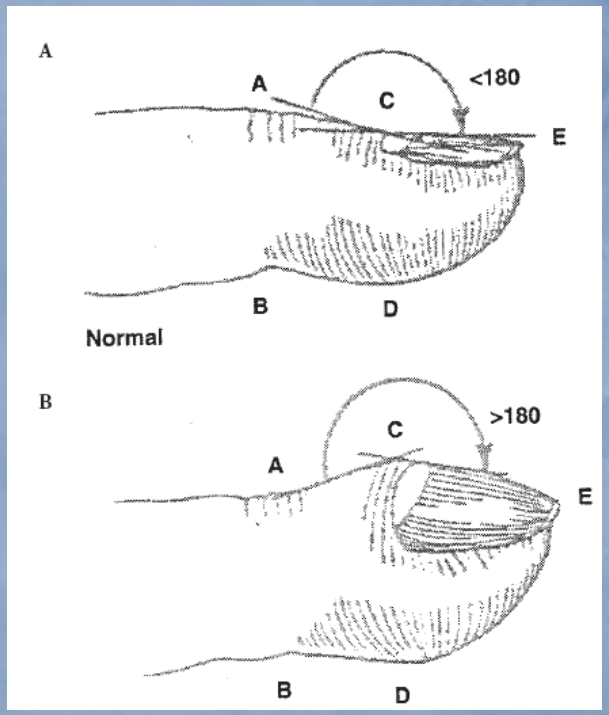
- Cough
- Finger clubbing

- Inspiratory crackles
- Weight loss, malaise, fatigue

Raghu G *et al*, AJRCCM 2011

Idiopathic pulmonary fibrosis
Clinical presentation

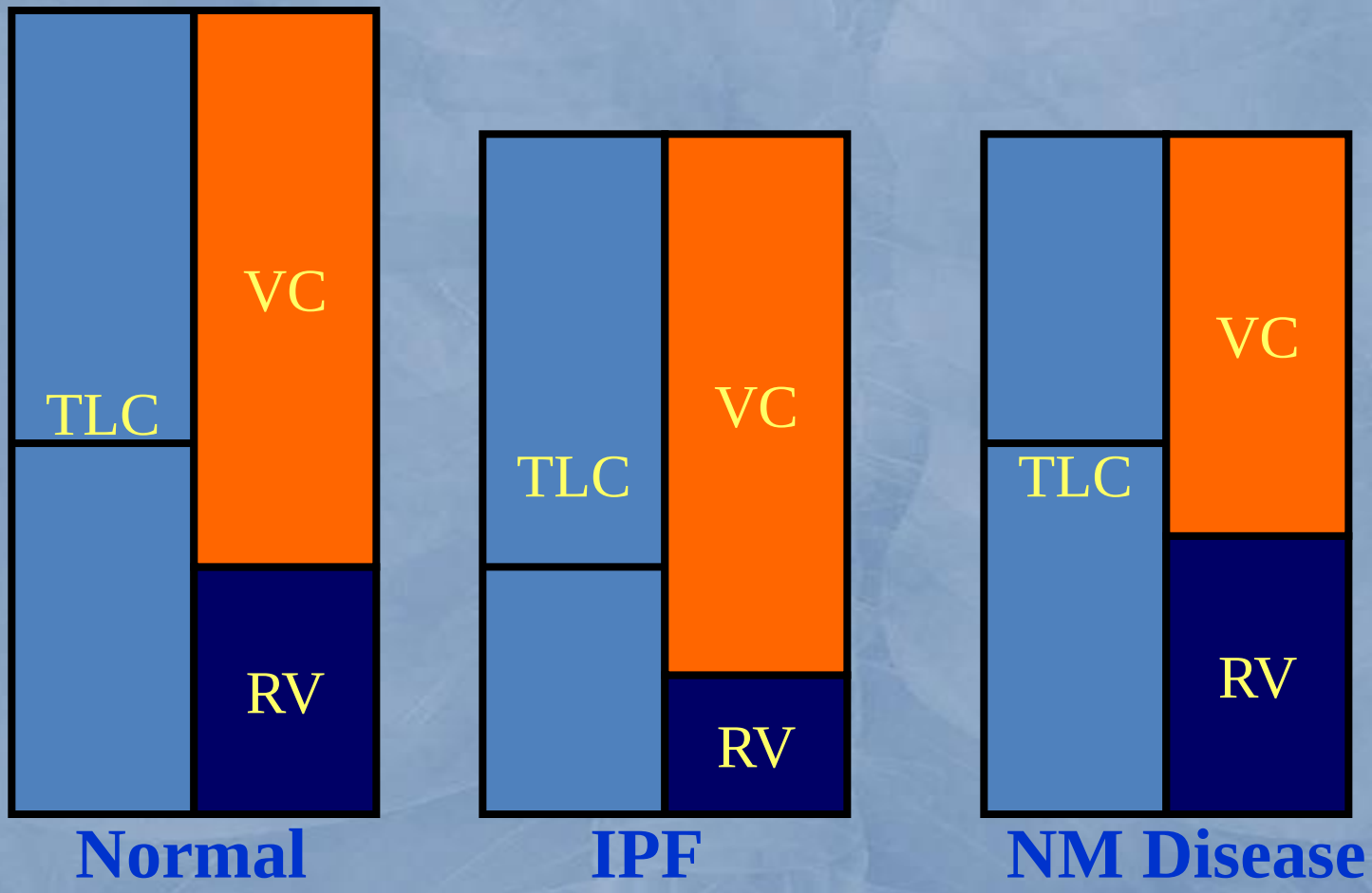




Raghu G *et al*, AJRCCM 2011

Idiopathic pulmonary fibrosis
Λειτουργικός έλεγχος αναπνοής

- Μείωση όγκων (TLC), χωρητικοτήτων (FVC) πνεύμονος (μικρός πνεύμων)
- Μειωμένη διάχυση (TLco)
- Ελάττωση πνευμονικής διατασιμότητας (compliance)



Idiopathic pulmonary fibrosis
Αέρια αίματος

- Υποξυγοναιμία (PaO2) με φυσιολογικό ή χαμηλό $PaCO_2$ –ΧΑΑ υποξαιμικού τύπου.
- Αυξημένη κυψελιδοαρτηριακή διαφορά οξυγόνου [$P(A\text{-}a)O_2$]
- Φυσιολογικό PaO2, πτώση με την άσκηση ή τον ύπνο
- Διαδοχικές μετρήσεις, αναξιοπιστία οξυμετρίας
- Αυξημένο $PaCO_2$ σε τελικά στάδια

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

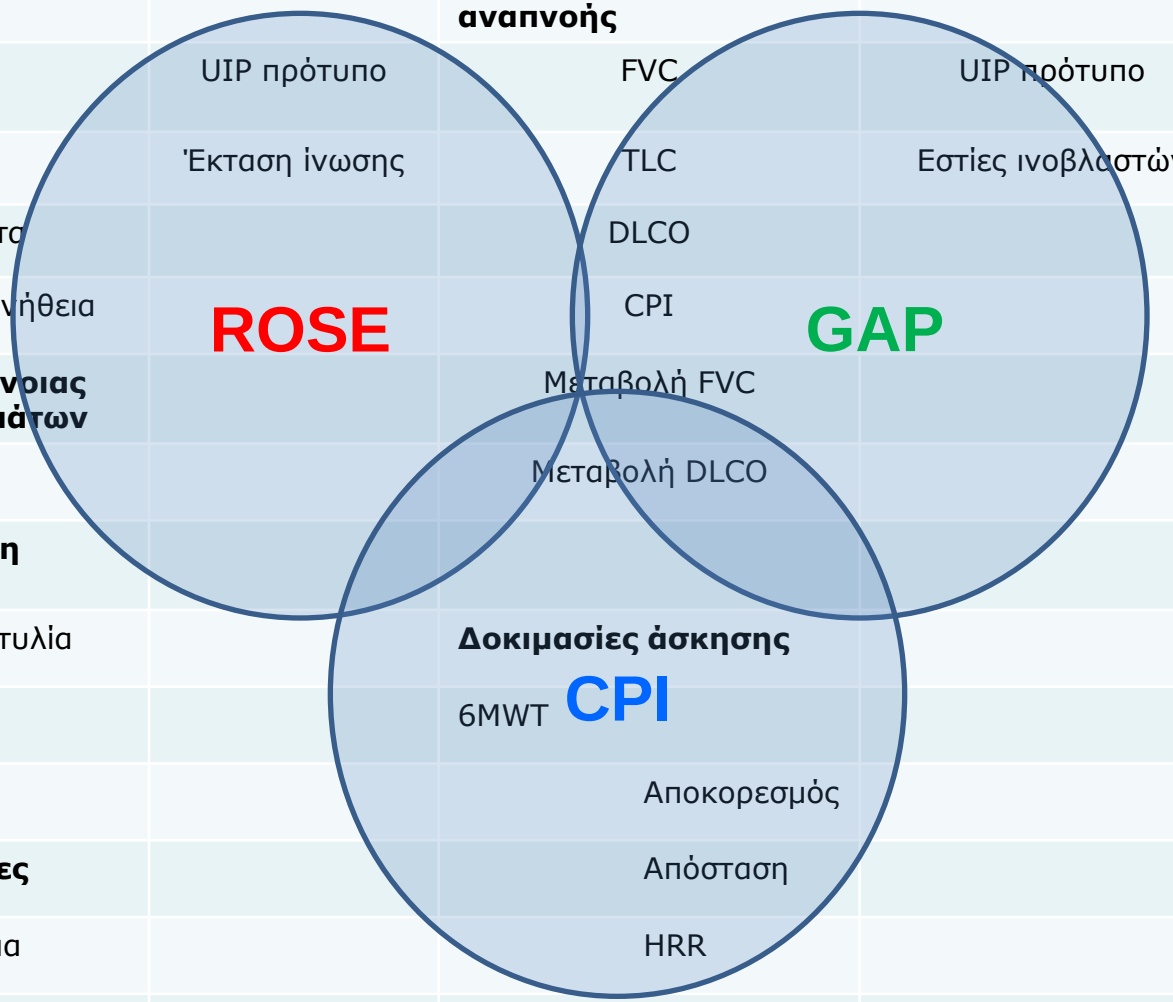
American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 2002

ΔΕΙΚΤΕΣ ΒΑΡΥΤΗΤΑΣ ΚΑΙ ΠΡΟΓΝΩΣΗΣ

Κλινικοί	Ακτινολογικοί	Φυσιολογικοί	Παθολογοανατομικοί	Βιοδείκτες
Δημογραφικοί	**HRCT**	**Λειτουργικός έλεγχος αναπνοής**		**Ορού**
Ηλικία	UIP πρότυπο	FVC	UIP πρότυπο	BNP
Φύλο	Έκταση ίνωσης	TLC	Εστίες ινοβλαστών	Αλβουμίνη
Εθνικότητα		DLCO		KL-6M
Καπνιστική συνήθεια		CPI		MP-7
Κλίμακες δύσπνοιας βάσει συμπτωμάτων		Μεταβολή FVC		CCL-18
		Μεταβολή DLCO		SP-A & -D
Φυσική εξέταση				Κυκλοφορούντα ινοκύτταρα
Πληκτροδακτυλία		**Δοκιμασίες άσκησης**		**BAL**
BMI		6MWT		SP-A & -D
		Αποκορεσμός		MMP-3, -7, -8, -9
Συννοσηρότητες		Απόσταση		CCL -2, -17, -22
Εμφύσημα		HRR		Ουδετεροφιλία
Πνευμονική υπέρταση		Άλλες		



Ley B *et al*, AJRCCM 2011

American Thoracic Society Documents

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

The diagnosis of IPF requires:

A. exclusion of other known causes of interstitial lung disease

B. the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy

C. specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

Raghu G *et al*, AJRCCM 2011

American Thoracic Society Documents

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

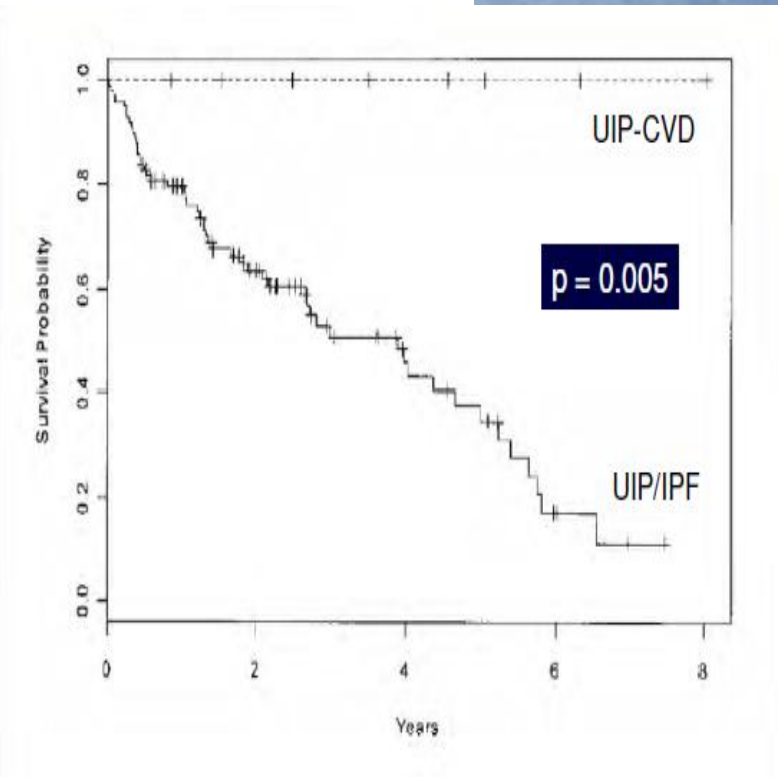
A. Exclusion of other known causes

- **Careful history (including family history), physical examination focusing on co-morbidities, medication use, environmental exposures, CTD**
- **No validated tools. The questionnaire available through the ACCP may be of use**
- **It is of particular importance to evaluate patients thoroughly for possible chronic HP**

Raghu G *et al*, AJRCCM 2011

Clinical conditions associated with UIP pattern

- Idiopathic pulmonary fibrosis (IPF)
- Collagen vascular disease
- Drug toxicity
- Chronic hypersensitivity pneumonitis
- Asbestosis
- Familial idiopathic pulmonary fibrosis
- Hermansky-Pudlak syndrome



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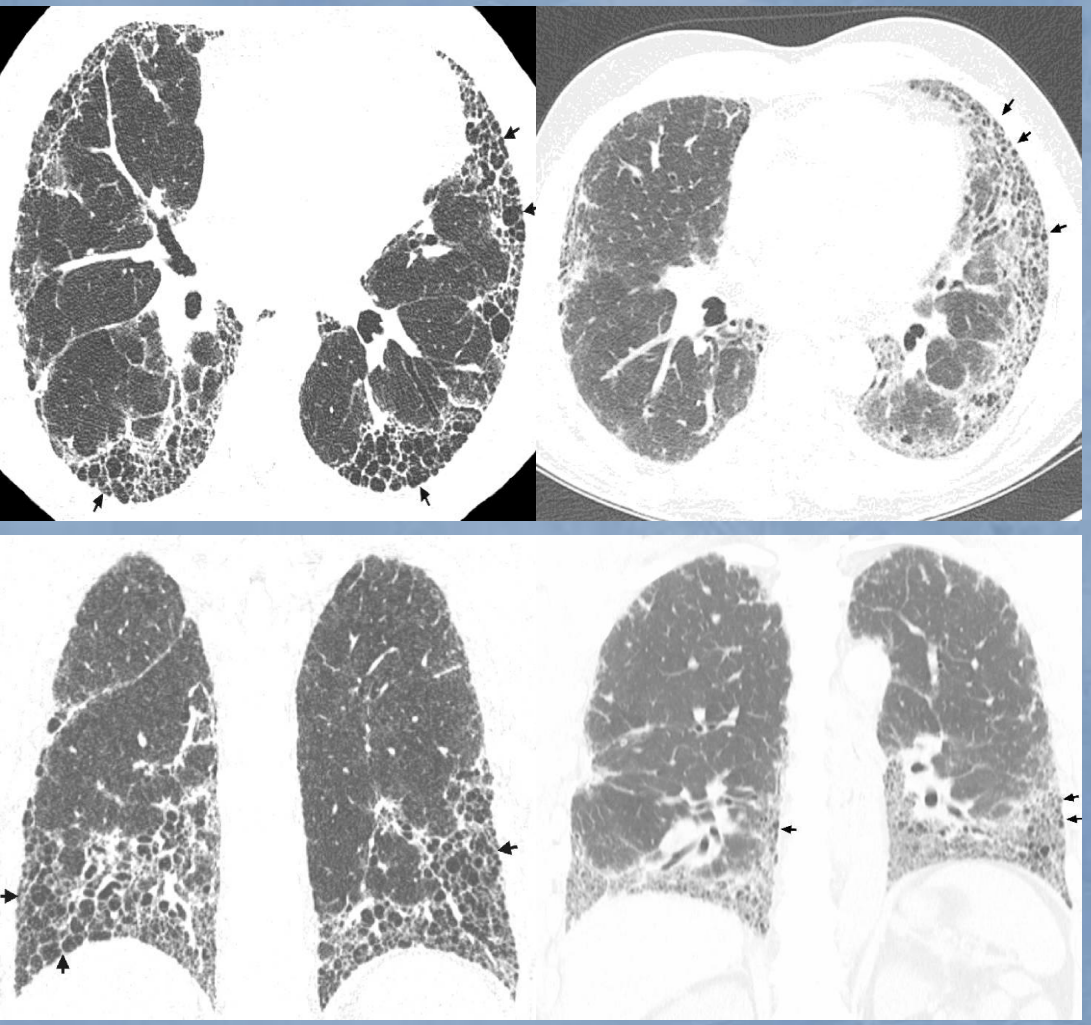
Raghu G *et al*, AJRCCM 2011

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)

HRCT Images: UIP Pattern
(Extensive honeycombing)

HRCT Images: UIP Pattern
(Less severe honeycombing)

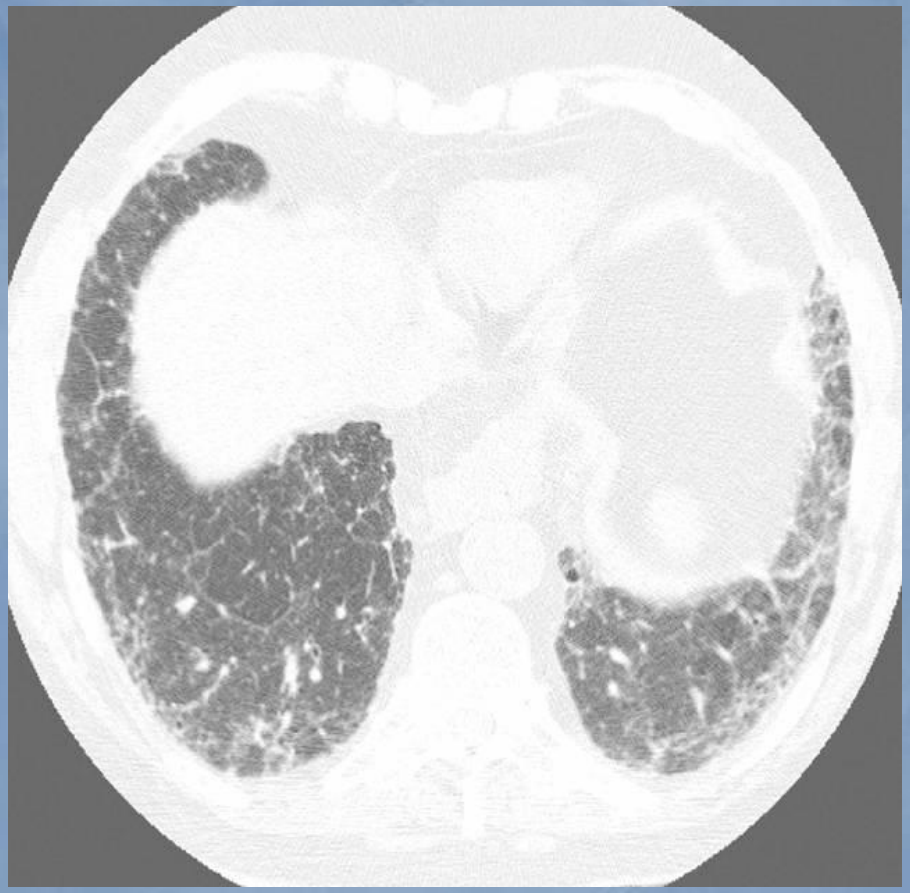


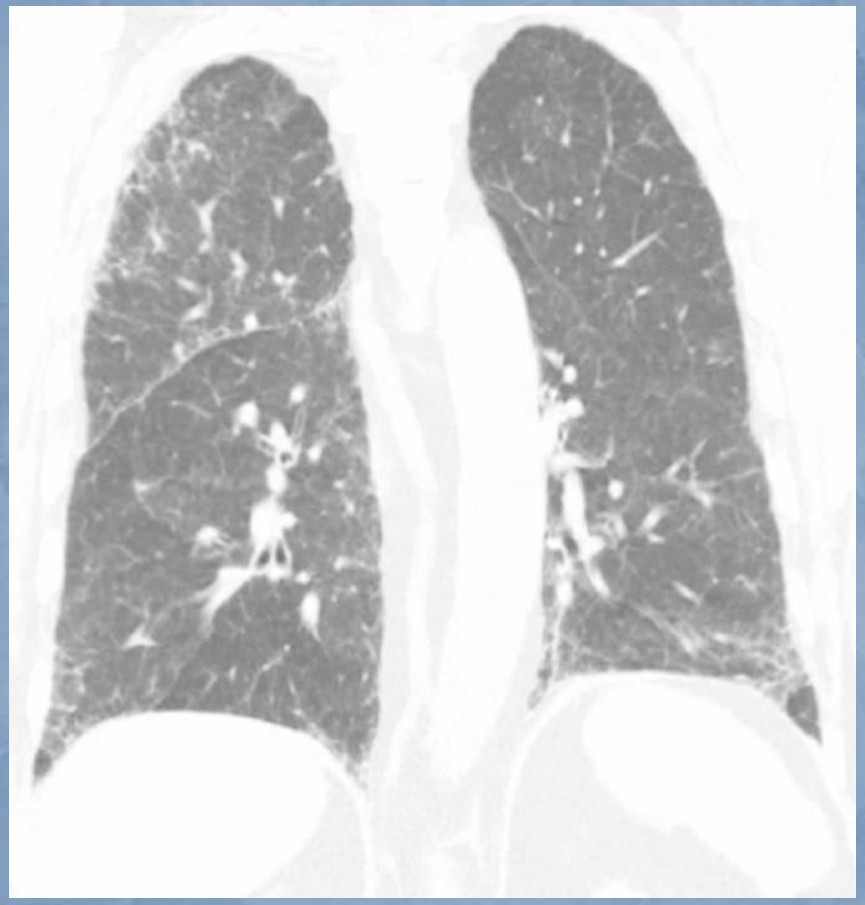
Honeycombing (HRCT)

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

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

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





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Raghu G *et al*, AJRCCM 2011

American Thoracic Society Documents

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

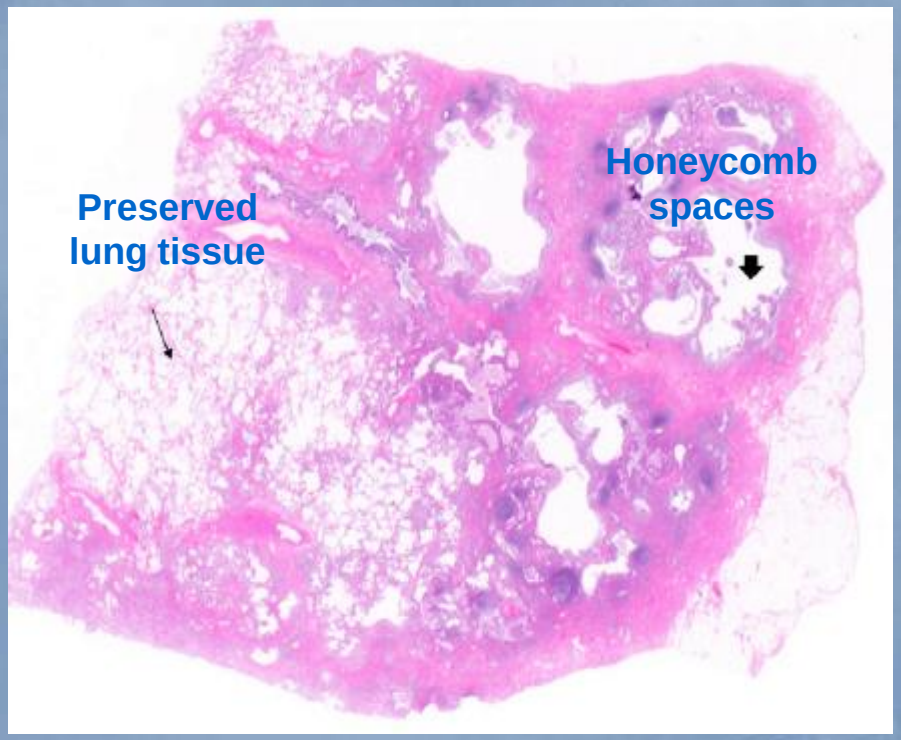
Histopathological criteria for UIP pattern

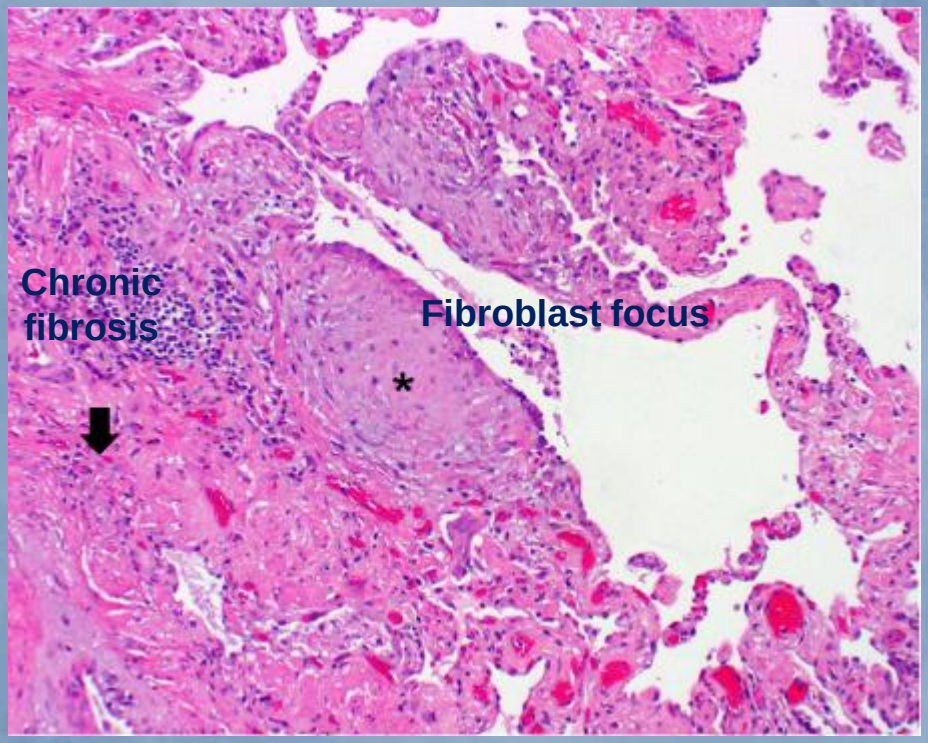
TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• 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‡	• 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

Raghu G *et al*, AJRCCM 2011

Histopathological criteria for UIP pattern



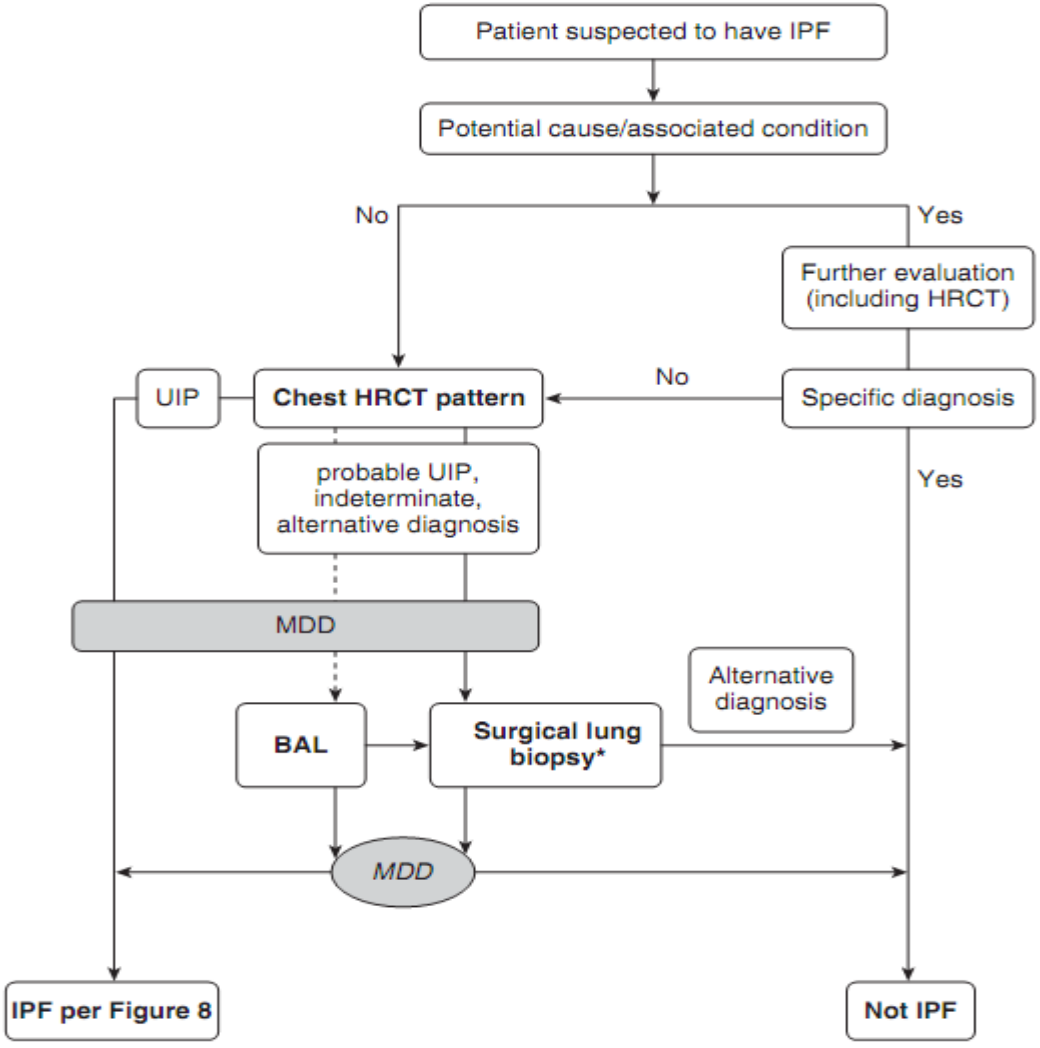


Diagnosis of Idiopathic Pulmonary Fibrosis

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Jeffrey L. Myers, Luca Richeldi, Christopher J. Ryerson, David J. Lederer, Juergen Behr, Vincent Cottin, Sonye K. Danoff, Ferran Morell, Kevin R. Flaherty, Athol Wells, Fernando J. Martinez, Arata Azuma, Thomas J. Bice, Demosthenes Bouros, Kevin K. Brown, Harold R. Collard, Abhijit Duggal, Liam Galvin, Yoshikazu Inoue, R. Gisli Jenkins, Takeshi Johkoh, Ella A. Kazerooni, Masanori Kitaichi, Shandra L. Knight, George Mansour, Andrew G. Nicholson, Sudhakar N. J. Pipavath, Ivette Buendía-Roldán, Moisés Selman, William D. Travis, Simon Walsh, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society

This official clinical practice guideline of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) was approved by the ATS, JRS, and ALAT May 2018, and the ERS June 2018

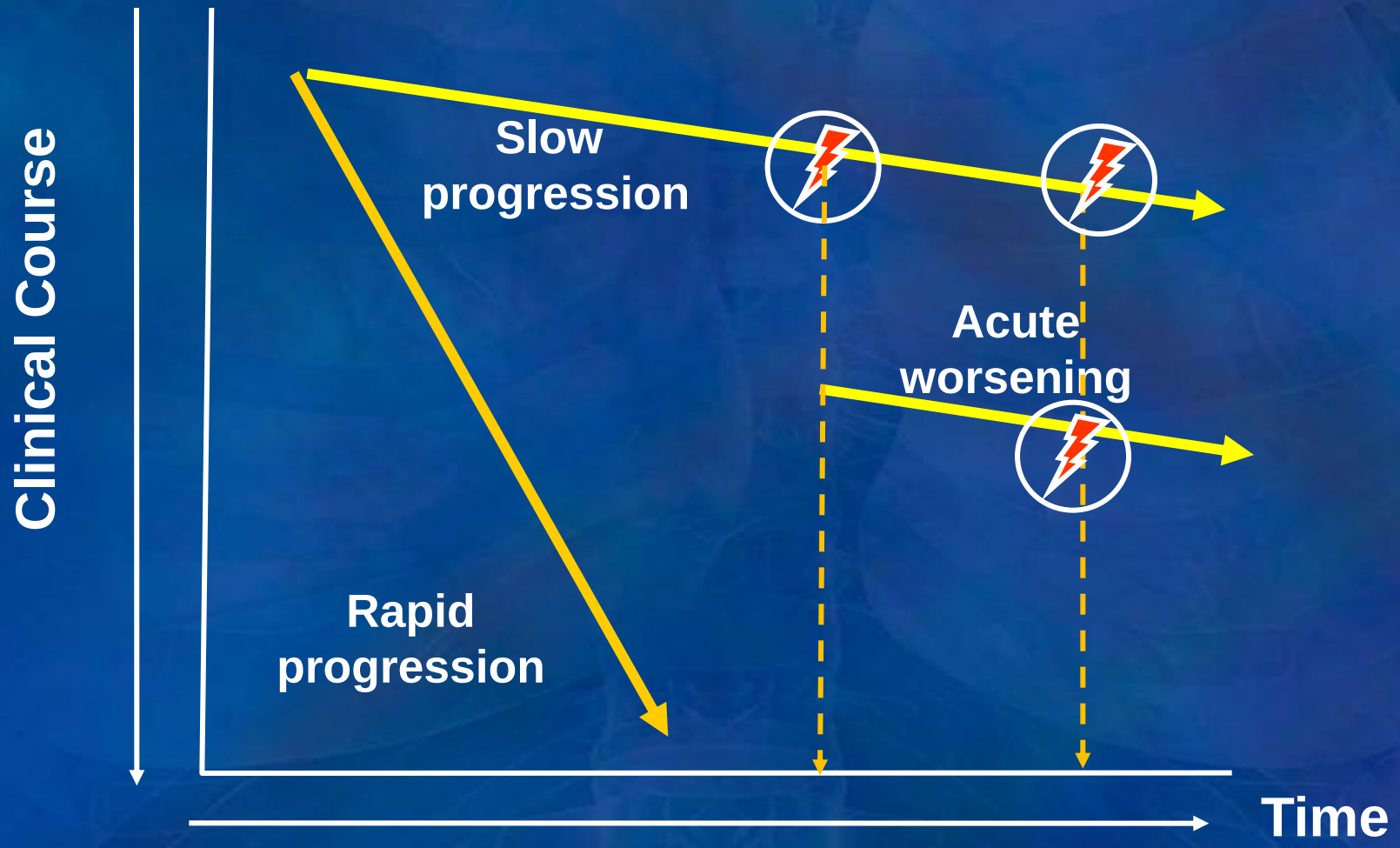


Raghu G *et al*, AJRCCM 2018

American Thoracic Society Documents

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

Natural History of IPF: is variable and unpredictable



Acute Exacerbation of Idiopathic Pulmonary Fibrosis

An International Working Group Report

Harold R. Collard[1], Christopher J. Ryerson[2], Tamera J. Corte[3], Gisli Jenkins[4], Yasuhiro Kondoh[5], David J. Lederer[6], Joyce S. Lee[7], Toby M. Maher[8,9], Athol U. Wells[9], Katerina M. Antoniou[10], Juergen Behr[11], Kevin K. Brown[12], Vincent Cottin[13], Kevin R. Flaherty[14], Junya Fukuoka[15], David M. Hansell[16], Takeshi Johkoh[17], Naftali Kaminski[18], Dong Soon Kim[19], Martin Kolb[20], David A. Lynch[21], Jeffrey L. Myers[22], Ganesh Raghu[23], Luca Richeldi[24], Hiroyuki Taniguchi[5], and Fernando J. Martinez[25]

Table 3. Proposed Revised Definition and Diagnostic Criteria for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Revised definition

An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality

Revised diagnostic criteria

- Previous or concurrent diagnosis of IPF*
- Acute worsening or development of dyspnea typically <1 mo duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern†
- Deterioration not fully explained by cardiac failure or fluid overload

Am J Respir Crit Care Med Vol 194, Iss 3, pp 265–275, Aug 1, 2016

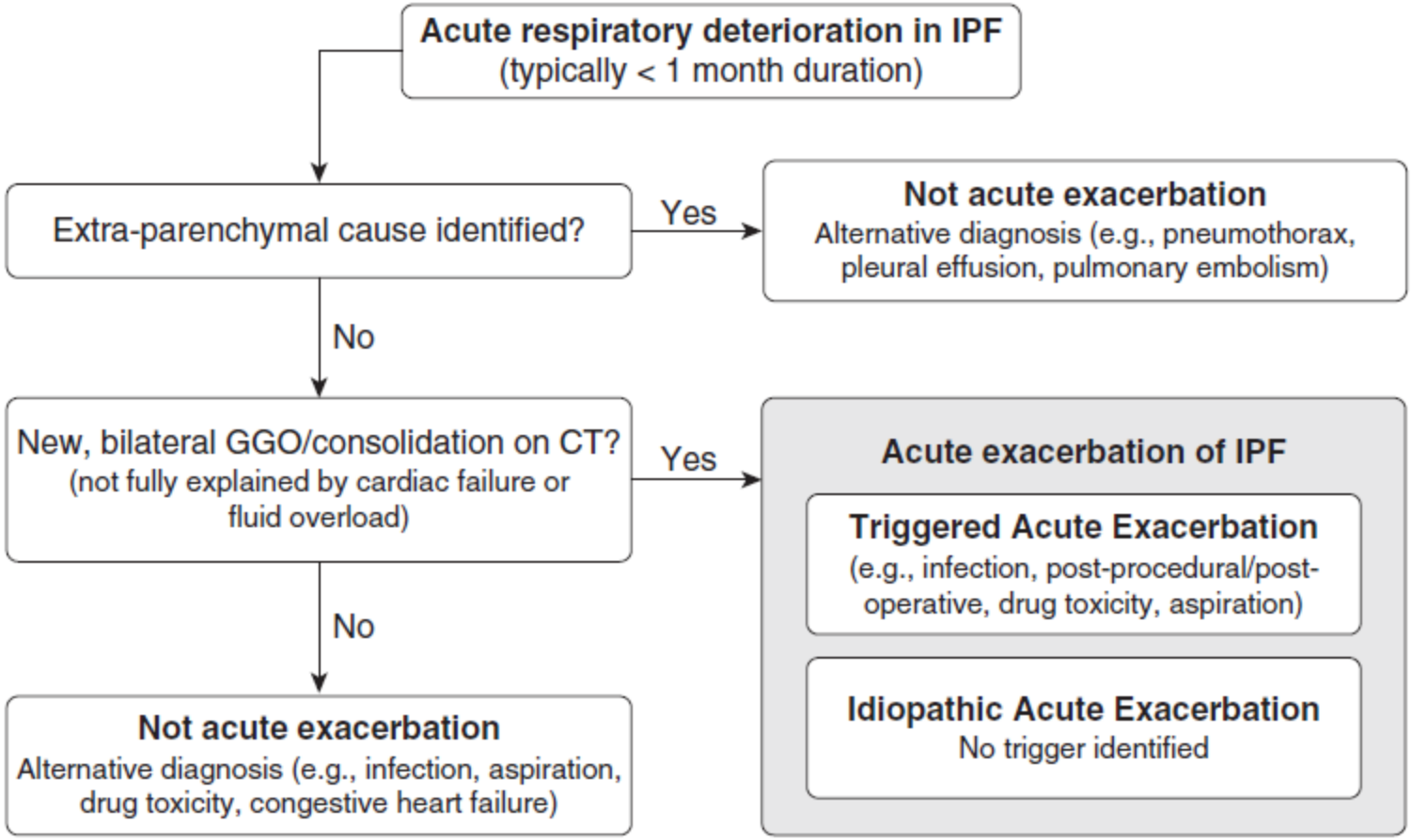
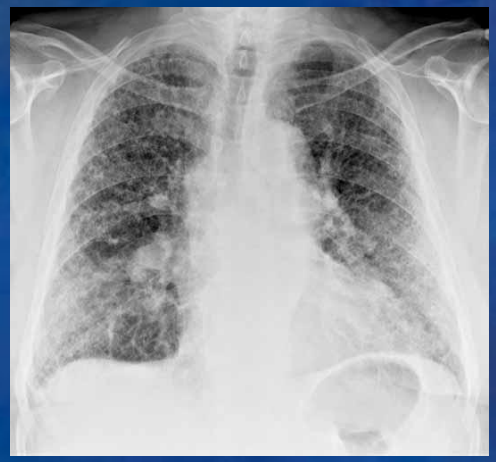


Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification (GGO)/consolidation on computed tomography (CT) that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found.

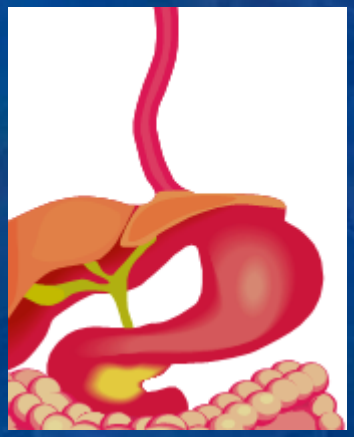
Κύριες συννοσηρότητες της IPF

Πνευμονική υπέρταση



Σύνδρομο αποφρακτικών απνοιών

- Εμφύσημα
- Καρκίνος πνεύμονα



ΓΟΠΝ

Κατάθλιψη

Raghu G *et al*, AJRCCM 2011

ΘΕΡΑΠΕΥΤΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ

❖ **Πιρφενιδόνη / Nintedanib**: Η πρώτες εγκεκριμένες φαρμακευτικές ουσίες από EMEA & FDA για την IPF, οι οποίες επιβραδύνουν την πορεία της νόσου.

❖ **Δεν υπάρχουν δεδομένα επί των οποίων να διατυπωθούν συστάσεις για τη θεραπεία των συνοδών νοσημάτων που σχετίζονται με την IPF, όπως το σύνδρομο αποφρακτικών απνοιών στον ύπνο.**

❖ Η μεταμόσχευση πνεύμονα είναι μια εφικτή επιλογή για επιλεγμένους ασθενείς με IPF και αποτελεί σήμερα μια αναγνωρισμένη θεραπευτική επιλογή

Raghu G *et al*, AJRCCM 2011

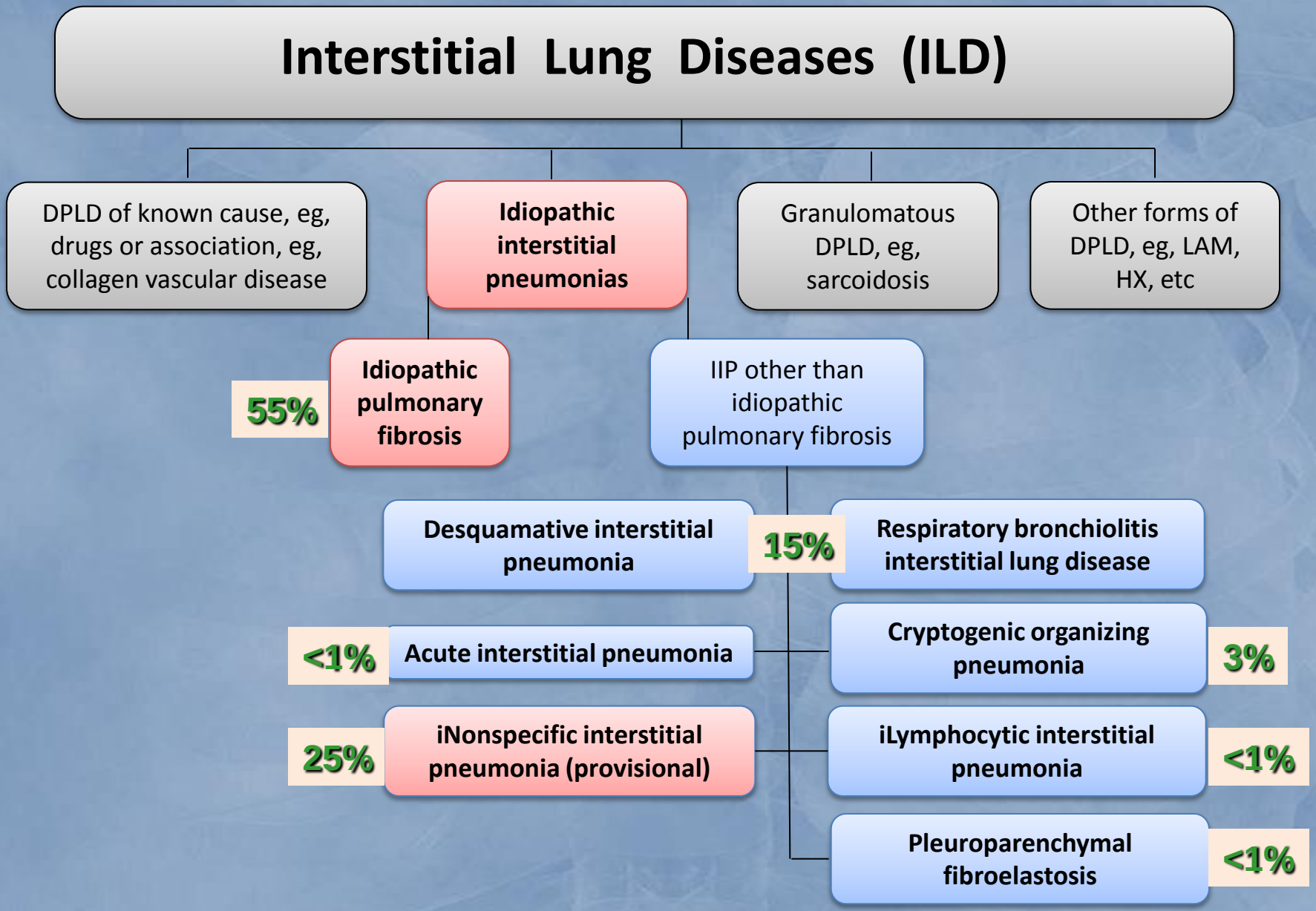
CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

Interstitial Lung Diseases (ILD)



Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

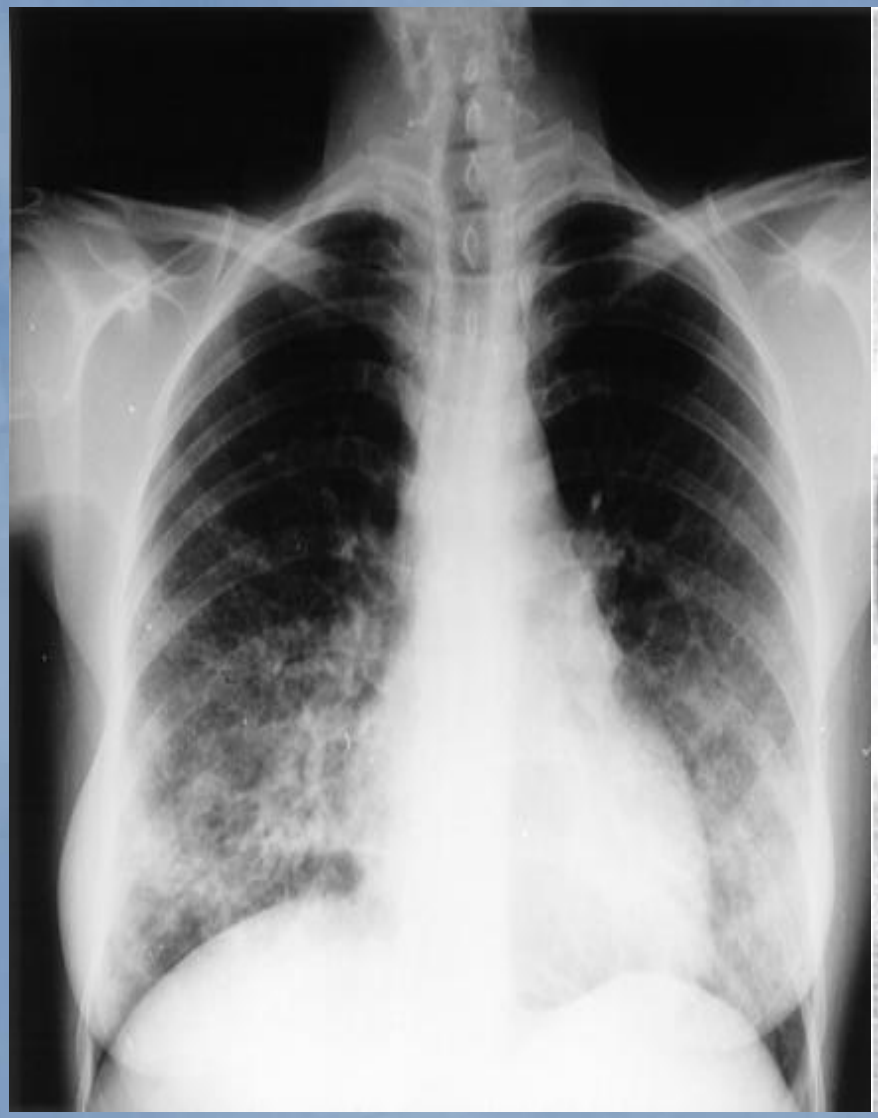
Idiopathic Nonspecific Interstitial Pneumonia

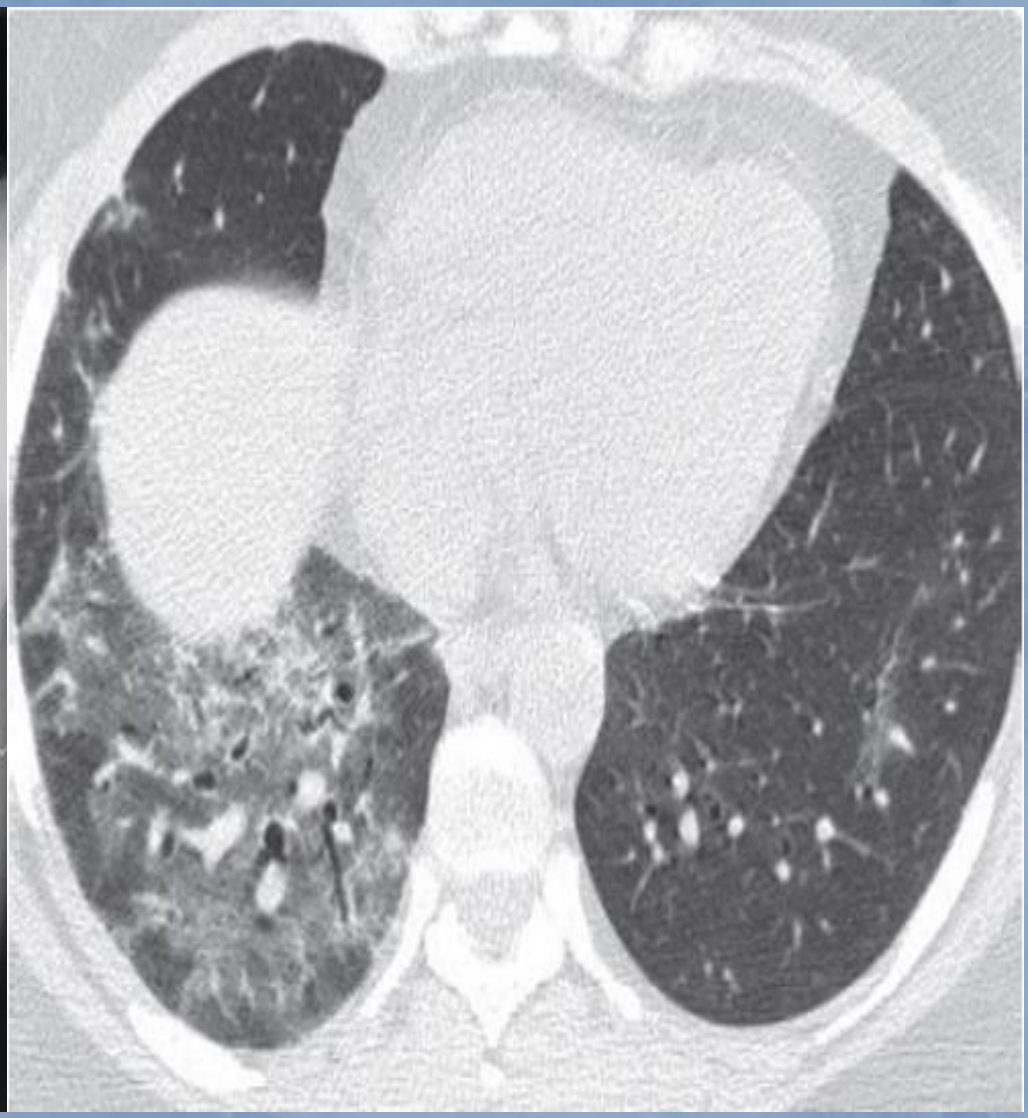
Report of an American Thoracic Society Project

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]

Idiopathic NSIP is a distinct clinical entity

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



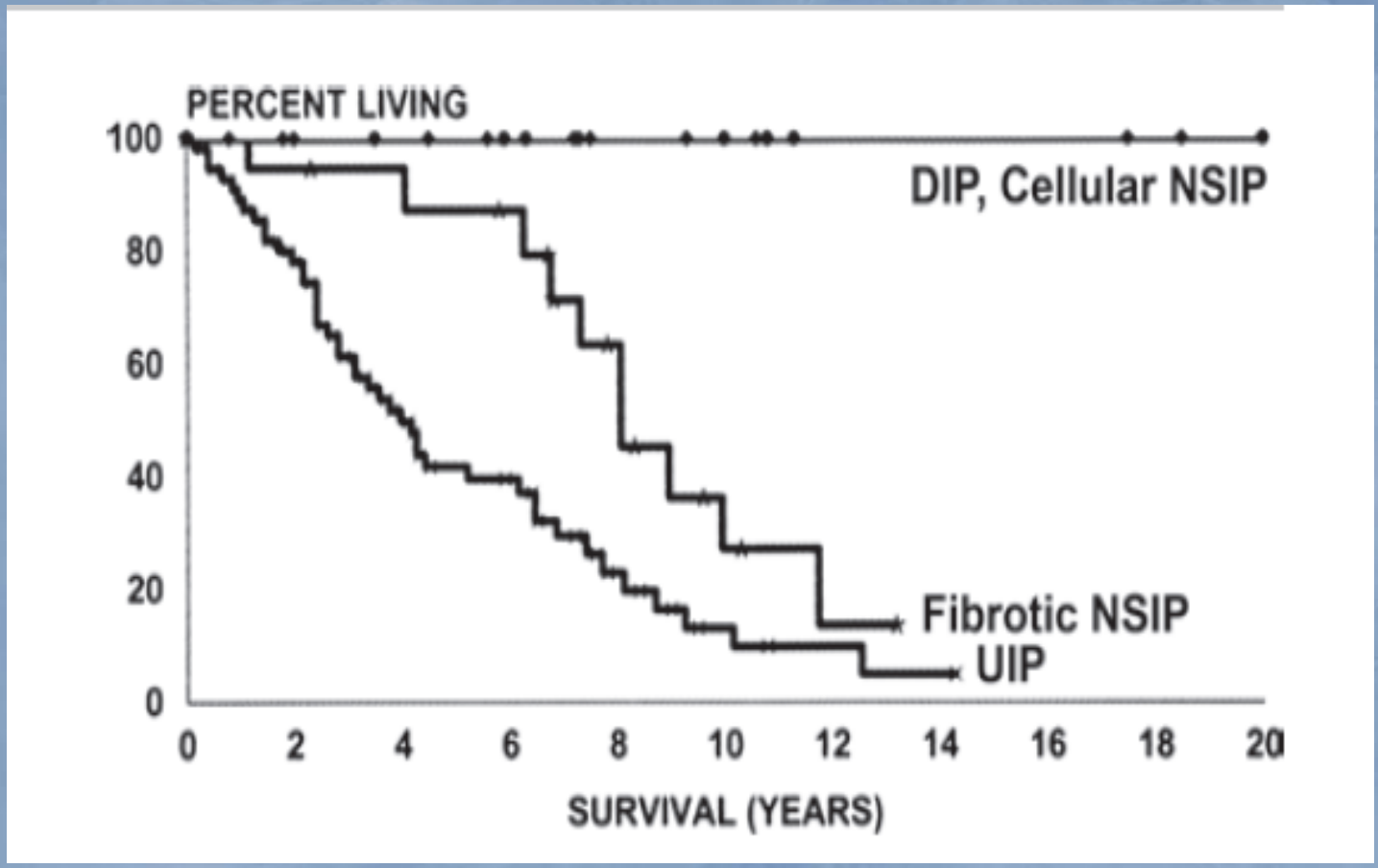


Infiltrative bilateral opacities in all cases

V.Cottin. Am J Respir Crit Care Med 1998;

Ground-Glass Abnormality

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



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

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

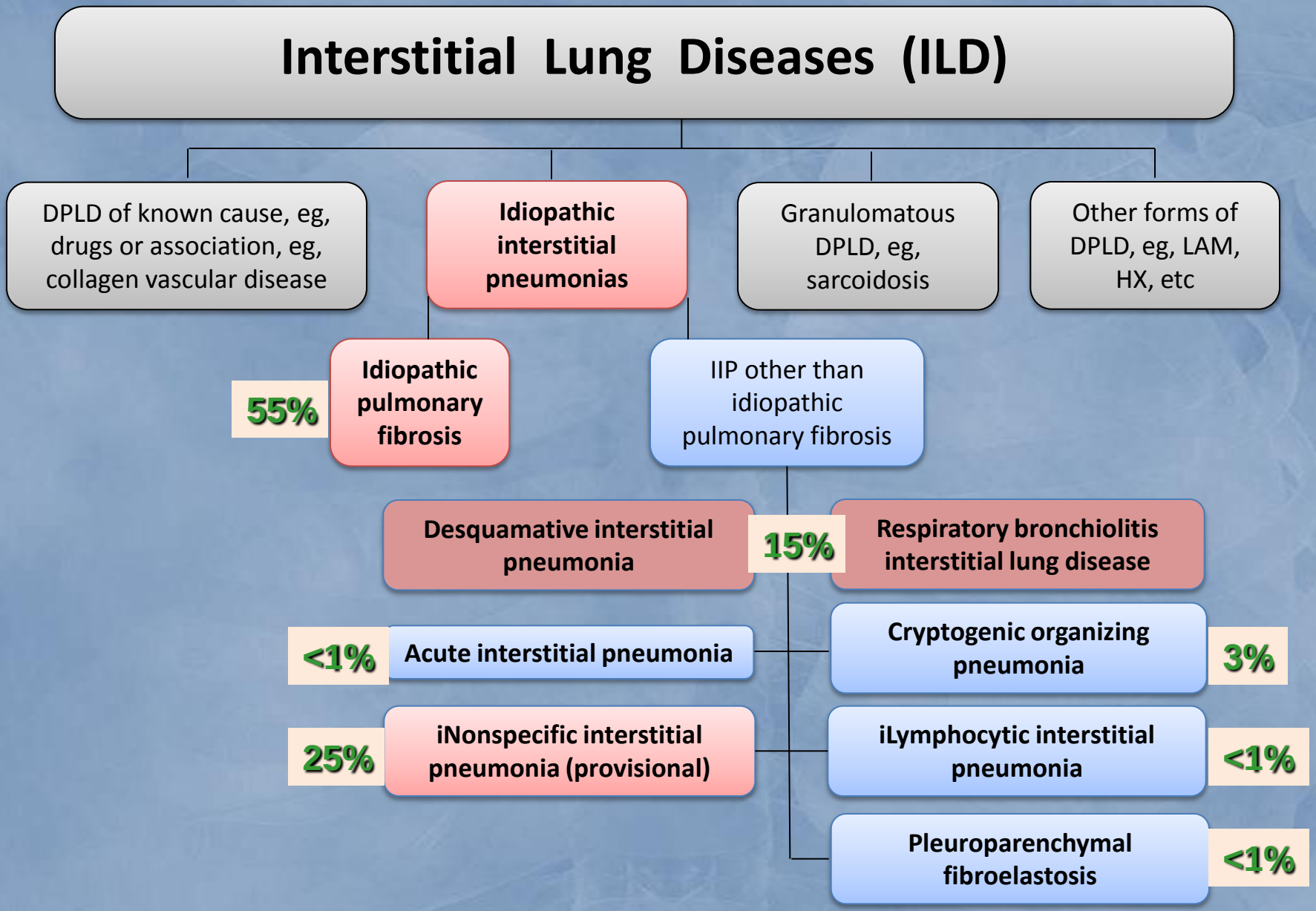
Non Specific Interstitial Pneumonia (NSIP)

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

- Biopsy is needed
- Different 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

Interstitial Lung Diseases (ILD)



Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

Cigarette smoking and diffuse lung disease

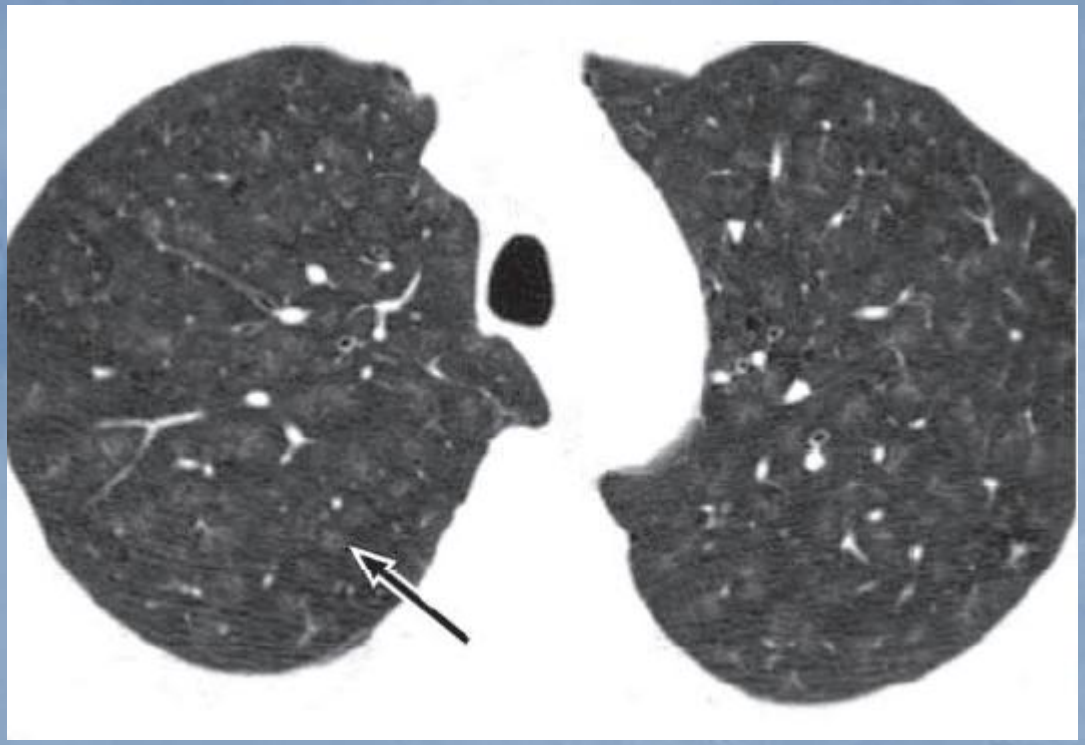
Respiratory bronchiolitis-interstitial lung disease

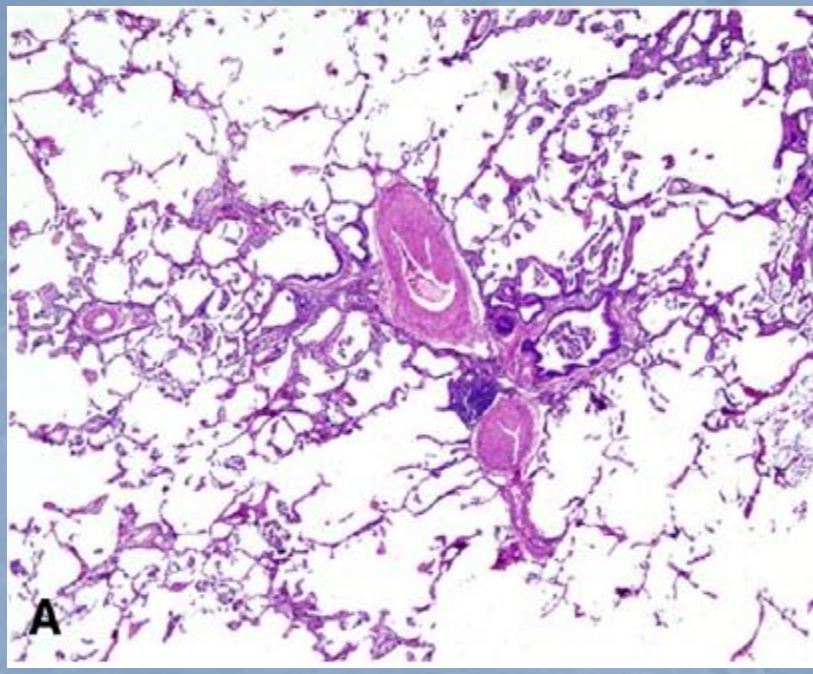
	RBILD
Smoking	100%
Age	3rd–5th decades
Sex M:F	Slight male dominance
Occurrence in children	No
Onset	Insidious
Presenting symptoms	Dyspnoea, cough
Crackles	~50%
Clubbing	Rare
Chest radiograph	Interstitial or normal
HRCT	Patchy ground glass
Pulmonary function	Mixed defect or normal
Treatment	Smoking cessation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

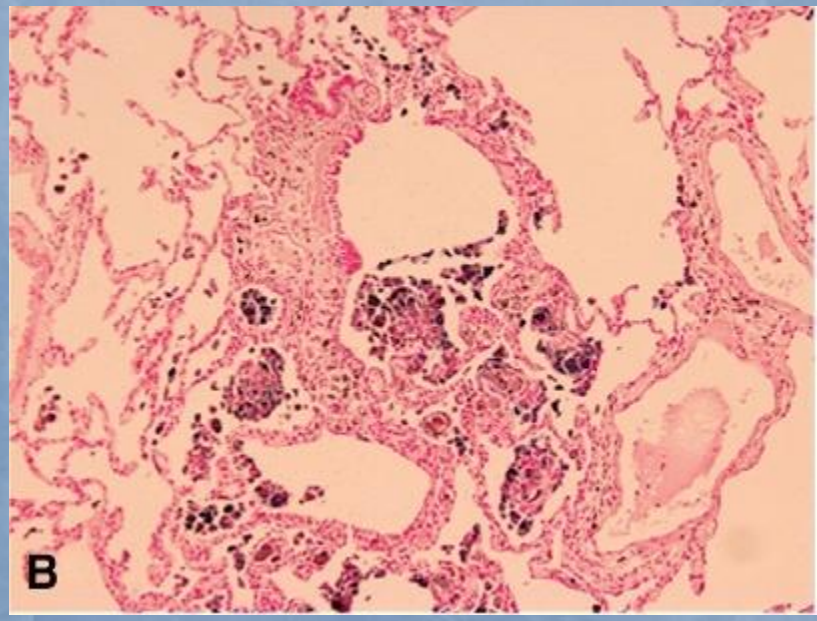
Ryu JH, et al. Eur Respir J 2001; 17: 122-132





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

Moderate

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

Ryu JH, et al. Eur Respir J 2001

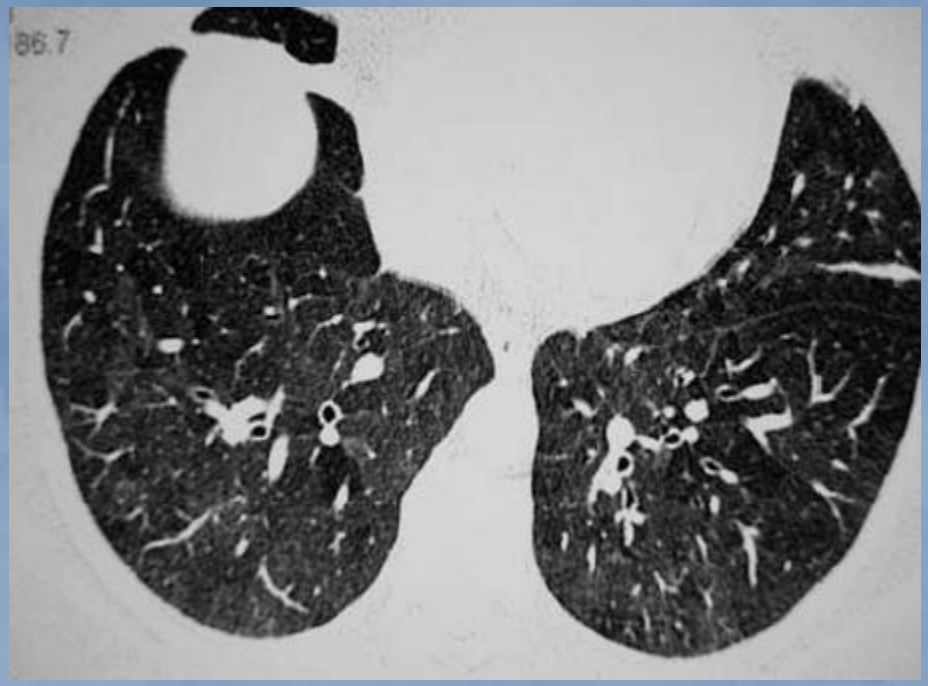
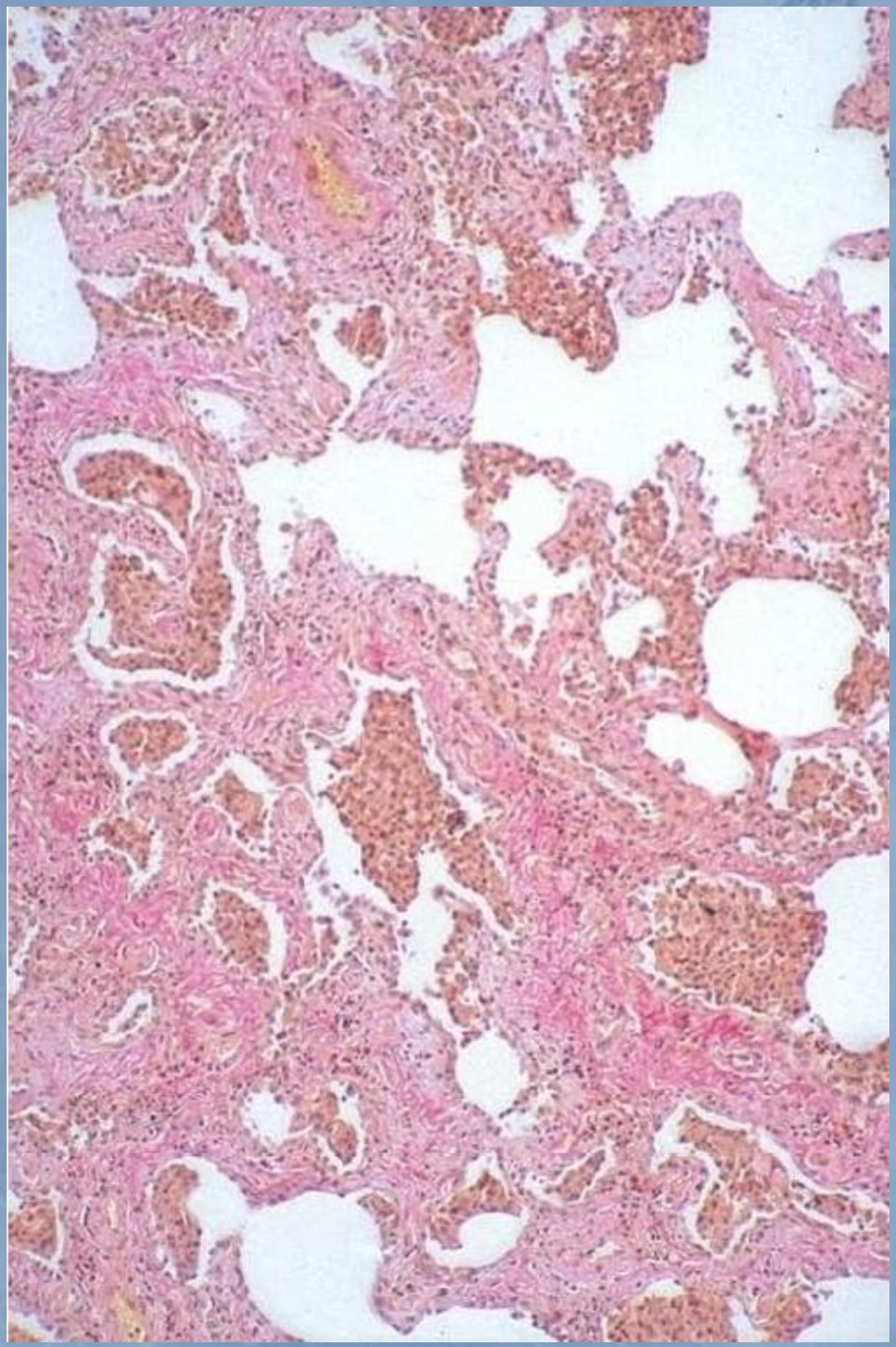


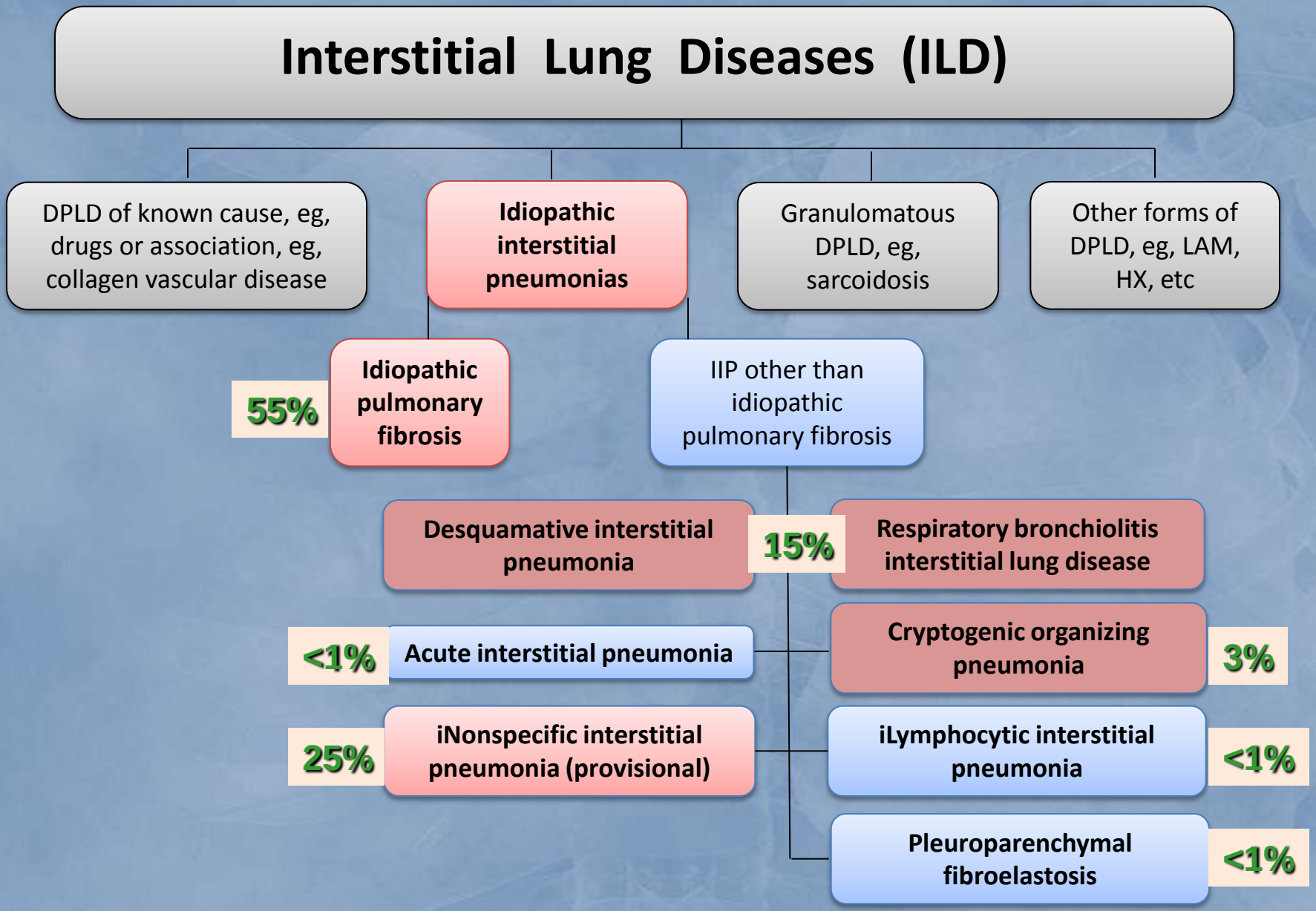
Table 3
High-Resolution CT Findings of DIP

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



Attili AK, et al. Radiographics 2008

Interstitial Lung Diseases (ILD)



Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

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

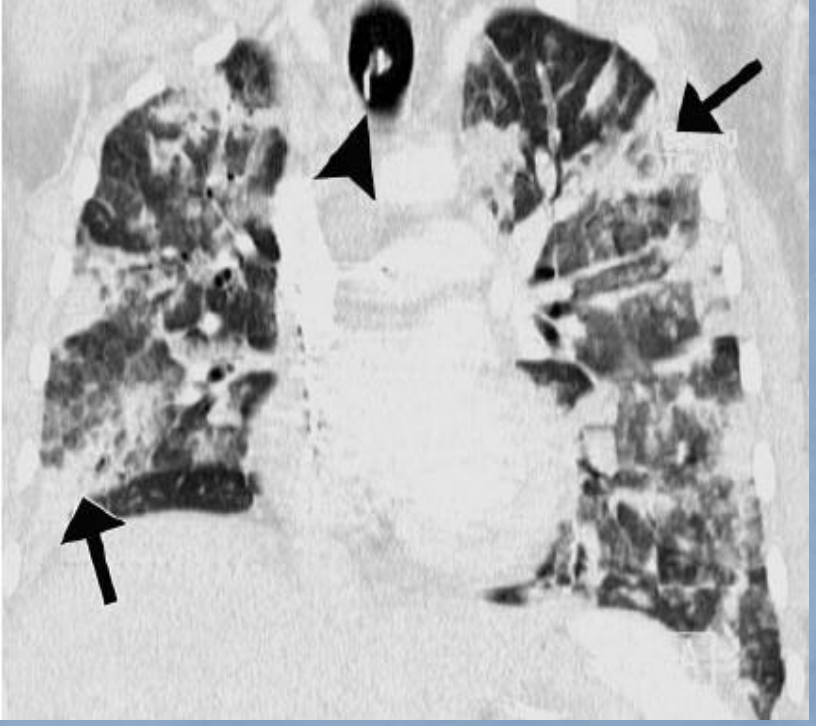
Cryptogenic organising pneumonia

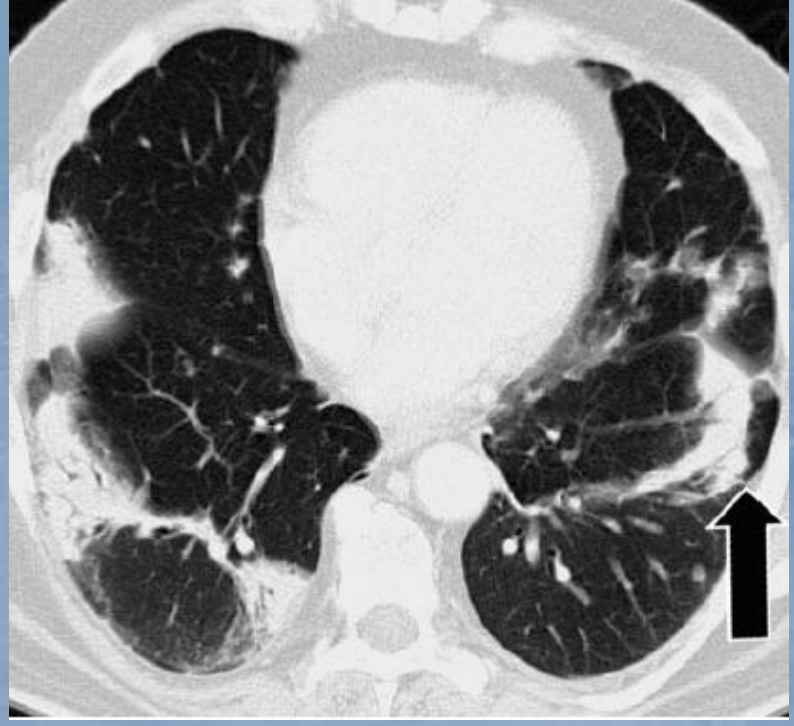
J-F. Cordier

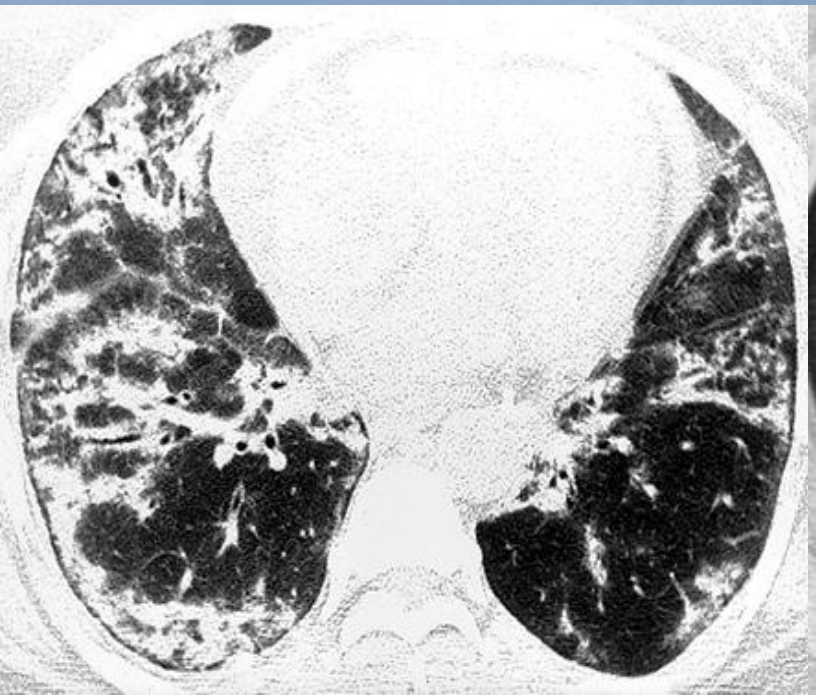
A DISTINCT ENTITY AMONG THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

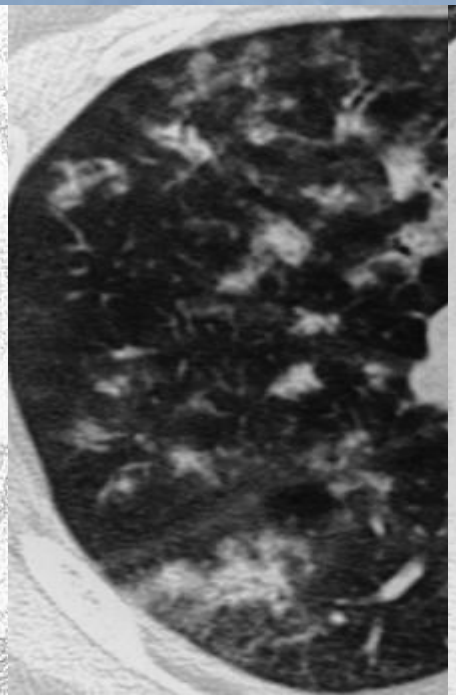
Cryptogenic Organizing Pneumonia (COP)

- 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









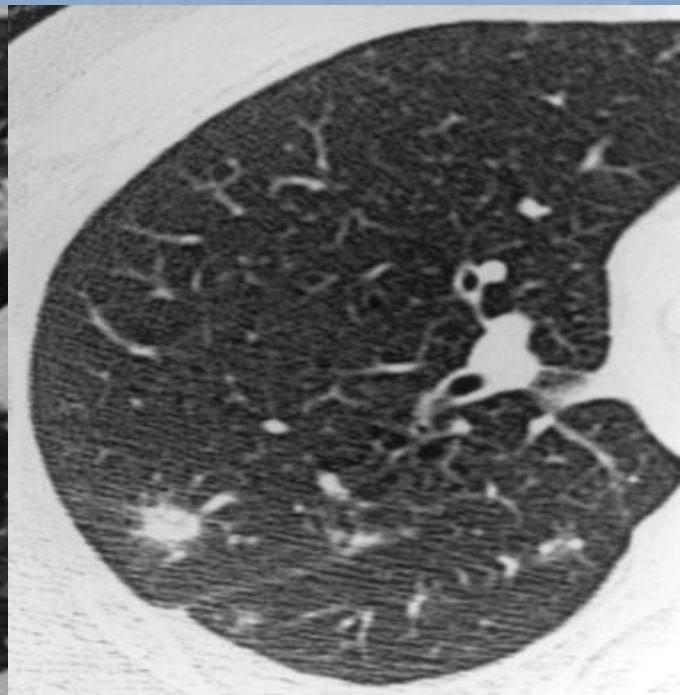


TABLE 9. CLINICAL SETTINGS ASSOCIATED WITH ORGANIZING PNEUMONIA PATTERN

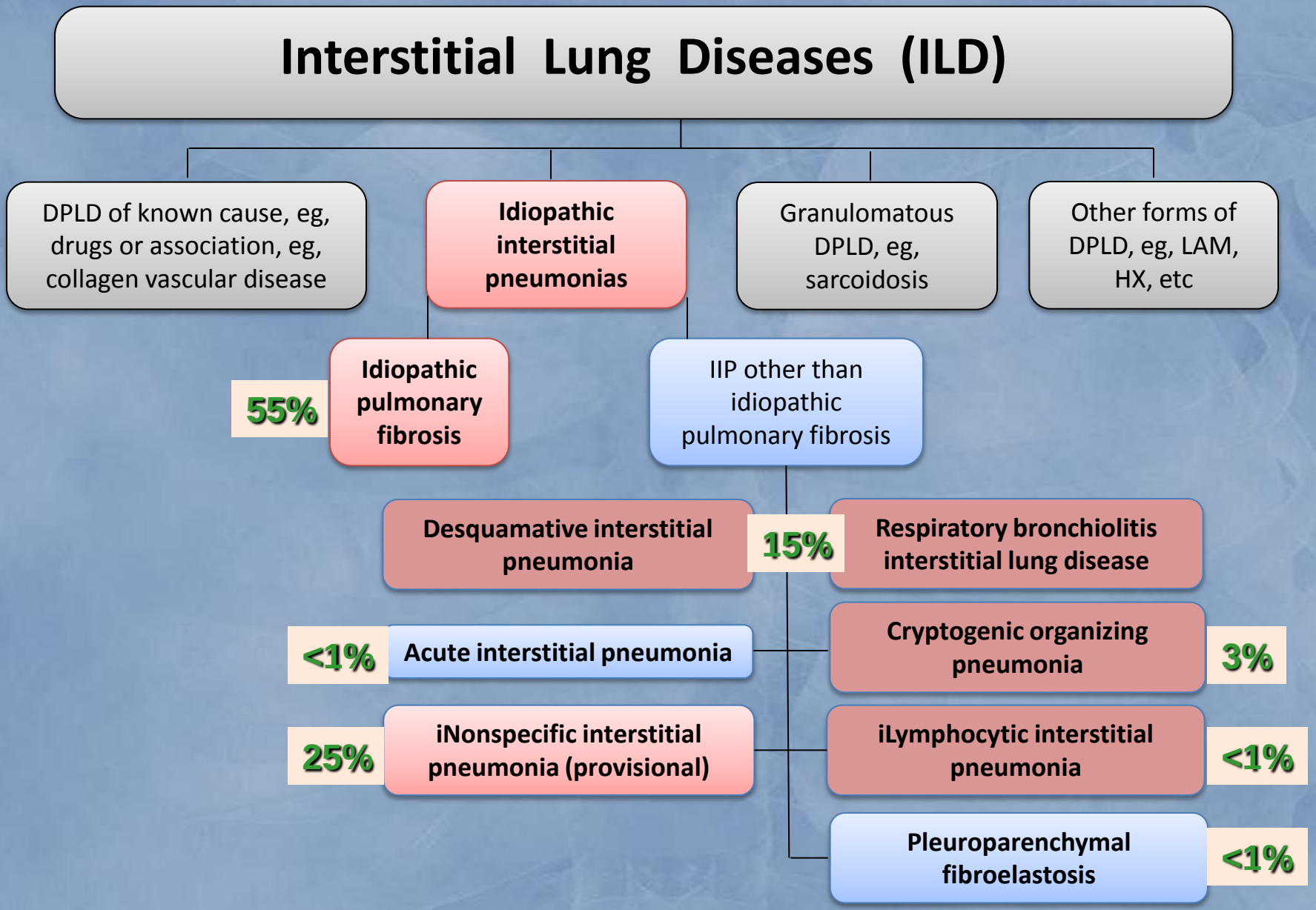
As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
Organizing diffuse alveolar damage
Organizing infections
Organization distal to obstruction
Organizing aspiration pneumonia
Organizing drug reactions, fume, and toxic exposures
Collagen vascular disease
Extrinsic 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.

Cryptogenic Organizing Pneumonia (COP)
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

Interstitial Lung Diseases (ILD)

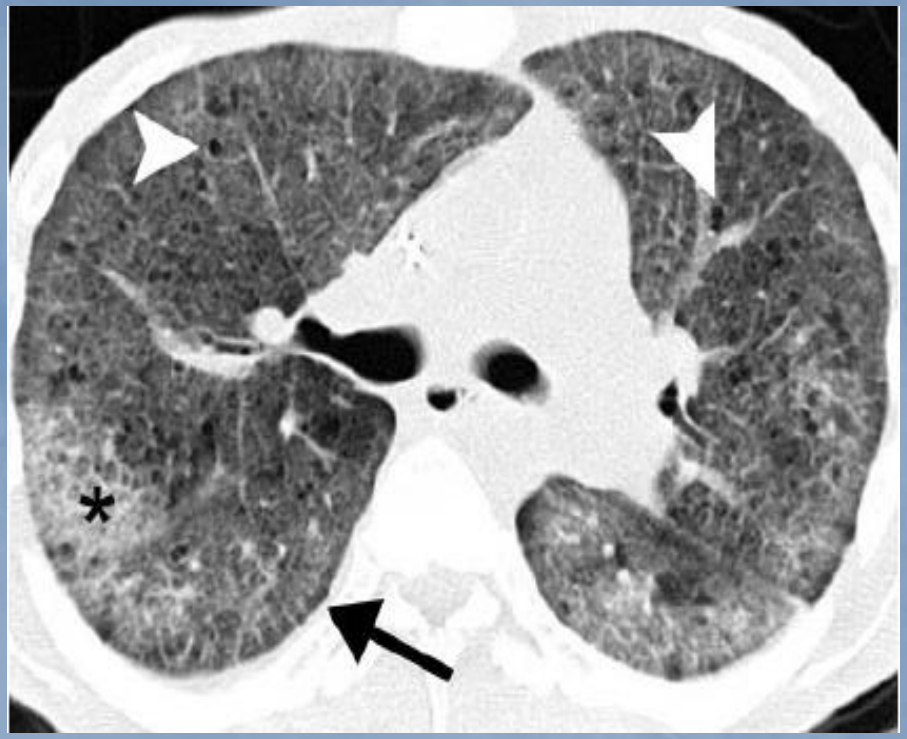


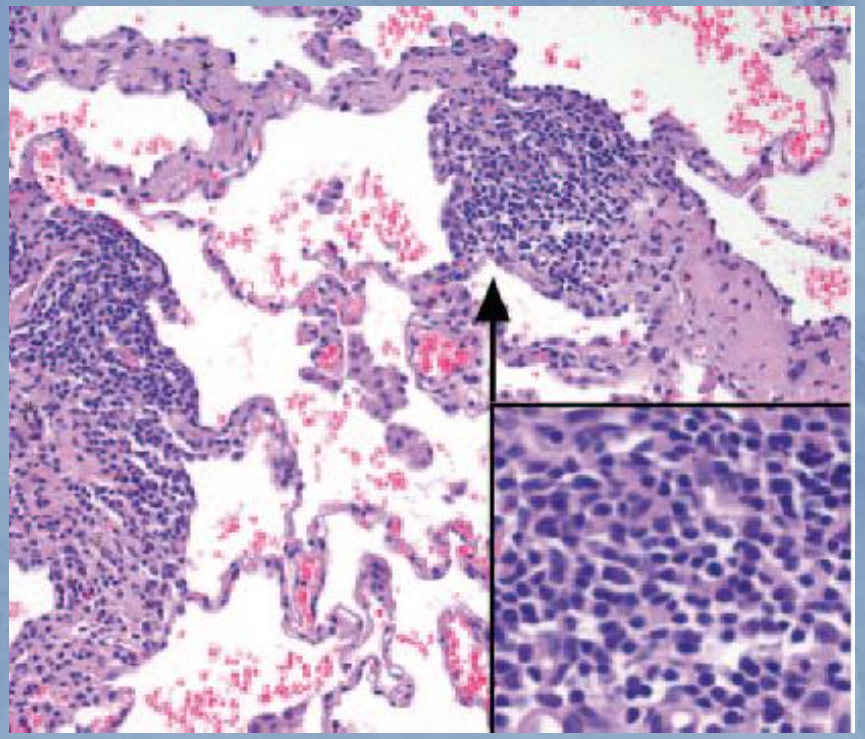
Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

Lymphocytic Interstitial Pneumonia (LIP)

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

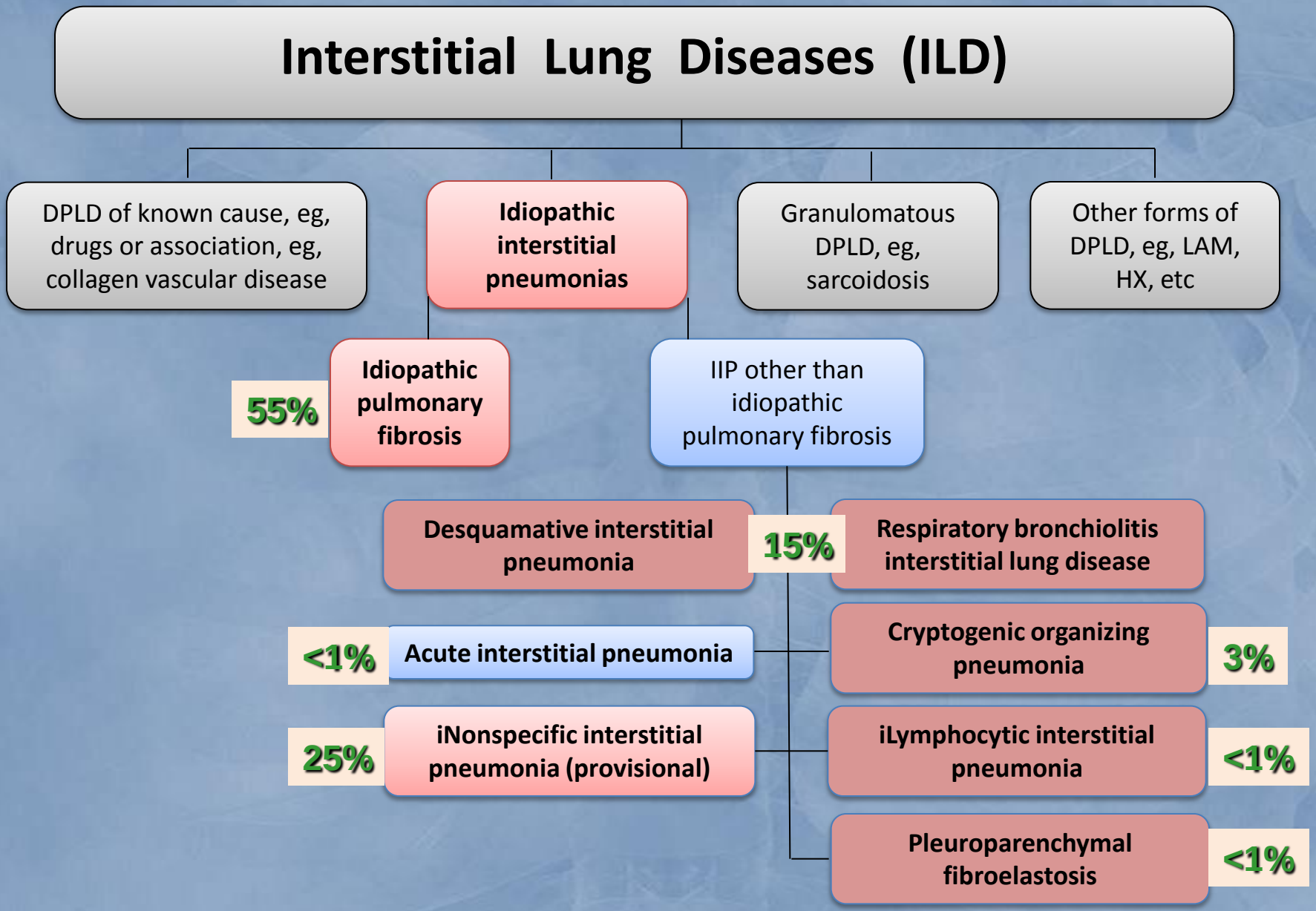
Eur Respir J 2006; 28: 364–369





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.

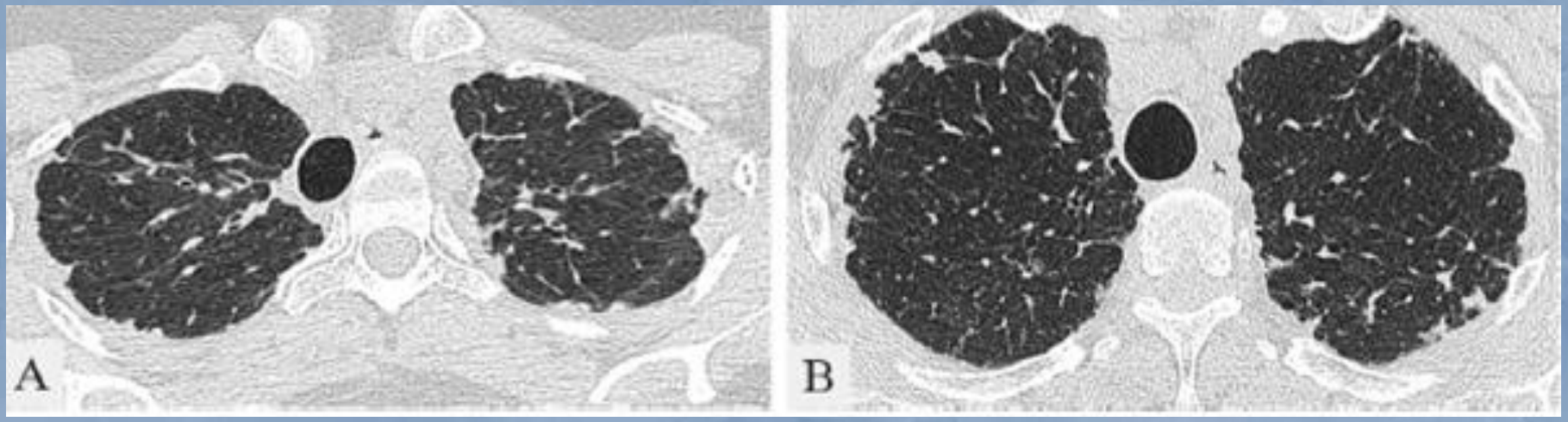
Interstitial Lung Diseases (ILD)

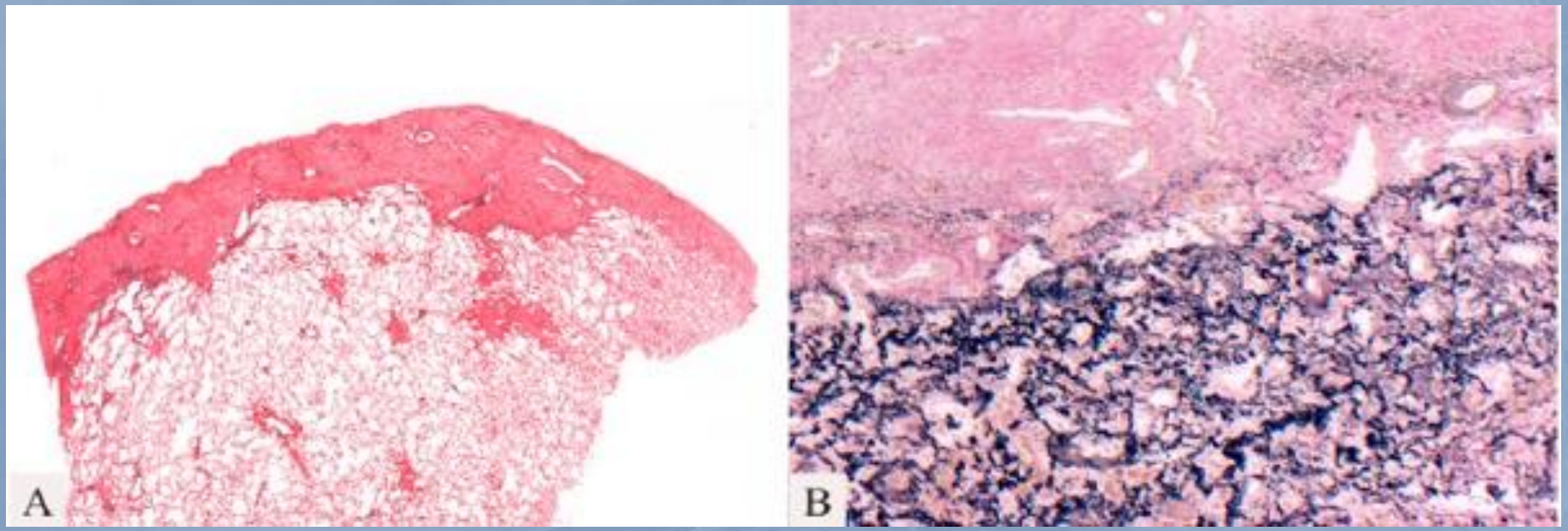


Travis WD, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2013

Pleuroparenchymal Fibroelastosis (PPFE)

PPFE is a rare condition that consists of fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes. HRCT shows dense subpleural consolidation with traction bronchiectasis, architectural distortion, and upper lobe volume loss (Figures 7A and 7B) (113). The fibrosis is elastotic, and intraalveolar fibrosis is present (Figures 8A and 8B) (113–117). It presents in adults with a median age of 57 years and has no sex predilection (113). Approximately half of patients have experienced recurrent infections. Pneumothorax is common. A minority has familial interstitial lung disease and nonspecific auto-antibodies. Histologically, biopsies may show mild changes of PPFE or other patterns such as UIP. Disease progression occurs in 60% of patients with death from disease in 40% (113, 118).


A
B


A
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Interstitial Lung Diseases

- ILD of Known Cause or Association
  - Medications
  - Radiation
  - Connective Tissue Disease
  - Vasculitis & DAH
  - Hypersensitivity Pneumonitis
  - Pneumoconioses
- Idiopathic Interstitial Pneumonias
- Sarcoidosis & Other Granulomatous Diseases
- Other
  - LAM
  - Pulmonary LCH
  - Eosinophilic Pneumonias
  - Alveolar Proteinosis
  - Genetic Syndromes

Adapted from: ATS/ERS Guidelines for IIP. *Am J Respir Crit Care Med* 2002

Hypersensitivity pneumonitis (HP)

- **Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a complex syndrome of varying intensity, clinical presentation, and natural history, caused by an exaggerated immune response to the inhalation of a large variety of organic particles.**
- ***It can progress to disabling, fatal, end-stage lung disease.***

Hypersensitivity pneumonitis (HP)

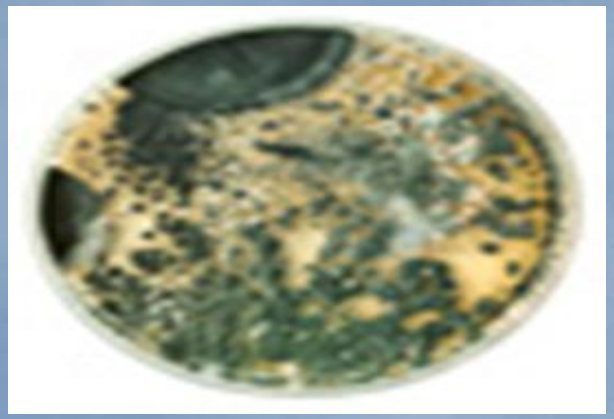
Etiology

More than 300 aetiologies of exposures to airborne antigens, including, but not limited to:

- ***agricultural dusts,***
- ***bioaerosols,***
- ***microorganisms (fungal, bacterial, or protozoal),***
- ***inorganic chemicals***
- ***ingestion of drugs***

Table 1
Examples of Hypersensitivity Pneumonitis

Disease	Antigen Source	Putative Antigen
Bird fancier's disease	Various birds	Protein in avian feces, feathers
Cheese worker's lung	Moldy cheese	*Penicillium* species
Coffee worker's lung	Coffee bean	Unknown
Farmer's lung	Moldy hay	Thermophilic actinomycetes
Furrier's lung	Animal fur	Protein in animal fur
Hot tub lung	Warm water	*Mycobacterium avium* complex
Humidifier lung	Warm water	Thermophilic actinomycetes
Japanese summer disease	Moldy houses	Various fungi
Machine worker's lung	Metal-cutting fluid	*Mycobacterium* species, Gram-negative bacilli
Malt worker's lung	Moldy malt	*Aspergillus* species
Mushroom worker's lung	Mushrooms	Mushroom spores, various other fungi
Peat moss worker's lung	Moldy peat moss	Various fungi
Sauna bather's lung	Sauna water	Various fungi
Sequoiosis	Moldy redwood dust	Various fungi
Suberosis	Cork	*Aspergillus* species, cork dust



Hypersensitivity pneumonitis (HP)

Clinical presentation

ACUTE HP

Presents 4–8 h after often heavy exposure with fever, malaise, cough, dyspnea and chest tightness.

The symptoms remit over 24–48 h in the absence of further exposure and repeat after reexposure *(Monday morning fever*).

SUBACUTE HP

Continued lower-level exposure.

Dyspnea, productive cough and fatigue develop insidiously and weight loss is common. Inspiratory crackles.

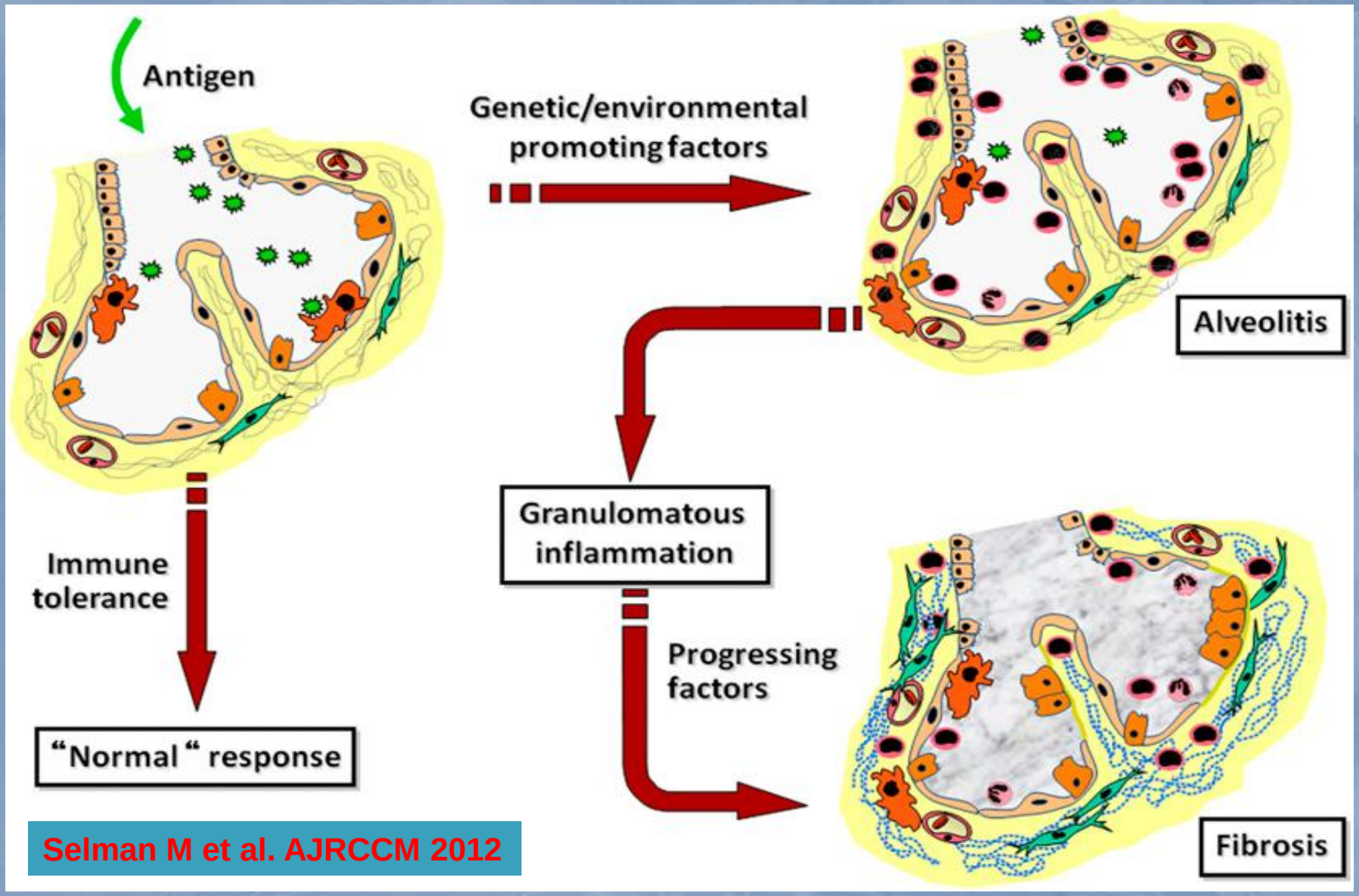
CHRONIC HP

No history of acute symptoms, diffuse pulmonary fibrosis which must be distinguished from IPF and fibrotic NSIP.

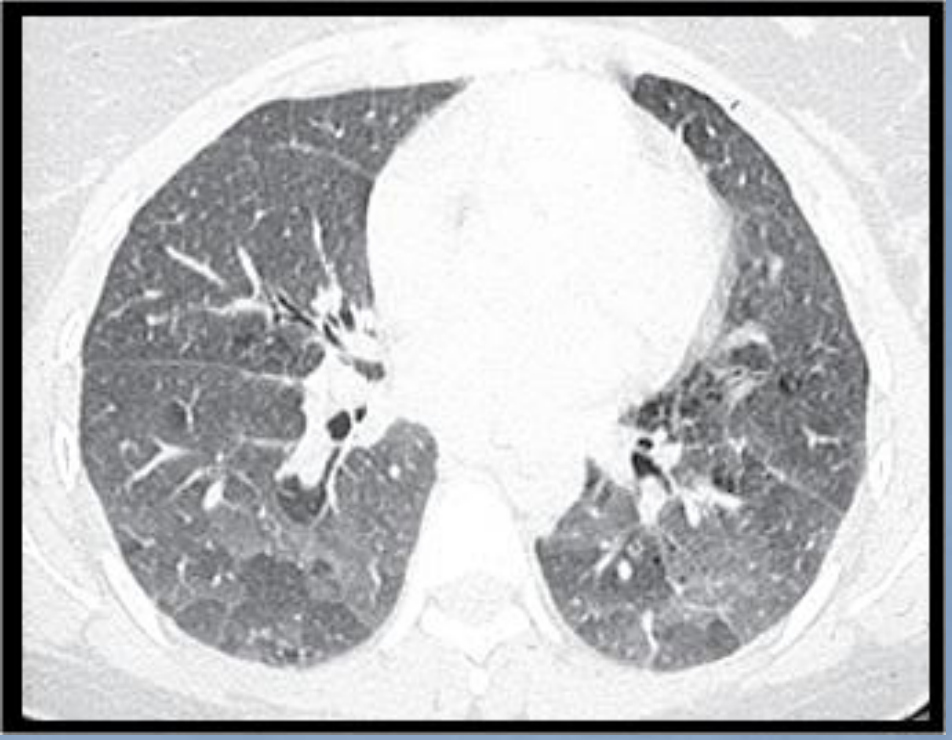
ACUTE EXACERBATION HP

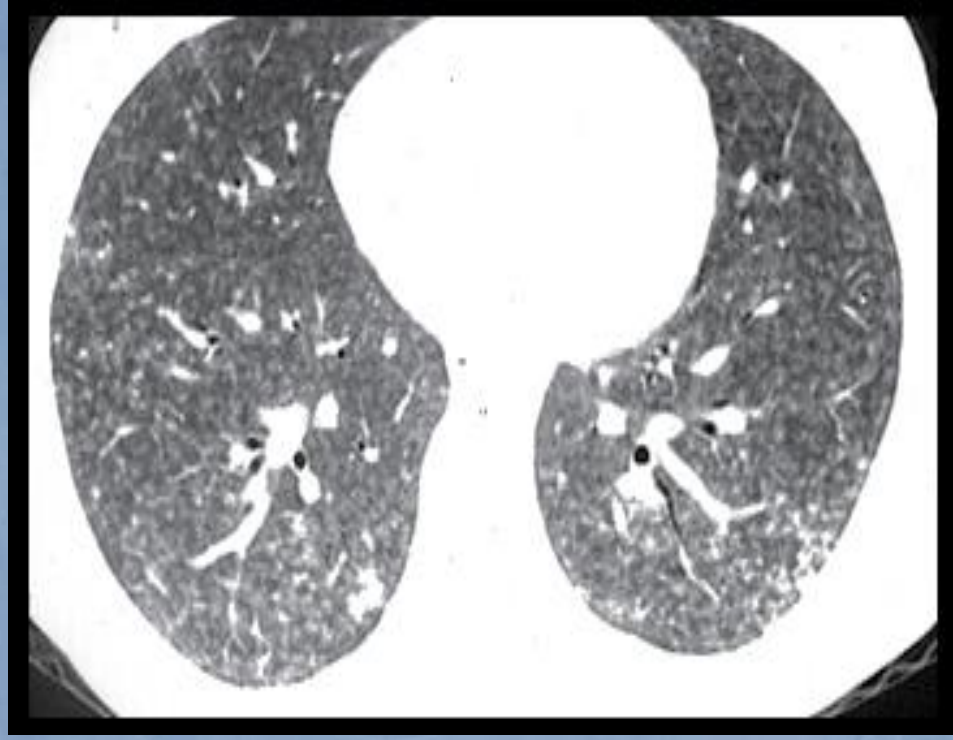
Hypersensitivity pneumonitis (HP)

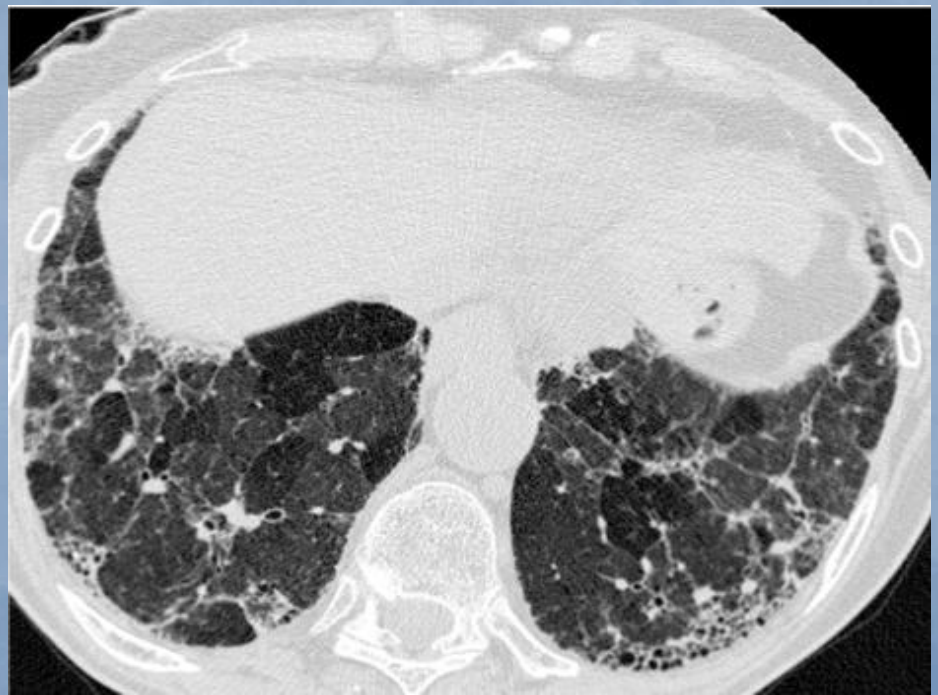
Pathogenesis



Selman M et al. AJRCCM 2012







Hypersensitivity pneumonitis (HP)

Diagnostic criteria

MAJOR	MINOR
1. Compatible Symptoms	1. Bibasilar crackles
2. Evidence of antigen exposure	2. Arterial hypoxemia
3. Compatible HRCT changes	3. Low diffusion
4. BALF lymphocytosis (>40%)	
5. Compatible biopsy findings	
6. Positive inhalational challenge	*Schuyler M, Cormier Y. CHEST 1997*

Hypersensitivity pneumonitis (HP)

Conclusion

- HP represents an immunologic reaction to an inhaled-organic- antigen.
- The prevalence and incidence of HP vary.
- Clinical presentations are acute, subacute, or chronic.
- The diagnosis of HP requires a high index of suspicion and should be included in the differential diagnosis of any ILD. In difficult cases MDD is essential.
- Avoidance of the causative antigen, is important.
- Corticosteroids may have a role in severe or progressive disease.

Conclusions

- ✓ IPF –non IPF
- ✓ Search for etiologic parameters (environmental, professional, drugs, CVD)
- ✓ Multidisciplinary approach-specific diagnosis- prognosis-appropriate treatment options
- ✓ Search for the genetic and biologic profile for each patient
- ✓ Early intervention
- ✓ Management of comorbidities
- ✓ New approach to the AE-IPF as a DAD upon IPF idiopathic or not idiopathic
- ✓ Participation of patients in clinical trials

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

‘ΜΟΝΑΔΕΣ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ’

2017-2018

Διάχυτα διάμεσα νοσήματα των πνευμόνων (ΔΔΠ) ΙΙ

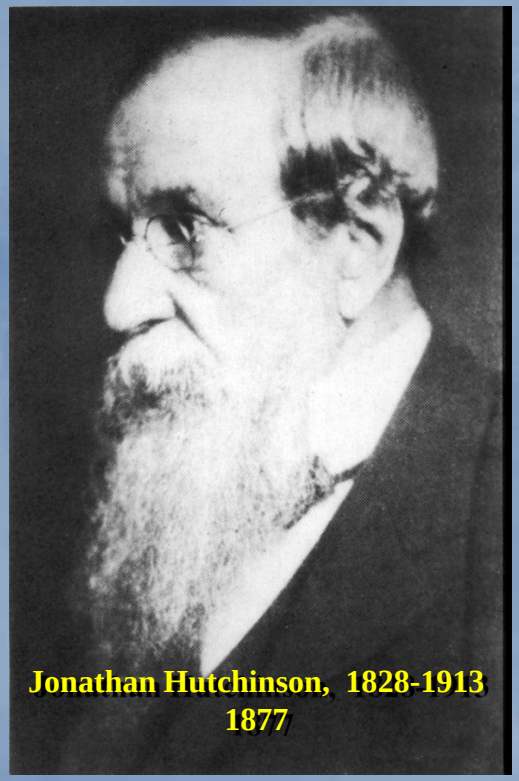
Σαρκοείδωση

Λυκούργος Κολιλέκας
Επιμελητής Α’ ΕΣΥ
7η Πνευμονολογική Κλινική
ΝΝΘΑ ‘’ Η ΣΩΤΗΡΙΑ”

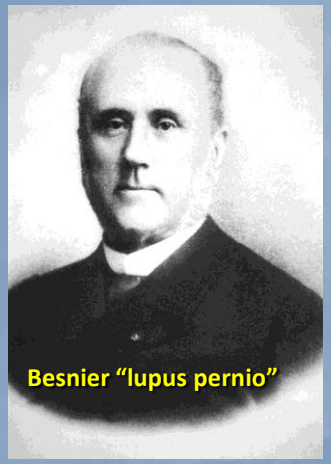
Interstitial Lung Diseases

- ILD of Known Cause or Association
  - Medications
  - Radiation
  - Connective Tissue Disease
  - Vasculitis & DAH
  - Hypersensitivity Pneumonitis
  - Pneumoconioses
- Idiopathic Interstitial Pneumonias
- **Sarcoidosis** & Other Granulomatous Diseases
- Other
  - LAM
  - Pulmonary LCH
  - Eosinophilic Pneumonias
  - Alveolar Proteinosis
  - Genetic Syndromes

Adapted from: ATS/ERS Guidelines for IIP. *Am J Respir Crit Care Med* 2002

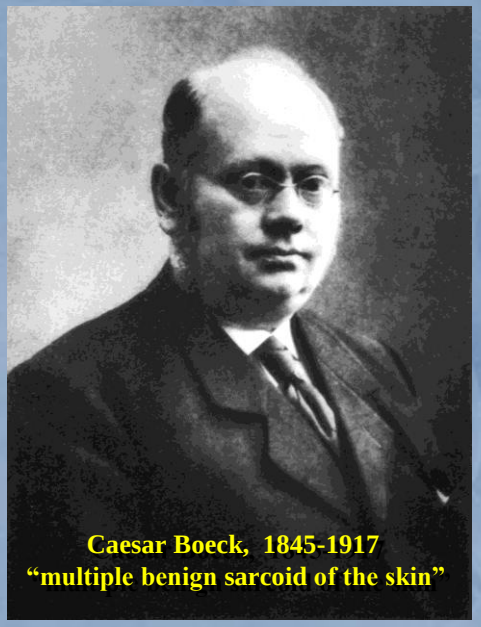


Jonathan Hutchinson, 1828-1913
1877

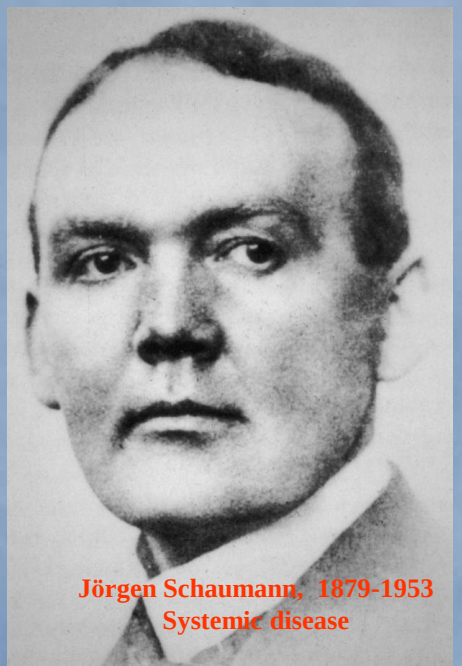


Besnier "lupus pernio"

FIGURE 1.2 The first patient with sarcoidosis described by J. Hutchinson had multiple, raised, dusty-red patches on his feet, fingers, and arms.



Caesar Boeck, 1845-1917
"multiple benign sarcoid of the skin"



Jörgen Schaumann, 1879-1953
Systemic disease

American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Statement on Sarcoidosis

This Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) was adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999

Sarcoidosis is a multisystem granulomatous disorder of unknown cause(s).

It commonly affects young and middle-aged adults

Frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved.

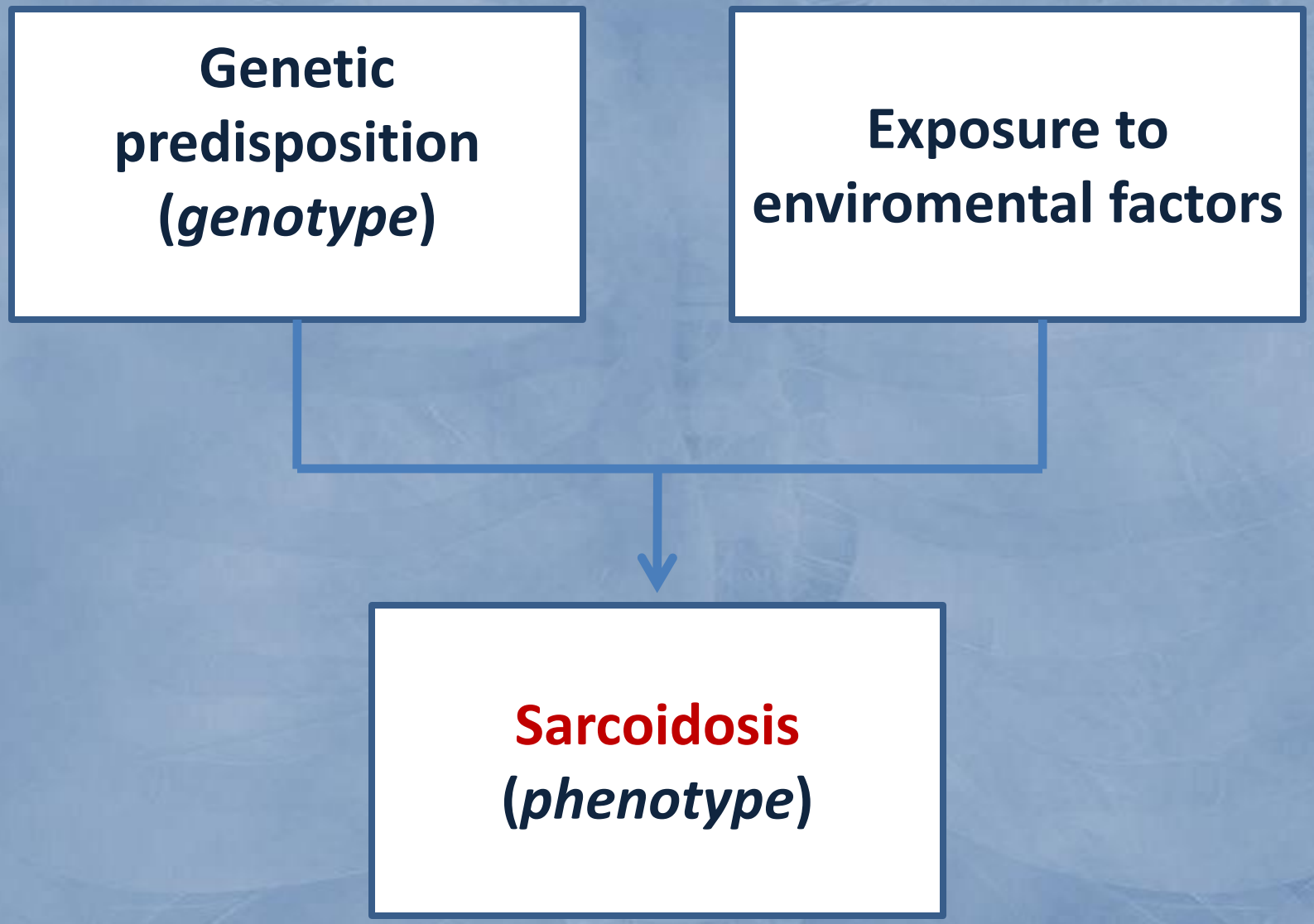
The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas.

EPIDEMIOLOGY

Ethnic Group	Incidence per 100,000	Peak Decade of Incidence	Percent Increased Risk in Females
European Americans	3–10	4th–5th	10–20
African Americans	35–80	3rd–4th	30
Northern Europeans	15–20	3rd	30
Southern Europeans	1–5	4th–5th	33
Japanese	1–2	3rd	10–20
Greece	1,07		

Rybicki A, *et al. Semin Respir Crit Care Med 2007*
Karakatsani A, *et al. Respir Med 2007*

AETIOLOGY


Genetic predisposition (*genotype*)
Exposure to enviromental factors
Sarcoidosis (*phenotype*)

GENETIC PREDISPOSITION

- Sarcoidosis develops in genetically predisposed individuals that are exposed to unknown antigens.
- There is a statistically significant increased risk for the disease among family members of sarcoidosis patients
- The disease differs in different ethnic groups.
- It is a genetically complex disease, with many genes contributing, both as risk factors but also with an influence on the disease course.
- The strongest genetic associations with sarcoidosis are found within the major histocompatibility complex (MHC) [human leukocyte antigen (HLA) in humans]-region on chromosome 6. This region includes, besides the HLA class I and class-II genes.

SUMMARY OF HLA ASSOCIATION STUDIES OF SARCOIDOSIS

HLA	Risk Alleles	Finding
HLA-A	A*1	Susceptibility
HLA-B	B*8	Susceptibility in several populations
HLA-DPB1	*0201	Not associated with sarcoidosis
HLA-DQB1	*0201	Protection, Löfgren's syndrome, mild disease in several populations
	*0602	Susceptibility/disease progression in several groups
HLA-DRB1	*0301	Acute onset/good prognosis in several groups
	*04	Protection in several populations
	*1101	Susceptibility in whites and African Americans. Stage II/III chest X-ray
HLA-DRB3	*1501	Associated with Löfgren's syndrome
	*0101	Susceptibility/disease progression in whites

Newman L, *et al. AJRCCM 2004*
Iannuzzi M, *et al. AJRCCM 2007*
Iannuzzi M, *Semin Respir Crit Care Med 2007*

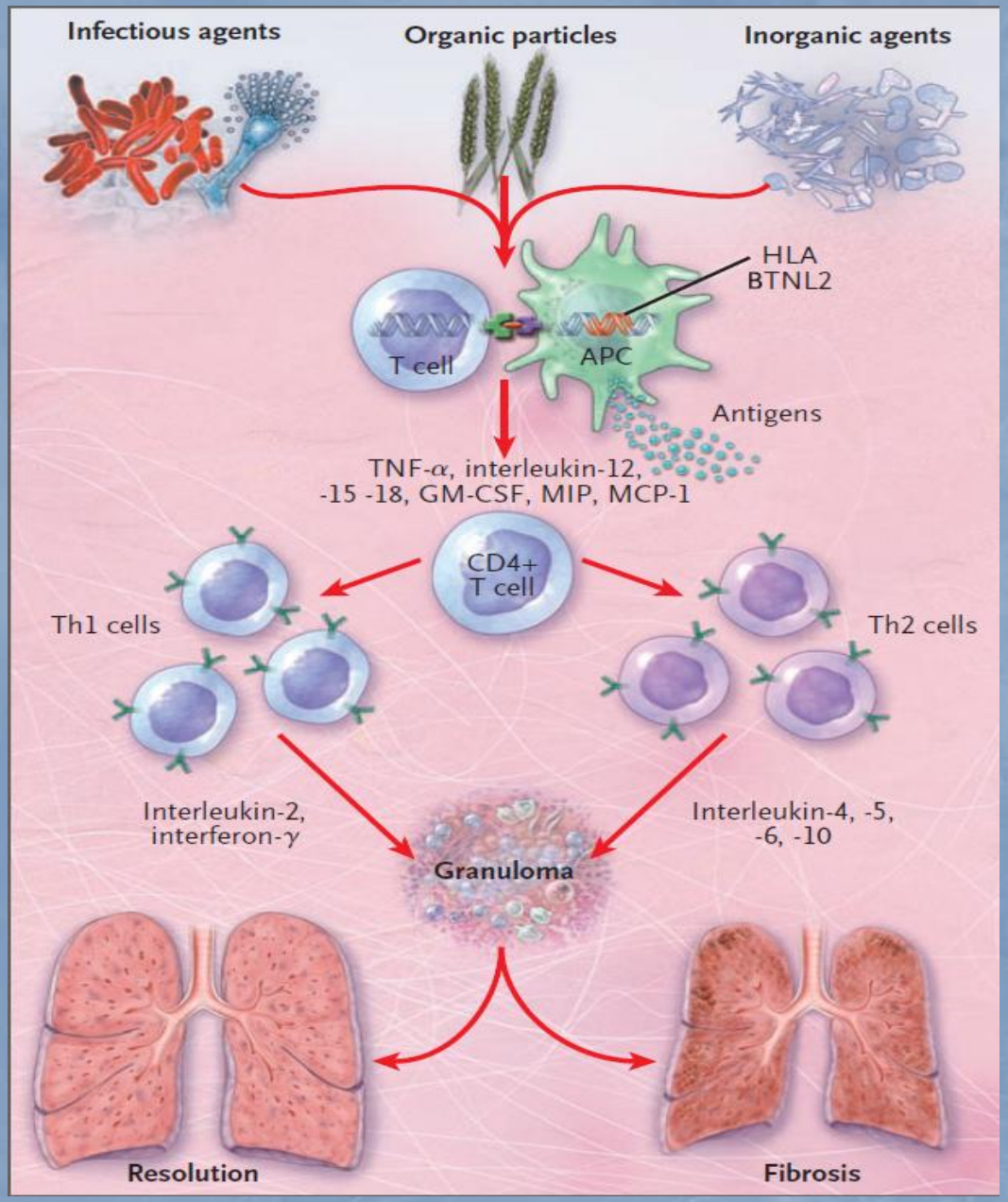
ENVIROMENTAL FACTORS

Table 2. – Potential infectious organisms or organic/inorganic substances triggering sarcoidosis

Category of trigger	Trigger
Infectious agents	*Mycobacterium tuberculosis*
	Atypical mycobacterial species
	Cell wall-deficient mycobacterial forms
	Propionibacterium acnes/granulosum
	Rickettsia helvetica
	Borrelia burgdorferi
	Mycoplasma spp.
	Viruses (*e.g.* human herpes viruses, Epstein–Barr)
Inorganic substances	Aluminium
	Zirconium
	Man-made mineral fibres
	Silica
	Silicone
	Clay
	Talc
Organic substances	Pine tree pollen
	Starch

Grutters J, *et al. Eur Respir Mon 2009*

IMMUNOPATHOGENESIS



The interaction between antigen-presenting cells (APCs) expressing HLA class II molecules and CD4+ T lymphocytes is considered pivotal for the inflammatory process that eventually leads to granuloma formation.

Iannuzzi M, *et al. NEJM 2007*

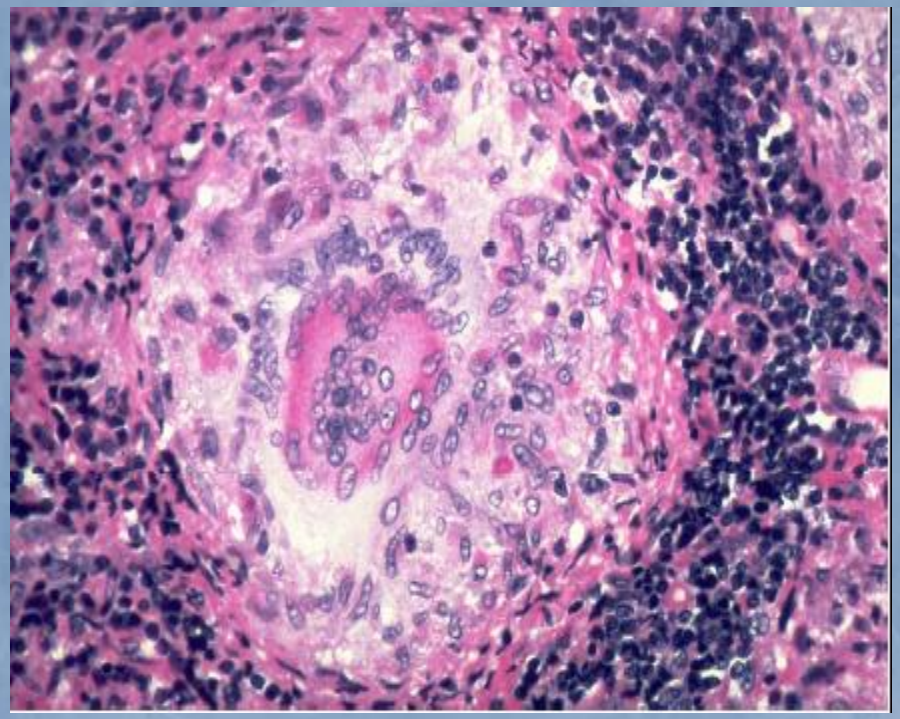
PATHOLOGOANATOMY-GRANULOMA

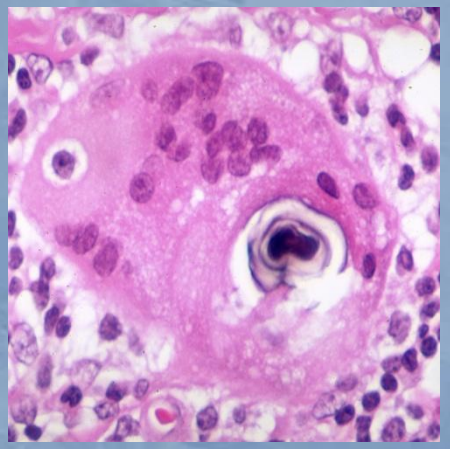
- The sarcoid granuloma usually consists of a compact (organized) collection of mononuclear phagocytes (macrophages and epithelioid cells).

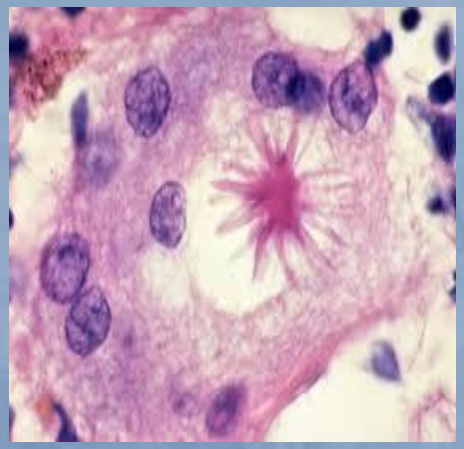
- Typically, there is no necrosis within the sarcoid granuloma; however, on occasion, there is a small to moderate amount of necrosis.

- Usually, giant cells fuse within the sarcoid granuloma to form multinucleated giant cells. These granulomas are typically surrounded by lymphocytes in the periphery.

- A variety of inclusions may be present within the sarcoid granuloma including asteroid bodies, Schaumann's bodies, birefringent crystals, and Hamazaki–Wesenberg bodies; however these inclusions are not specific or diagnostic of sarcoidosis.







ΣΑΡΚΟΕΙΔΩΣΗ
Συστηματική νόσος

Ο ασθενής με τη νόσο
«προσεγγίζει και προσεγγίζεται»
(από) γιατρούς διαφόρων ειδικοτήτων

General practitioner
Fever, anorexia, weight loss, lymphadenopathy, parotid enlargement, acute arthritis, nasal stuffiness, hoarseness

Dermatologist
Erythema nodosum
Lupus pernio
Maculopapular rash, scars, keloids, nodules

Cardiologist
Dyspnea, cardiac failure, heart block
Arrhythmias, abnormal ECG
Sudden death

Chest physician
Dyspnea, cough, wheezing, abnormal chest X ray, cor pulmonale, lung function impairment

Radiologist
Abnormal chest X-ray, bilateral hilar lymphadenopathy, interstitial fibrosis, bone cysts

Rheumatologist
Arthritis
Bone cysts

Nephrologist
Renal failure

Urologist
Hypercalciuria

Ophthalmologist
Iritis, choroiditis, keratoconjunctivitis, glaucoma, cataract, enlarged lacrimal glands, dry eye

Neurologist
Cranial nerve palsies, papilledema, meningitis, myopathy, peripheral neuropathy, space occupying lesions

Endocrinologist
Diabetes insipidus
Hypercalcemia
Hyperthyroidism

Hepatologist
Liver granuloma
Portal hypertension
Abnormal liver function tests

Hematologist
Anemia
Leucopenia
Thrombocytopenia
Hypersplenism

Otorhinolaryngologist
Parotid enlargement
Hoarseness
Nasal stuffiness

FREQUENCY OF ORGAN INVOLVEMENT

Lung - 90%
Lymph nodes - 75-90%
Pleura - 1-5%
Skin - 25%
Eye - 25%
Nasal mucosa - 20%
Larynx - 5%
Bone marrow - 15-40%
Spleen -50-60%
Liver -60-90%
Kidney - Rare
Calcium disorder - 11%
CNS - 5%
Bones - 5%
Joints - 25-50%
Heart - 5%
Endocrine glands - Rare
Parotid gland - 10%
GI tract - Rare

SARCOIDOSIS
The central role of pulmonary specialist

Since the intrathoracic manifestations are the most frequent, and the pulmonary specialist usually sees most of the patients

If there is a need for consultation of another organ specialist during the follow-up, the pulmonary physician will transfer the patient, but should keep the general management of the patient during the course of his disease

In this regard, the management of patients with sarcoidosis requires a **multidisciplinary approach**

ΣΑΡΚΟΕΙΔΩΣΗ
Συχνό πρόβλημα για το πνευμονολόγο

- Η πλέον συνήθης διάχυτη πνευμονοπάθεια
- Ο πνεύμονας και οι λεμφαδένες νοσούν σχεδόν πάντα
- Η φτωχή πρόγνωση που παρατηρείται σε μειοψηφία ασθενών οφείλεται πρωταρχικά στη προοδευτικά εξελισσόμενη πορεία της πνευμονικής προσβολής, στην συμμετοχή καρδιάς και ΚΝΣ

CLINICAL ASPECTS

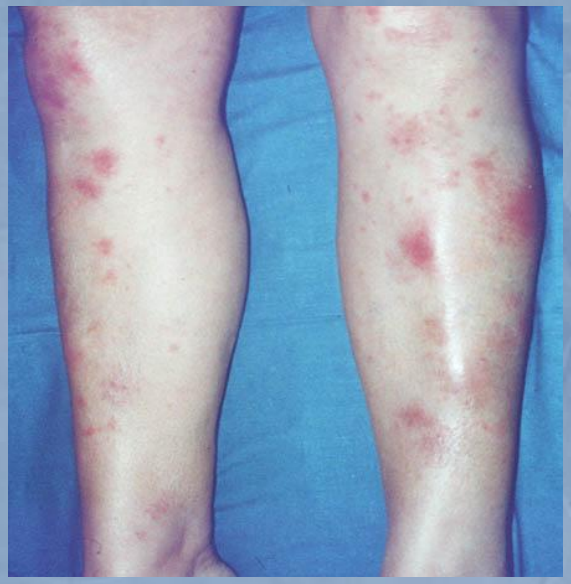
- Presentation depends on the extent and severity of the organ involved.
- Approximately 5% of cases are asymptomatic and incidentally detected by CXR.
- Systemic symptoms occur in 45% of cases such as:
  - Fever
  - Anorexia
  - Fatigue
  - Night sweats
  - Weight loss
- Dyspnea on exertion, cough, chest pain, and hemoptysis (rare) occur in 50% of cases.

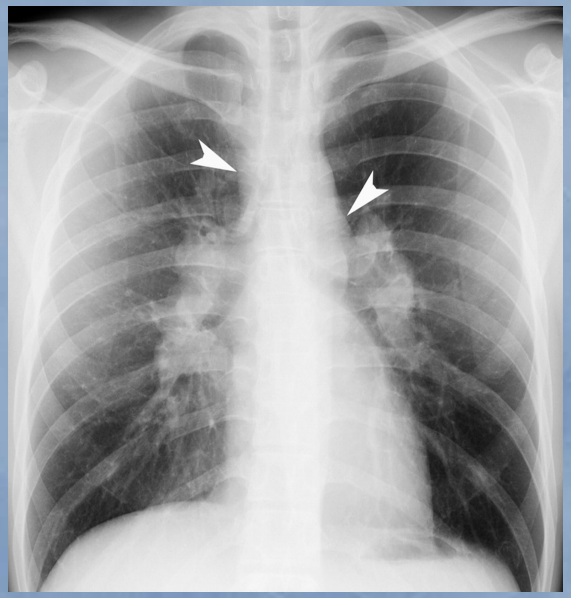
Löfgren's syndrome

an acute presentation consisting of:

- Fever
- Arthralgia
- Erythema nodosum
- Bilateral hilar adenopathy (BHL)

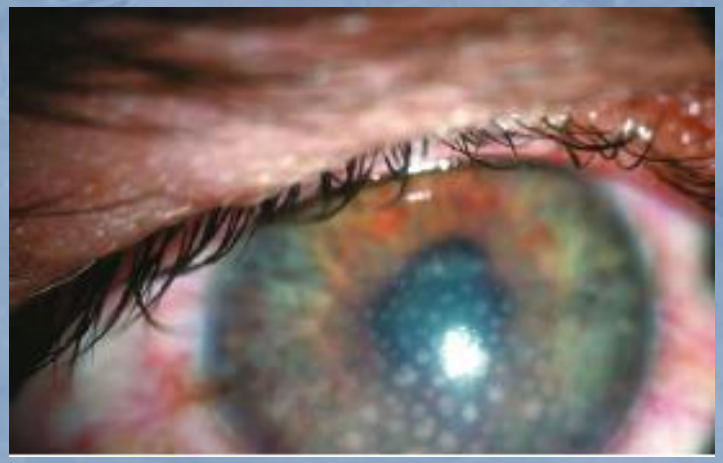
- Occurs in 9 to 34% of patients.

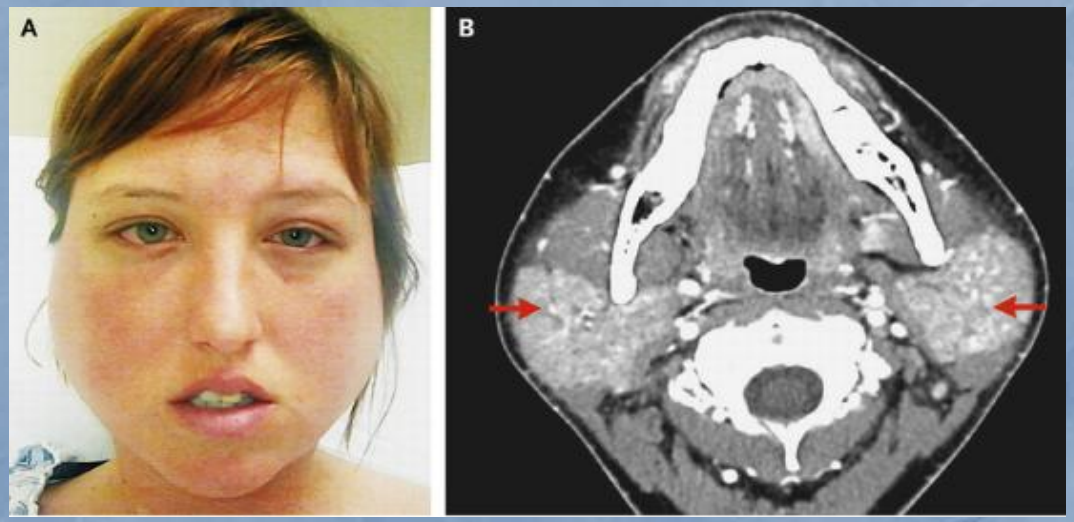


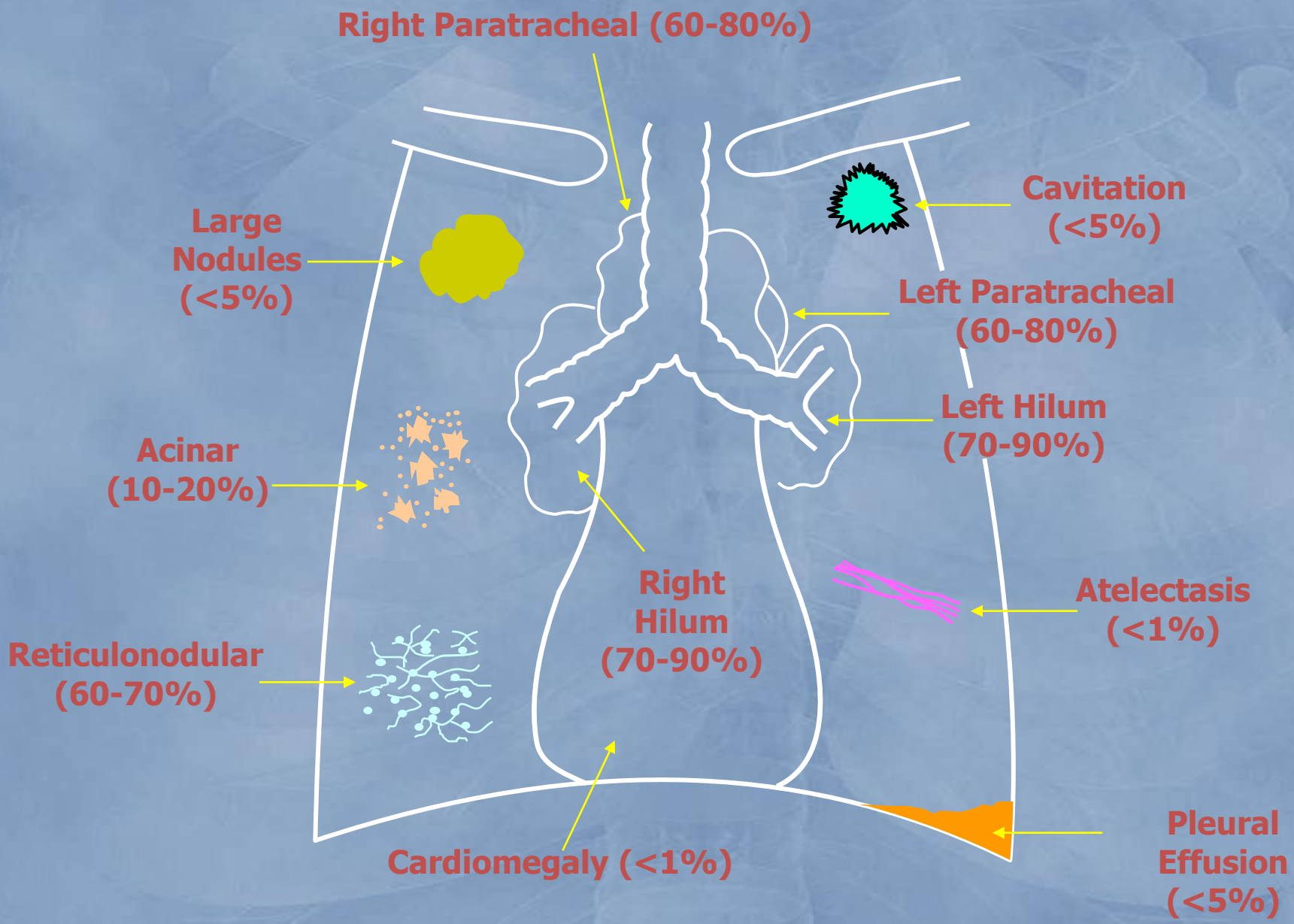


Heerford's syndrome

- Anterior Uveitis
- Fever (often)
- Parotid enlargement
- Facial palsy (often)

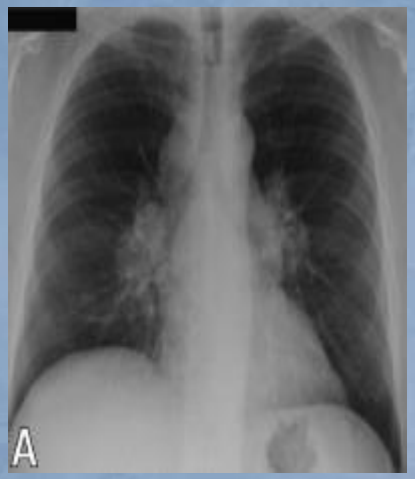


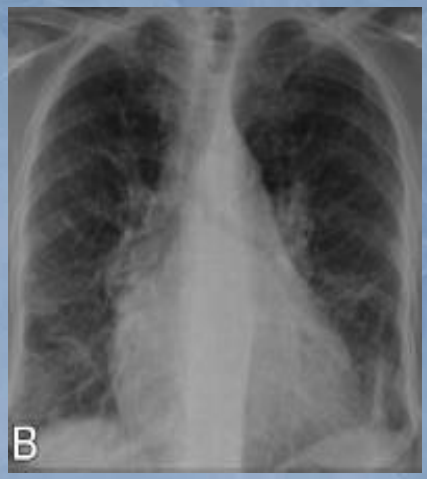


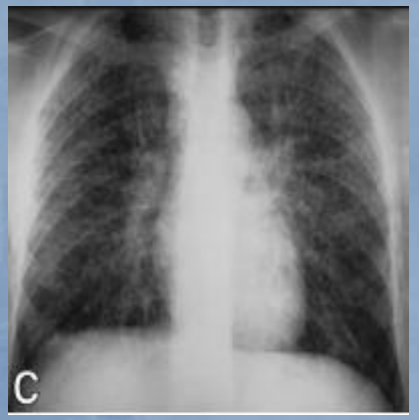

Right Paratracheal (60-80%)
Cavitation (<5%)
Large Nodules (<5%)
Left Paratracheal (60-80%)
Left Hilum (70-90%)
Acinar (10-20%)
Right Hilum (70-90%)
Atelectasis (<1%)
Reticulonodular (60-70%)
Cardiomegaly (<1%)
Pleural Effusion (<5%)

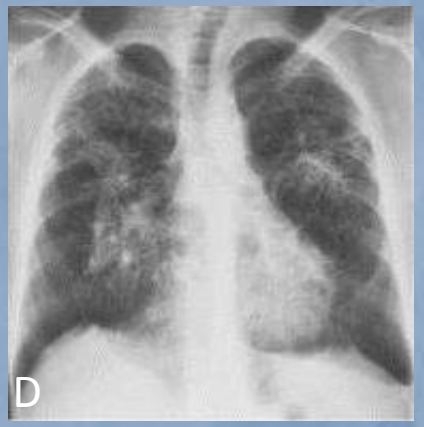
Staging of Sarcoidosis on the Basis of Chest Radiographs

STAGE 0	No abnormalities	5%–10%
STAGE 1	Lymphadenopathy (fig. A)	50%
STAGE 2	Lymphadenopathy + pulmonary infiltration (fig. B)	25%–30%
STAGE 3	Pulmonary infiltration (fig. C)	10%–12%
STAGE 4	Fibrosis	5% (up to 25% during the course of the disease)





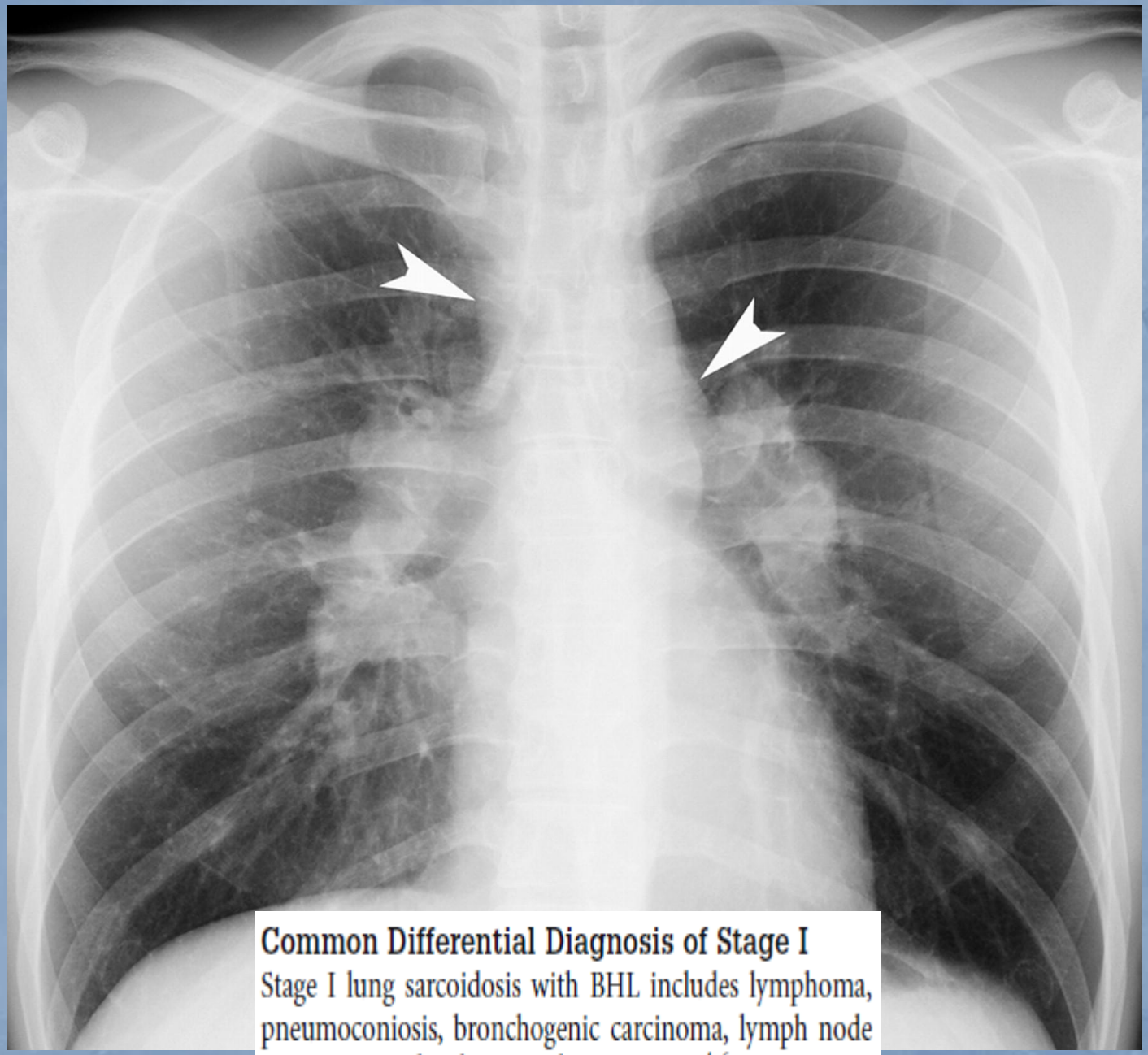




Radiographic stage	Chest X-ray	Frequency (%)	Resolution (%)
0	Normal	5–15	
I	BHL	25–65	60–90
II	BHL and pulmonary infiltrates	20–40	40–70
III	Pulmonary infiltrates without BHL	10–15	10–20
IV	Advanced pulmonary fibrosis	5	0

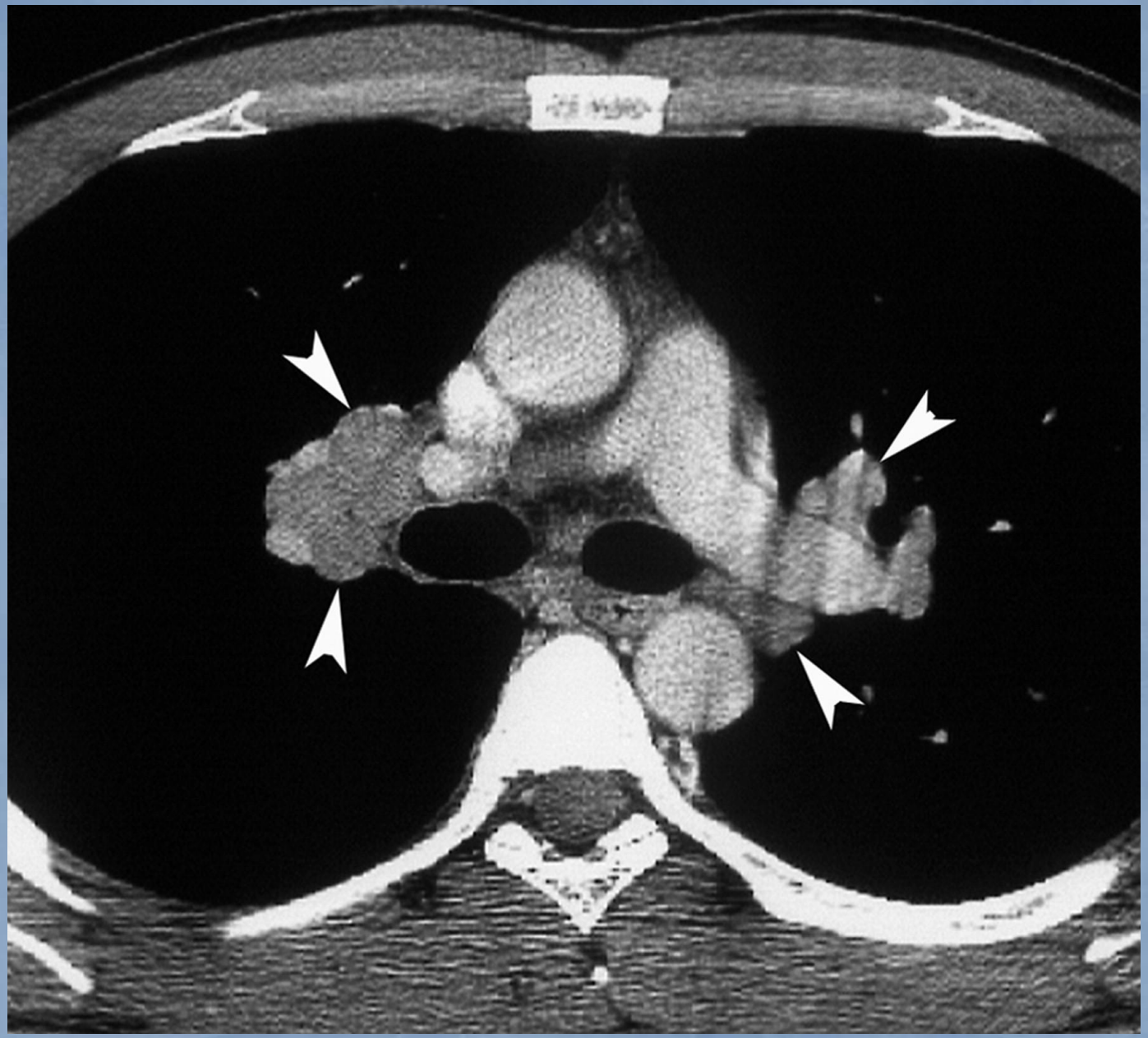
Prognostic information

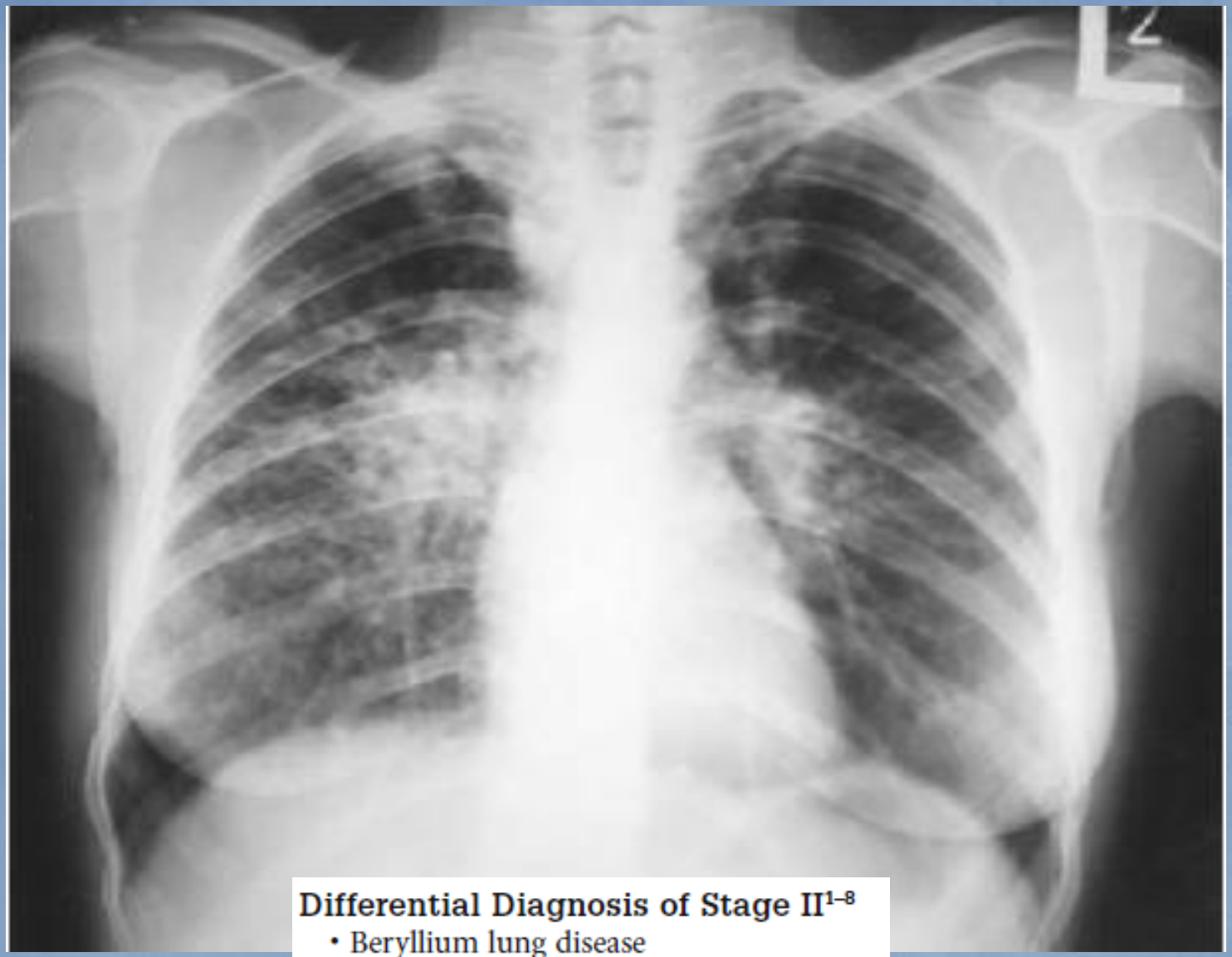
Great interobserver variability



Common Differential Diagnosis of Stage I

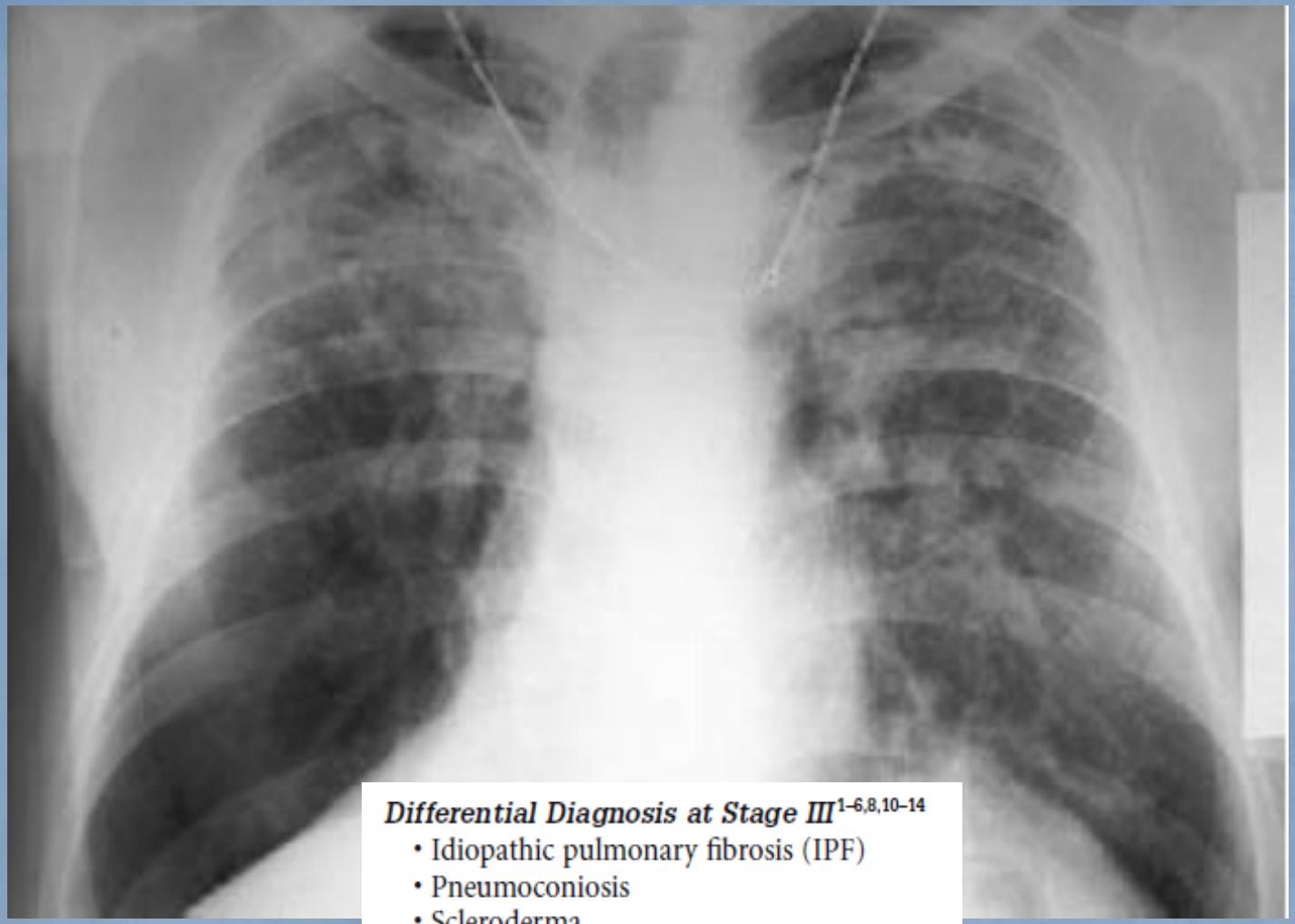
Stage I lung sarcoidosis with BHL includes lymphoma, pneumoconiosis, bronchogenic carcinoma, lymph node metastasis, and pulmonary hypertension.[4–6]





Differential Diagnosis of Stage II[1–8]

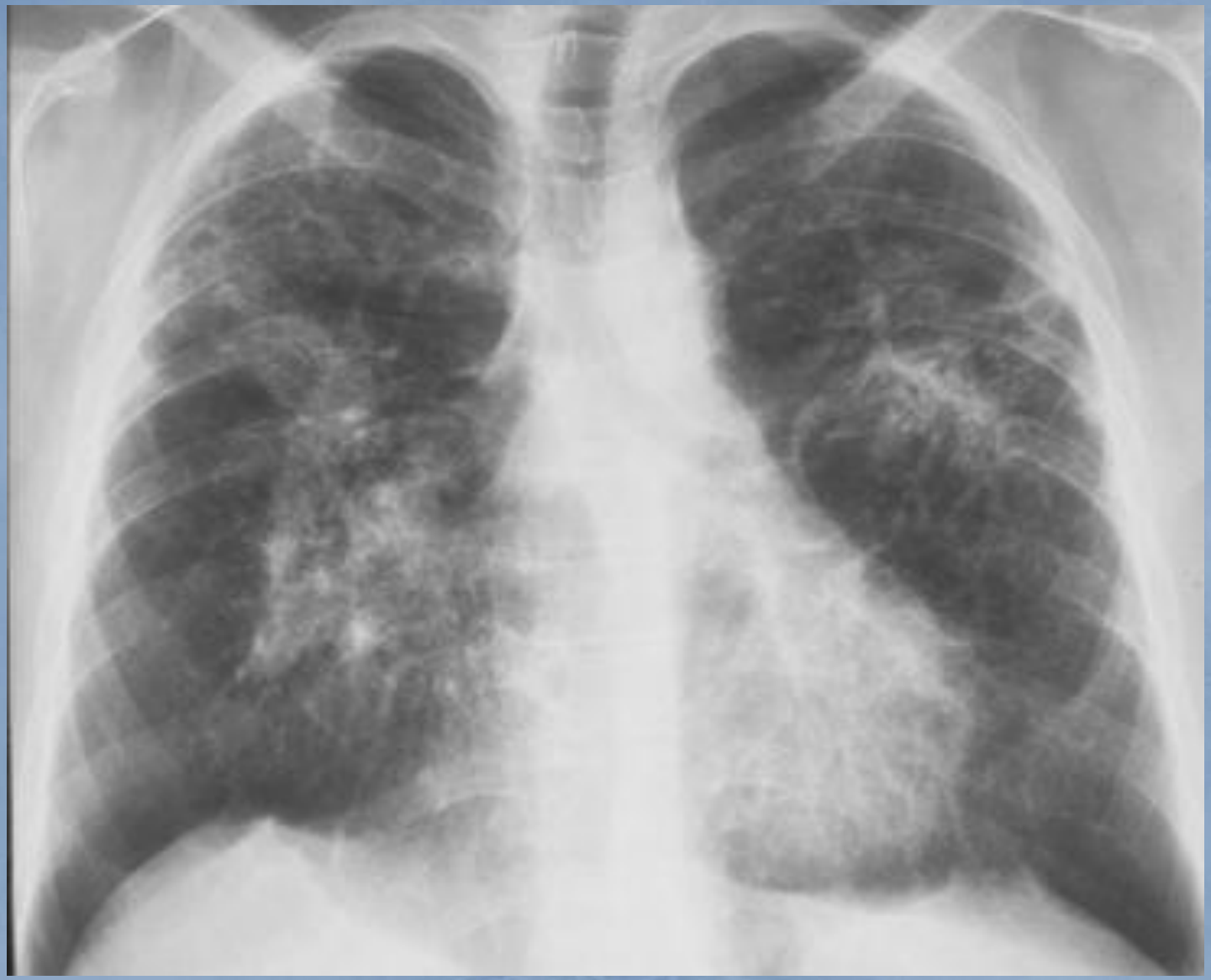
- Beryllium lung disease
- Silicosis
- Tuberculosis
- Lymphangitic carcinoma
- Coccidioidomycosis
- Brucellosis



Differential Diagnosis at Stage III[1–6,8,10–14]

- Idiopathic pulmonary fibrosis (IPF)
- Pneumoconiosis
- Scleroderma
- Rheumatoid lung
- Lupus erythematosus, lung involvement

- Extrinsic alveolitis
- Lymphangitic carcinomatosis
- Tuberculosis (upper lobe localization)
- Eosinophilic granuloma
- Hemosiderosis
- Drug reaction



CHEST HRCT FINDINGS

Table 1
Typical and Atypical Features of Pulmonary Sarcoidosis at High-Resolution CT

Typical features
Lymphadenopathy: hilar, mediastinal (right paratracheal), bilateral, symmetric, and well defined
Nodules: micronodules (2–4 mm in diameter; well defined, bilateral); macronodules (≥5 mm in diameter, coalescing)
Lymphangitic spread: peribronchovascular, subpleural, interlobular septal
Fibrotic changes: reticular opacities, architectural distortion, traction bronchiectasis, bronchiolectasis, volume loss
Bilateral perihilar opacities
Predominant upper- and middle-zone locations of parenchymal abnormalities
Atypical features
Lymphadenopathy: unilateral, isolated, anterior and posterior mediastinal
Airspace consolidation: masslike opacities, conglomerate masses, solitary pulmonary nodules, confluent alveolar opacities (alveolar sarcoid pattern)
Ground-glass opacities
Linear opacities: interlobular septal thickening, intralobular linear opacities
Fibrocystic changes: cysts, bullae, blebs, emphysema, honeycomb-like opacities with upper- and middle-zone predominance
Miliary opacities
Airway involvement: mosaic attenuation pattern, tracheobronchial abnormalities, atelectasis
Pleural disease: effusion, chylothorax, hemothorax, pneumothorax, pleural thickening, calcification
Pleural plaquelike opacities
Mycetoma, aspergilloma

Radiographics 2010

Clinical Radiology 65 (2010) 642–650

Contents lists available at ScienceDirect

Clinical Radiology

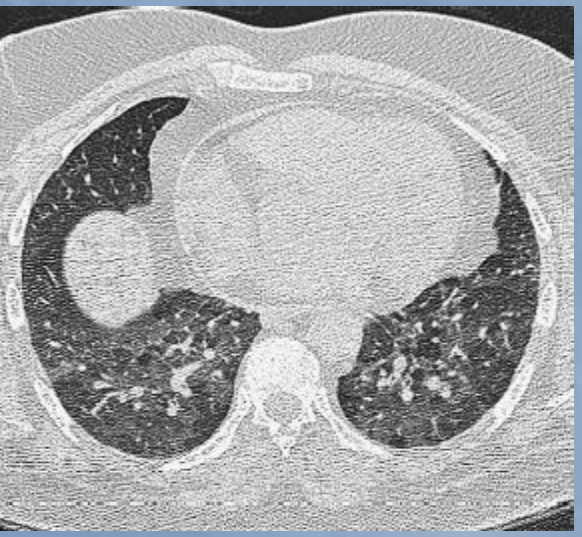
journal homepage: www.elsevierhealth.com/journals/crad

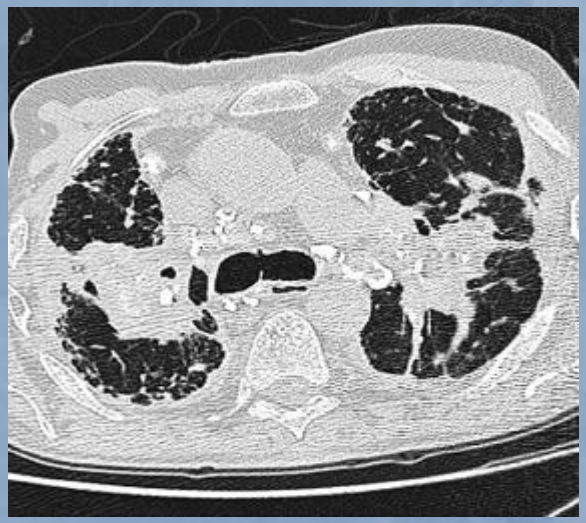
Pictorial Review

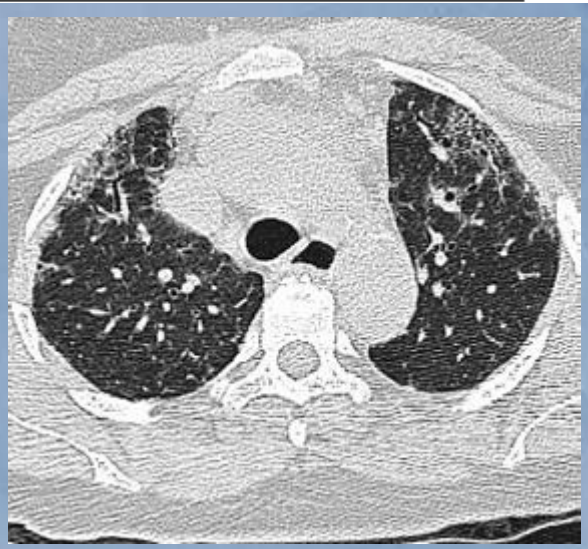
Pulmonary sarcoidosis: the 'Great Pretender'

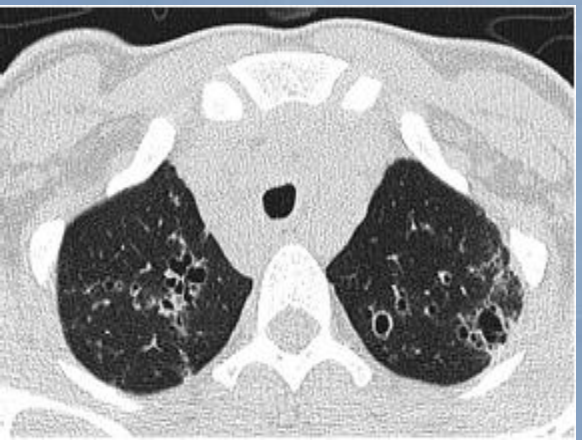
K.E. Hawtin [a,*], M.E. Roddie [a], F.A. Mauri [b], S.J. Copley [a]

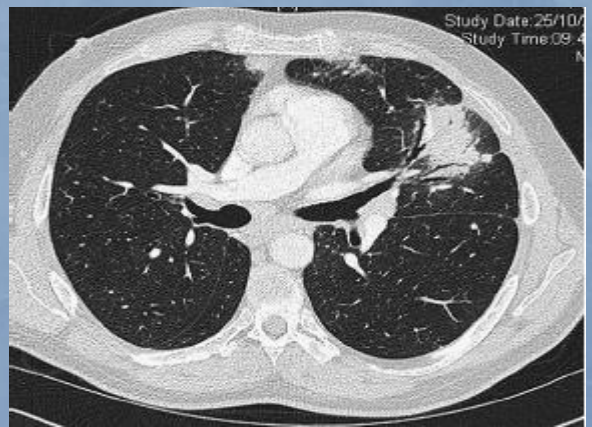
[a] Department of Radiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
[b] Department of Histopathology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK











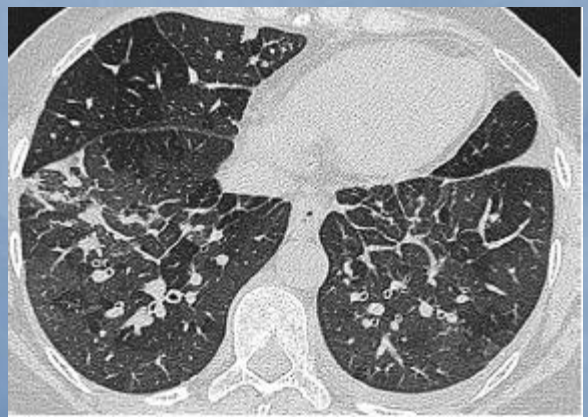


TABLE 3 Reversibility of sarcoidosis features observed on computed tomography (spontaneously or under therapy)

Reversible features	Irreversible features	Variable reversibility
Micronodules	Architectural distortion	Consolidation[#]
Nodules	Bronchial distortion	Ground-glass opacification[¶]
Peribronchovascular thickening	Honeycombing	Linear opacities[+]
	Bullae	

[#]: consolidations are wholly or partially reversible in most cases, in particular those with surrounding micronodules, representing coalescent granulomas. [¶]: a coarse texture or concomitant traction bronchiectasis increases the likelihood of underlying fibrosis. [+]: irregular distorted lines are more likely to be fibrotic.

Nunes H *et al. ERJ 2012*

ΣΑΡΚΟΕΙΔΩΣΗ
Αξονική τομογραφία

Είναι κοινή κακή πρακτική η κατάχρηση της ΑΤ τόσο στην αρχική εκτίμηση της νόσου όσο και κατά τη διάρκεια της παρακολούθησης

1. Άτυπα κλινικά ή ακτινολογικά ευρήματα
2. Ανίχνευση νόσου επί εδάφους φυσιολογικής Ro θώρακος
3. Ανίχνευση επιπλοκών (βρογχιεκτασίες, ίνωση, εμφύσημα, ασπεργίλλωμα)
4. Λοίμωξη ή νεοπλασία

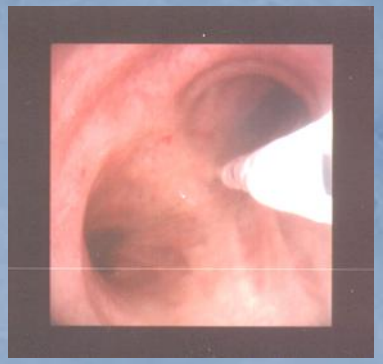
BRONCHOSCOPY

- Bronchoscopy
  (TBLB/ TBNA/ EBB/ BAL)

  EBB: diagnostic 40-60%

  TBLB: diagnostic ~70% (40-78%)

  TBNA: diagnostic 62%



Meta analysis, 15 studies

- Endosonography
  (EBUS- TBNA and EUS-FNA)

  EBUS-TBNA: diagnostic 79%

Agarwal R, *et al. Respir Med 2012*

ORIGINAL CONTRIBUTION

2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

- RCT: (TBLB + EBB vs. EBUS/EUS)

  + BAL was additionally performed in all patients

- Suspected sarcoidosis stage I/II
  need for tissue verification

- 14 hospitals across Europe (2009-2011)

2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

Table 3. Granuloma Detection and Diagnostic Yield for Sarcoidosis and the Final Diagnoses by Group

	No. (%)	
	Bronchoscopy (n = 149)	Endosonography (n = 154)
Detection of granulomas, consistent with the diagnosis of sarcoidosis	72 (48)	114 (74)
Diagnostic yield of granuloma detection in patients with sarcoidosis	72/136 (53)	114/142 (80)
Final diagnosis		
Sarcoidosis	136 (91)	142 (92)
Other diagnoses	13 (9)	12 (8)
Postinflammation/reactive mediastinal nodal disease	5	7
Nonspecific interstitial pulmonary fibrosis	3	0
Tuberculosis	1	1
Lymph node metastasis of non–small cell lung cancer	0	2
Metastatic thyroid cancer	1	0
Metastatic colon cancer	0	1
Wegener disease	1	0
Pneumoconiosis	0	1
Atypical pneumonia	1	0
Atypical interstitial nodules, diagnosis unknown	1	0

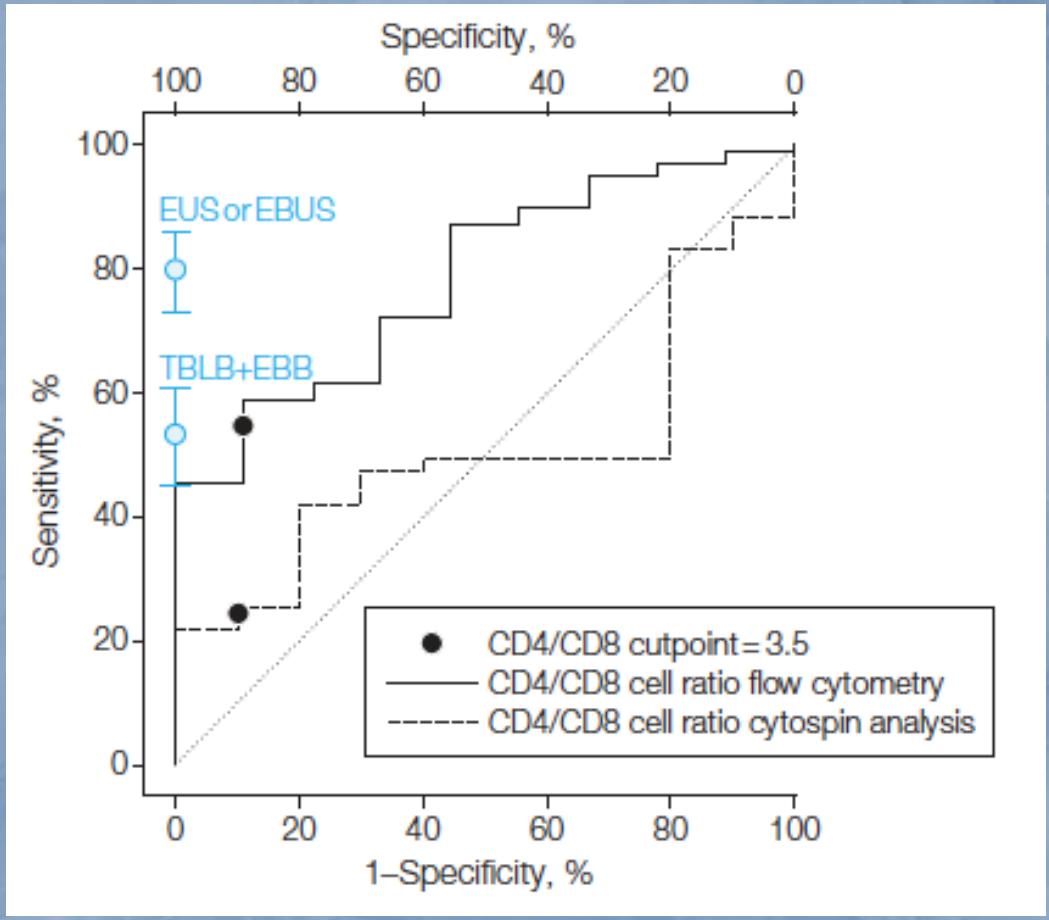
2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

Yield per stage

Stage I sarcoidosis	
Bronchoscopy **38%**	
Endosonography **84%**	
Stage II sarcoidosis	
Bronchoscopy **66%**	
Endosonography **77%**	



ORIGINAL CONTRIBUTION

2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

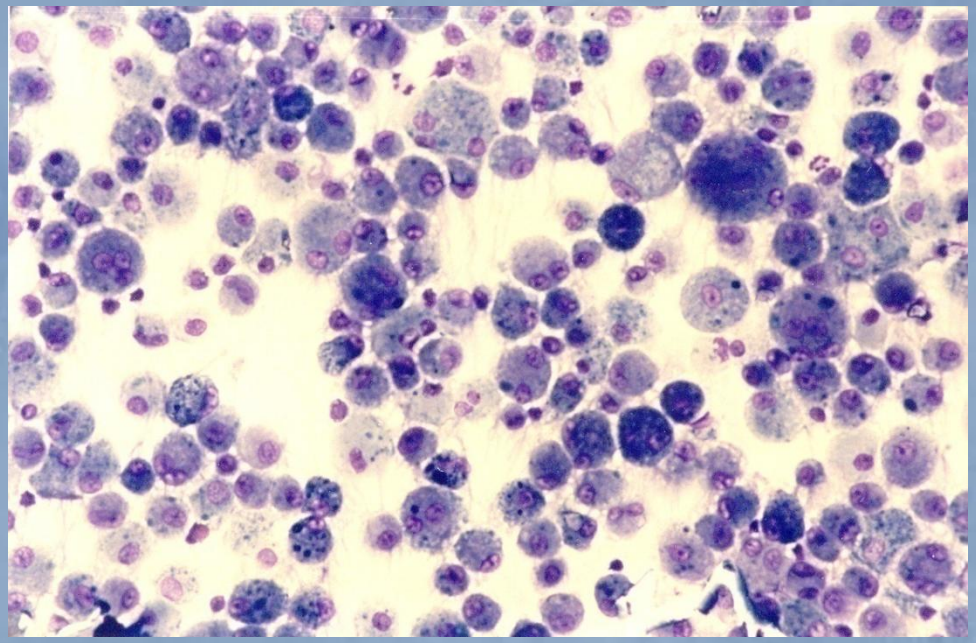
- Endosonography has higher diagnostic yield (**80% vs 53%**) in comparison with bronchoscopy (TBLB+EBB) for patients with stage I/II sarcoidosis

- Serious adverse events related to endosonography and bronchoscopy were rare

- The value of BAL in diagnosing sarcoidosis is limited

- (In case EBUS is not available, blind TBNA with onsite cytology + TBLB seems a good alternative)

BAL



BAL lymphocytosis is not specific for sarcoidosis

Sarcoidosis
Granulomatous infectious diseases (mycobacteria, fungi)
Hypersensitivity pneumonitis
Viral pneumonitis
Drug-induced alveolitis
Lymphocytic interstitial pneumonitis (LIP)/lymphoma
Nonspecific interstitial pneumonitis (NSIP)
Cryptogenic organizing pneumonia (COP)
Chronic beryllium disease
Radiation pneumonitis

Drent et al.

20% Sarcoidosis $CD_4/CD_8 < 2$

12% EAA $CD_4/CD_8 > 3,5$

Sarcoidosis Vasc Diffuse Lung Dis 1997

Kantrow et al.

Sarcoidosis CD_4/CD_8 highly variable

ERJ 1997

Table 1 Predictive Value of CD4:CD8 Ratio in Bronchoalveolar Lavage

Study	CD4:CD8 Ratio	Sensitivity	Specif
Costabel et al 1988[14]	>3.5	53	93
	>5.0	47	98
Winterbauer et al 1993[15]	>3.0	67	89
	>4.0	59	96
Thomeer, Demedts 1997[16]	>3.0	64	89
	>4.0	55	94
Korosec et al 2010[17]	>3.3	70	88

Costabel U, *et al. Semin Respir Crit Care Med 2007*

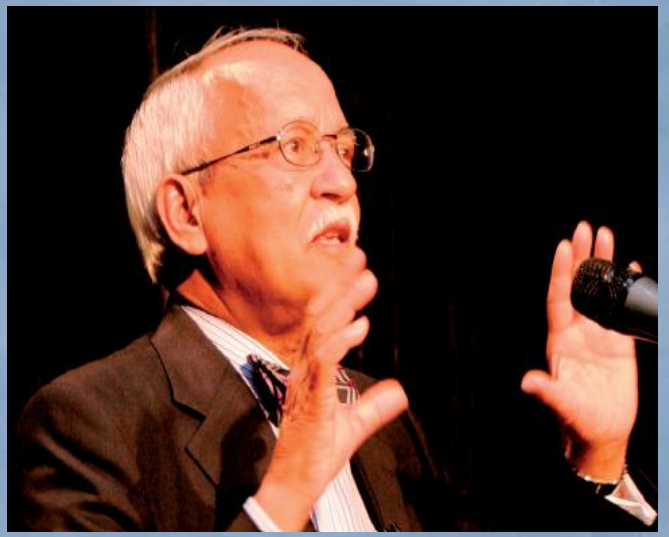
PFTs

"With no other disease did pulmonary physiologists have so much fun as with sarcoidosis."

Om P. Sharma

All varieties of abnormalities in pulmonary function tests can be seen in sarcoidosis

- A decreased diffusion capacity and a restrictive ventilatory defect are most often seen
- Almost 30 % of patients also have obstructive airway disease
- Bronchial hyper responsiveness is seen in up to 20 % of patients and is associated with the presence of microscopic non-necrotizing granulomas in the endobronchial mucosa



Baughman, *et al. AJRCCM 2001*

BIOMARKERS

Serum markers
Serum amyloid A
Soluble interleukin-2 receptor
Lysozyme
Chitotriosidase
sACE
Krebs von den Lungen-6
Interferon gamma induced protein 10
Neopterin
B cell activating factor

Angiotensin converting enzyme,(SACE), produced by epithelioid cells is often used at diagnosis and for sarcoidosis monitoring.

SACE is not accurate for diagnosing sarcoidosis because of a lack of both sensitivity and specificity, even after correction for a genetic insertion or deletion polymorphism that affects serum concentrations.

The use of a SACE threshold level of 2N gives a specificity higher ~90% but with a poor sensitivity, ~55%.

SACE can be increased in multiple conditions including those with clinical or pathological manifestations similar to sarcoidosis (e.g., tuberculosis, histoplasmosis, leprosy, lymphomas, asbestosis, Silicosis, diabetes mellitus, hyperthyroidism, LAM, Gaucher disease, or chronic beryllium disease, granulomatosis-associated common variable immune deficiency and drug-induced granulomatosis,.

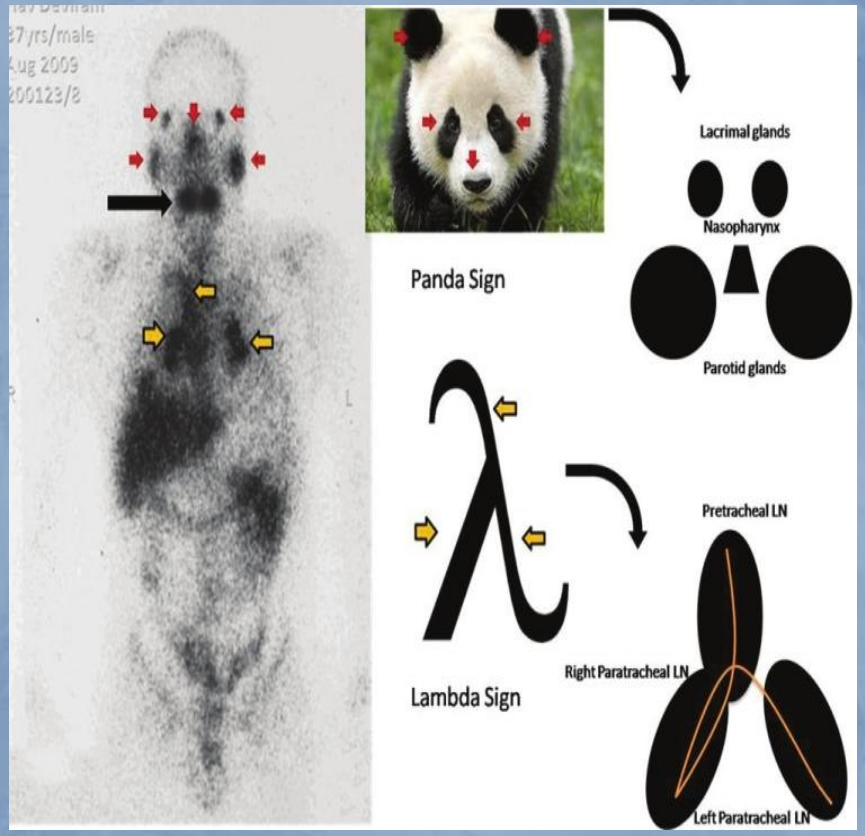
Valeyre D, *et al. Semin Respir Crit Care Med 2014*

Gallium Scintigraphy—An Obsolete Technique?

Some features can be suggestive of the disease such as the so-called “panda sign” or “lambda sign,”

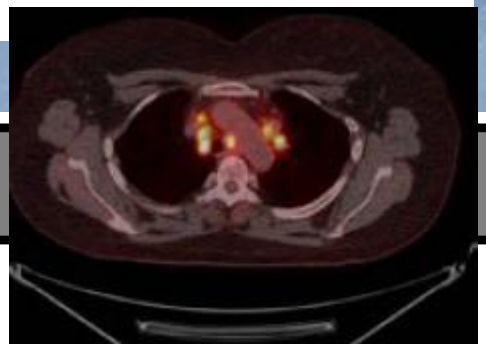
it is however not specific for sarcoidosis

higher radiation exposure (15mSv)



Adams H, *et al. Semin Respir Crit Care Med 2014*

FDG PET for Gauging of Sarcoid Disease Activity



Indications for ^{18}F-FDG PET/CT in sarcoidosis
- Obtaining histological proof of sarcoidosis
- Determining the presence of active disease in symptomatic patients with normal conventional markers
- Assessing the presence of active cardiac sarcoidosis, combined with CMR
- Evaluating disease activity in symptomatic patients with longstanding sarcoidosis or stage IV disease

Lower radiation exposure (4mSv) - expensive – disponibility – false positives in Ca

When favoring an all-in-one or a so-called one-stop-shop examination of cardiac and extra-CS, FDG PET imaging is the modality of choice.

Adams H, *et al. Semin Respir Crit Care Med 2014*
Keijers R *et al. ERJ 2012*

DIAGNOSTIC APPROACH

The diagnostic approach to sarcoidosis is a complex procedure.

There is no single diagnostic test for this disease. (e.g. the presence of non caseating granulomas in a single organ, such as skin, does not establish a diagnosis of sarcoidosis)

The diagnosis is based on three criteria:

- a compatible clinical and/or radiological picture,
- histological evidence of noncaseating granulomas,
- exclusion of other diseases that may produce a similar histological or clinical picture.

DIAGNOSTIC APPROACH

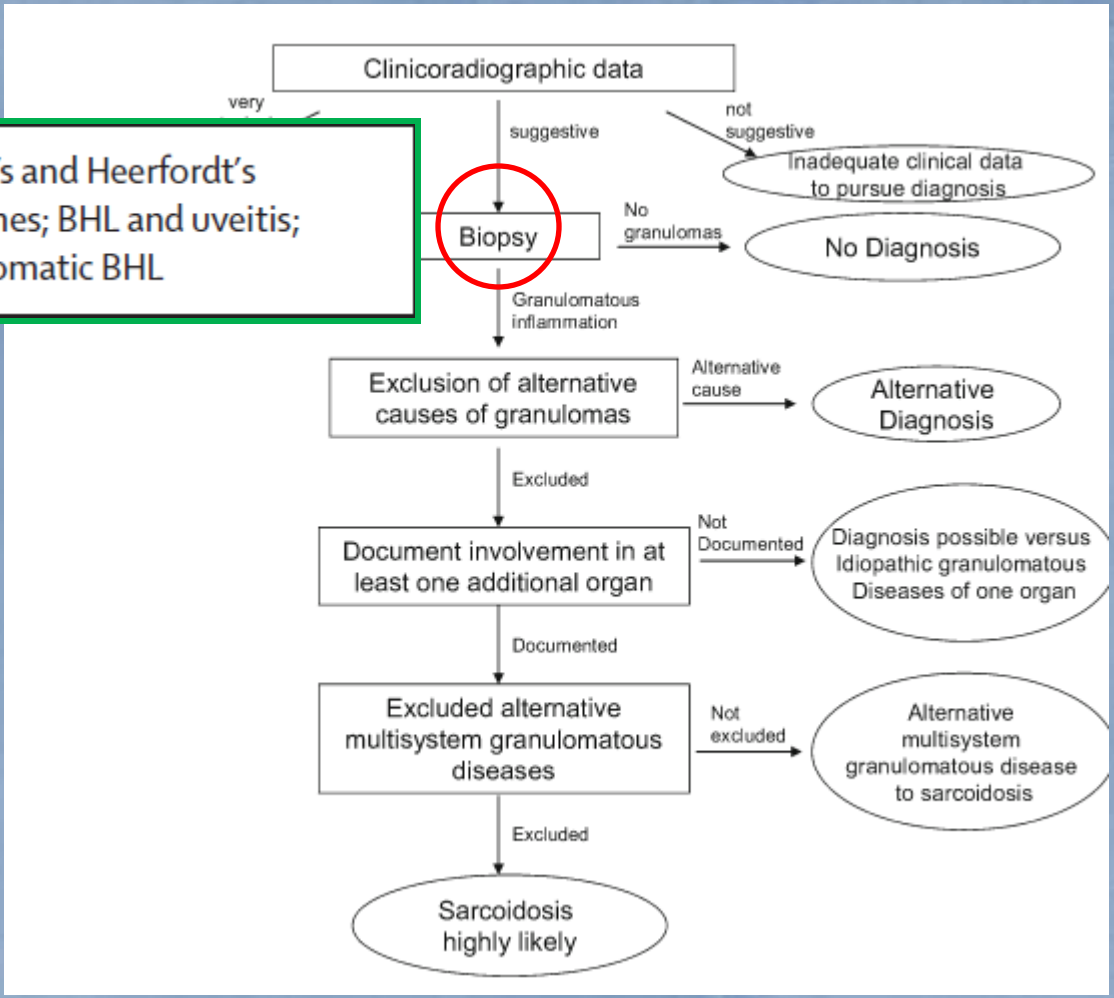
The diagnostic procedures should accomplish the following goals:

- **Provide histological confirmation of the disease;**
  Biopsies can be obtained from easily accessable organs
- **Evaluate the extent and severity of organ involvement;**
- **Assess whether the disease is stable or likely to progress;**
- **Determine if the patient will benefit from treatment.**

Costabel U. *ERS Monograph 2005*

DIAGNOSTIC APPROACH: multistep process

Löfgren's and Heerfordt's syndromes; BHL and uveitis; asymptomatic BHL



The presence of granulomatous inflammation in an isolated organ is not diagnostic of sarcoidosis, as, by definition, multiple organs should be involved.

Judson MA. *Clin Chest Med 2008*

Major pathologic Differential Diagnosis of Sarcoidosis at Biopsy

LUNG

- Tuberculosis
- Atypical mycobacteriosis
- Fungi
- Pneumocystis carinii
- Mycoplasma
- Hypersensitivity pneumonitis
- Pneumoconiosis: Beryllium (chronic beryllium disease), Titanium, Aluminum
- Drug reactions
- Aspiration of foreign materials
- Wegener's granulomatosis (Sarcoid-type granulomas are rare)
- Necrotizing sarcoid granulomatosis (NSG)

LYMPH NODE

- Tuberculosis
- Atypical mycobacteriosis
- Brucellosis
- Toxoplasmosis
- Granulomatous histiocytic necrotizing lymphademitis (Kikuchi's disease)
- Cat-scratch disease
- Sarcoid reaction in regional lymph nodes to carcinoma
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- Granulomatous lesions of unknown significance (the GLUS syndrome)

SKIN

- Tuberculosis
- Atypical mycobacteriosis
- Fungi
- Reaction to foreign bodies: beryllium, zirconium, tattooing, paraffin, etc.
- Rheumatoid nodules

LIVER

- Tuberculosis
- Brucellosis
- Schistosomiasis
- Primary biliary cirrhosis
- Crohn's disease
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- GLUS syndrome

BONE MARROW

- Tuberculosis
- Histoplasmosis
- Infectious mononucleosis
- Cytomegalovirus
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- Drugs
- GLUS syndrome

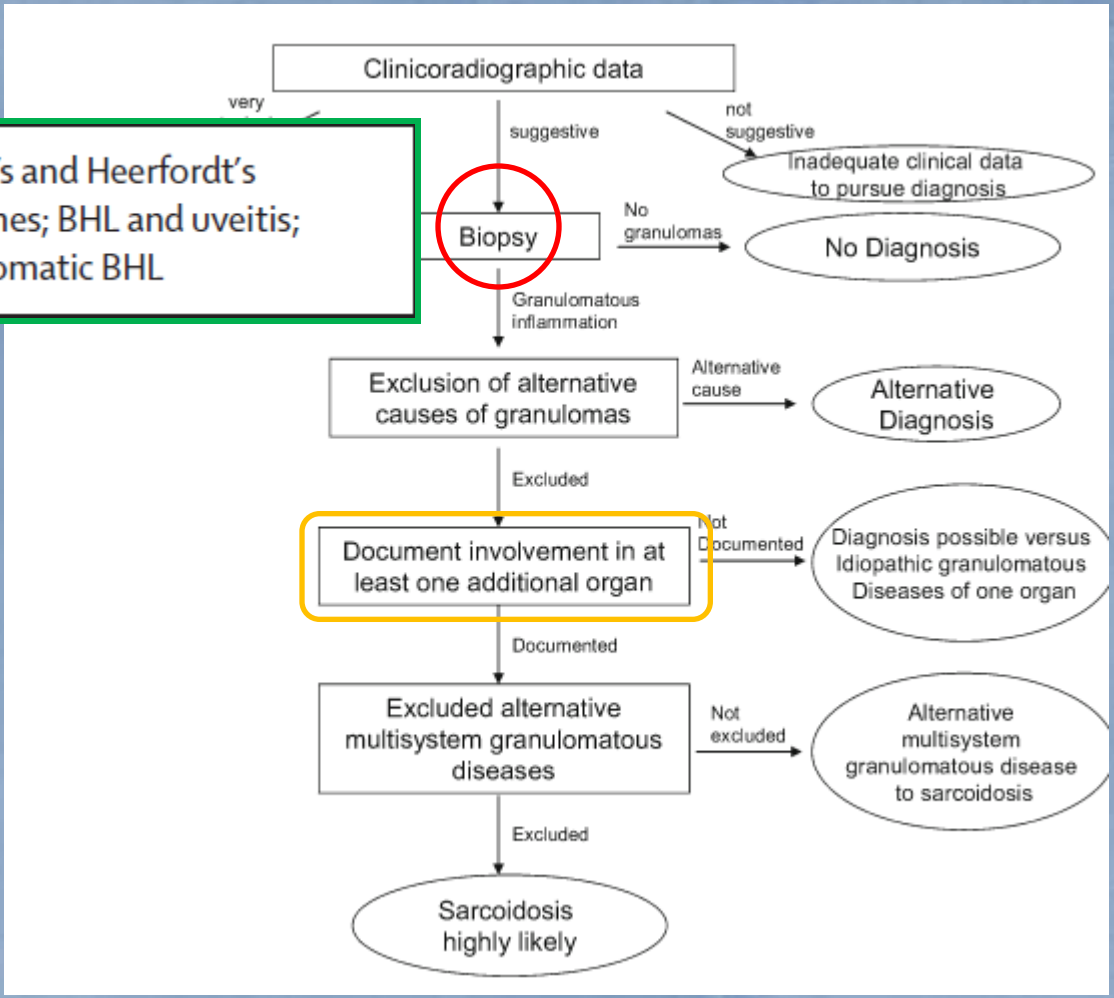
OTHER BIOPSY SITES

- Tuberculosis
- Brucellosis
- Other infections
- Crohn's disease
- Giant cell myocarditis
- GLUS syndrome

ATS/WASOG Statement. *AJRCCM 1999*

DIAGNOSTIC APPROACH: multistep process

Löfgren's and Heerfordt's syndromes; BHL and uveitis; asymptomatic BHL



The presence of granulomatous inflammation in an isolated organ is not diagnostic of sarcoidosis, as, by definition, multiple organs should be involved.

Judson MA. *Clin Chest Med 2008*

INITIAL WORK-UP

- **History and Physical examination:** family sarcoidosis, environmental, and occupational exposure (beryllium, aluminum …)

- **Chest radiography**

- **Pulmonary function tests:** spirometry with bronchodilator, TLC and DLCO

- **Blood** cell counts, calcemia/calciuria, renal and liver function, urine analysis
- Serum protein electrophoresis

- **Electrocardiogram (+ 24 hr Holter monitoring, echocardiography)**

- **Routine ophthalmologic examination** (slit-lamp, tonometric/funduscopic examination

- **Tuberculin skin test**

- **Others**[a]

[a]According to clinical presentation, diagnosis issues, and assessment of disease activity.

Valeyre D, *et al. Semin Respir Crit Care Med 2014*

Table 2. – Adverse prognostic factors in sarcoidosis

Type of factor
Lupus pernio
Chronic uveitis
Age of onset >40 yrs
Chronic hypercalcaemia
Nephrocalcinosis
Black race
Progressive pulmonary sarcoidosis
Nasal mucosal involvement
Cystic bone lesions
Neurosarcoidosis
Myocardial involvement

Costabel U. *ERS Monograph 2005*

Respiratory Medicine (2012) 106, 1351–1361

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

The treatment of pulmonary sarcoidosis

Marc A. Judson [a]

Decisions regarding treatment of sarcoidosis rely on several factors:

Symptoms

Organ involvement

Signs of functional impairment

The most sinister clinical complication of Sarcoidosis is the uncontrolled and unpredictable progress of granulomas to fibrosis

- Diffuse pulmonary fibrosis
- Liver cirrhosis
- Glaucoma, cataract, blindness
- Hydrocefalus
- Myocardial fibrosis

Corticosteroids suppress granulomas, interrupt the road to fibrosis and relieve symptoms

They control but not cure the disease

Stage	Frequency	Spontaneous remission
• 0	5-10%	
• I	50%	55-90%
• II	25%	40-70%
• III	15%	10-40%
• IV	5-10%	0%

The most satisfying therapy for the patient and physician in sarcoidosis is no treatment at all

TABLE 4 Criteria for corticosteroid treatment of sarcoidosis at St Antonius Hospital[#]

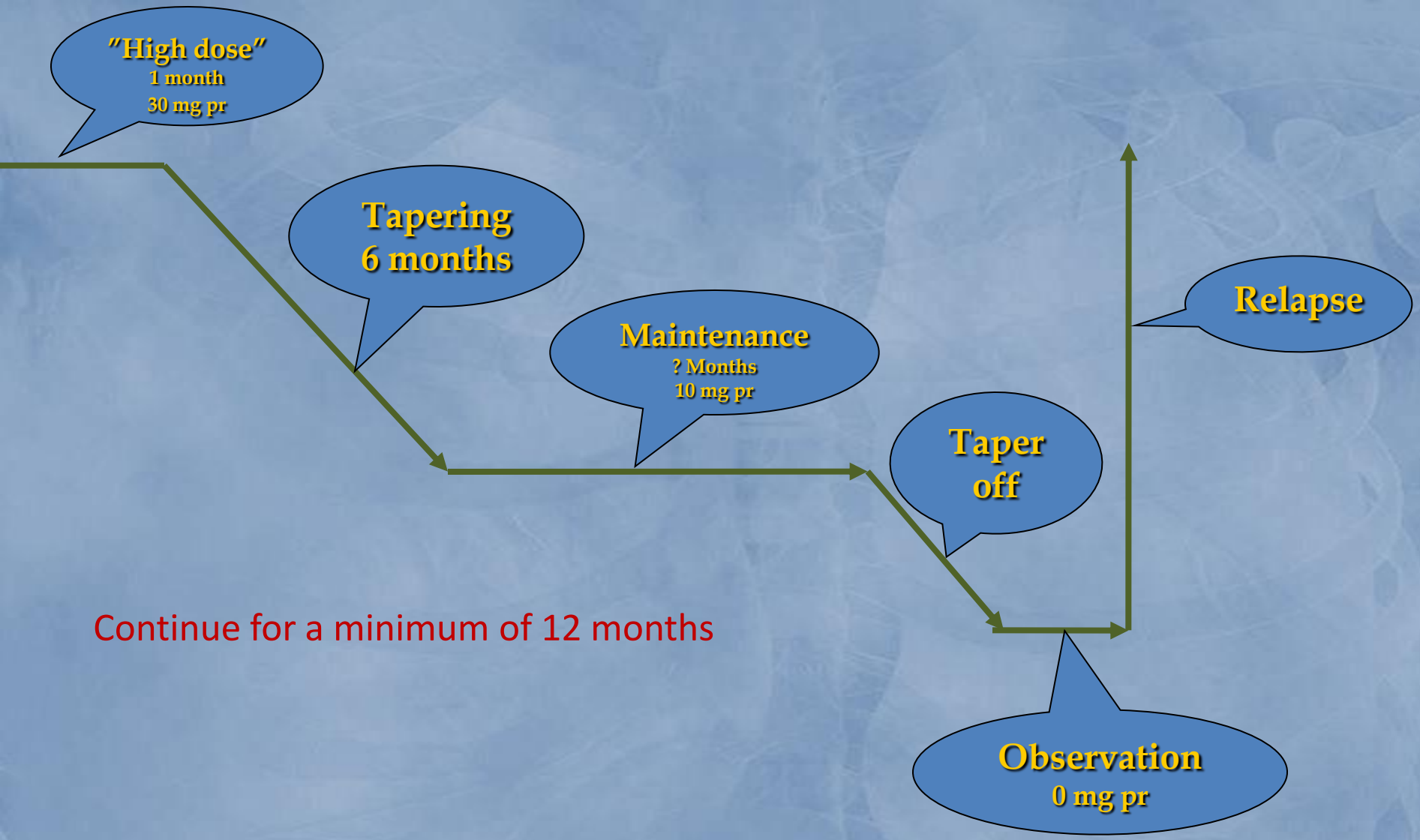
Absolute criteria

- Parenchymal disease with severe functional impairment on presentation (*i.e.* VC and/or $D_{L,CO}$ <50% pred)
- Severe airway obstruction on presentation (*i.e.* FEV_1 <50% pred)
- Progressive pulmonary disease with functional deterioration in the last 6-12 months (*e.g.* VC ⩾10% and/or $D_{L,CO}$ ⩾15% decrease from baseline)
- Evidence for significant and/or progressive lung fibrosis in the context of active disease
- Cardiac localisation
- Central nervous system localisation
- Sight-threatening ocular disease that cannot be controlled by local treatment
- Severe hypercalcaemia (usually >3.0 $mM \cdot L^{-1}$)
- Hypercalciuria with nephrocalcinosis and renal dysfunction
- Granulomatous interstitial nephritis
- Liver involvement with intrahepatic cholestasis, portal hypertension and/or hepatic failure
- Bone marrow involvement with pancytopenia

Relative criteria

- Symptomatic pulmonary disease with only mild/moderate lung function impairment
- Disfiguring skin involvement
- Symptomatology causing unacceptable reduction in quality of life (*e.g.* fever, fatigue and weight loss)

Grutters JC. *ERJ 2006*



Continue for a minimum of 12 months

Judson MA. *Respir Med 2012*

TABLE 1. TREATMENT OF PULMONARY SARCOIDOSIS

Chest X-ray stage 0/1
- No symptoms
  - No systemic therapy
    - Level 1A (123)

Chest X-ray stage 2 to 4
- Symptomatic
  - Treat with corticosteroids
    - Level 1A (89, 123)
  - Initial dosage of 20–40 mg prednisone or its equivalent
    - Level 1B (89, 124)
  - Treat for 12–24 mo
    - Level 1C (90, 91, 125)

Steroid-sparing alternatives for chronic pulmonary sarcoidosis
- Methotrexate
  - Dose of 5–15 mg once a week
    - Level 1A (126–128)
  - Folic acid 1 mg/d may reduce toxicity
    - Level 1B (129)
  - Azathioprine 50–200 mg daily
    - Level 1B (130, 131)
  - Leflunomide 10–20 mg daily
    - Level 1B (132)
  - Mycophenolate
    - Level 1C (101, 133, 134)

Treatment of refractory sarcoidosis
- Infliximab intravenously 3–5 mg/kg initially, 2 wk later, then once a month
  - Level 1A (18, 98)

Baughman, *et al. AJRCCM 2011*

Sarcoidosis
Treatment of serious systemic disease

• Heart	Steroids, anti-arrhythmics, pacemaker / defribillator, transplantation
• Liver - Spleen	Steroids
• CNS	Steroids (pulse), anti-TNF, cyclophosphamide, cladribine, cyclosporine, hydrocephalus (surgery)
• ↑ Ca	Diet ↓ Ca & vit. D, reduce exposure to sun light, Plaquenil, steroids
• Skin	Plaquenil, topical and systemic steroids
• Eyes	Topical and systemic steroids, cycloplegics, surgery

Iannuzzi M, *et al. NEJM 2007*

Other general principles

- Pneumocystis prophylaxis
- Prophylactic vaccinations
- Age appropriate cancer screening
- TB screening
- Osteoporosis prophylaxis
- Counselling regarding effect on pregnancy
- Thiopurine methyl transferase (TPMT) level

FOLLOW-UP

- Stage I disease: every 6 months
- Other stages: every 3 to 6 months
- Follow-up for a minimum of 3 years after therapy is discontinued
- If radiograph has normalized for 3 years, subsequent follow-up is not routinely required
- **Note:** Follow-up needs to be more vigilant after corticosteroid-induced remissions than after spontaneous remissions

There is not curative treatment for sarcoidosis.
The initiation of therapy is only justified when the potential benefits outweigh the risks…

Grutters *et al. ERJ 2006*

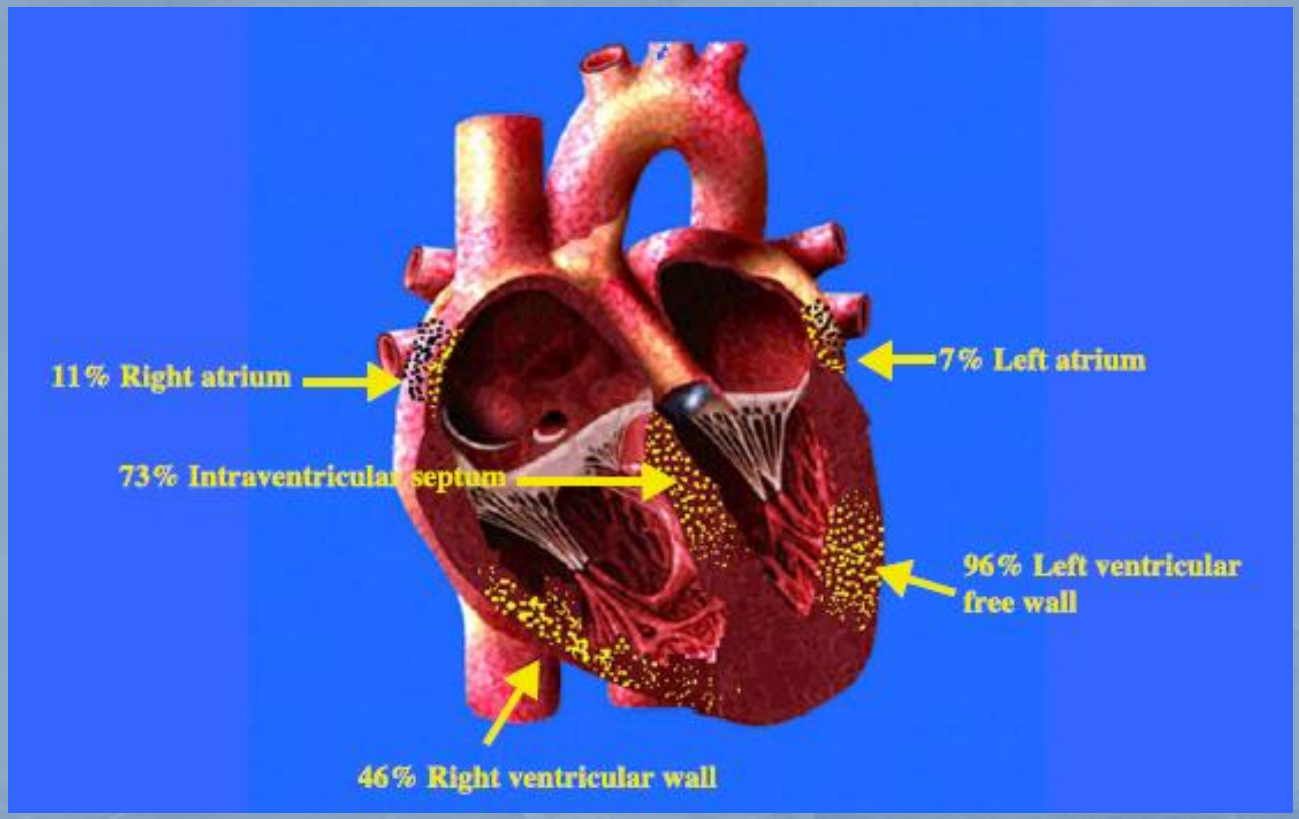
ATS/WASOG Statement on Sarcoidosis. *AJRCCM 1999*

FREQUENCY OF ORGAN INVOLVEMENT

Lung - 90%
Lymph nodes - 75-90%
Pleura - 1-5%
Skin - 25%
Eye - 25%
Nasal mucosa - 20%
Larynx - 5%
Bone marrow - 15-40%
Spleen -50-60%
Liver -60-90%
Kidney - Rare
Calcium disorder - 11%
CNS - 5%
Bones - 5%
Joints - 25-50%
Heart - 5%
Endocrine glands - Rare
Parotid gland - 10%
GI tract - Rare

Cardiac Involvement in Sarcoidosis

Cardiac involvement occurs in 20–27% of sarcoid patients in the United States and may be as high as 58% in Japan. The majority of these patients are asymptomatic; clinical evidence of cardiac sarcoidosis is present in ~5% of patients with sarcoidosis, but occult involvement is much higher (> 20%).



Lynch JP III, *et al. Semin Respir Crit Care Med 2014*

The clinical manifestations in cardiac sarcoidosis

Author	Year	*N*	AV block (%)	BBB (%)	SVT/V-Tach (%)	CHF (%)	SD (%)
Matsui [9]	1976	42	62	48	14	10	41
Roberts [12]	1977	26	27	12	35	30	65
Fleming [14]	1981	300	26	61	73	24	26
Yazaki [15]	1998	95	45	NA	18	26	12

N, number of patients; AV, atrioventricular; BBB, bundle branch block; SVT, supraventricular tachycardia; V-Tach, ventricular tachycardia; CHF, congestive heart failure; SD, sudden death.

Cardiac involvement may occur at any point during the course of sarcoidosis and may occur in the absence of pulmonary or systemic involvement.

Prognosis of CS is related to extent and site(s) of involvement. Most deaths due to CS are due to arrhythmias or conduction defects

The yield of endomyocardial biopsies is low

Currently, 18F-fluorodeoxyglucose positron emission tomography/computed tomography and gadolinium-enhanced magnetic resonance imaging scans are the key imaging modalities to diagnose CS

Lynch JP III, *et al. Semin Respir Crit Care Med 2014*

HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis

*Expert Consensus Recommendations on **Criteria for the Diagnosis of CS***

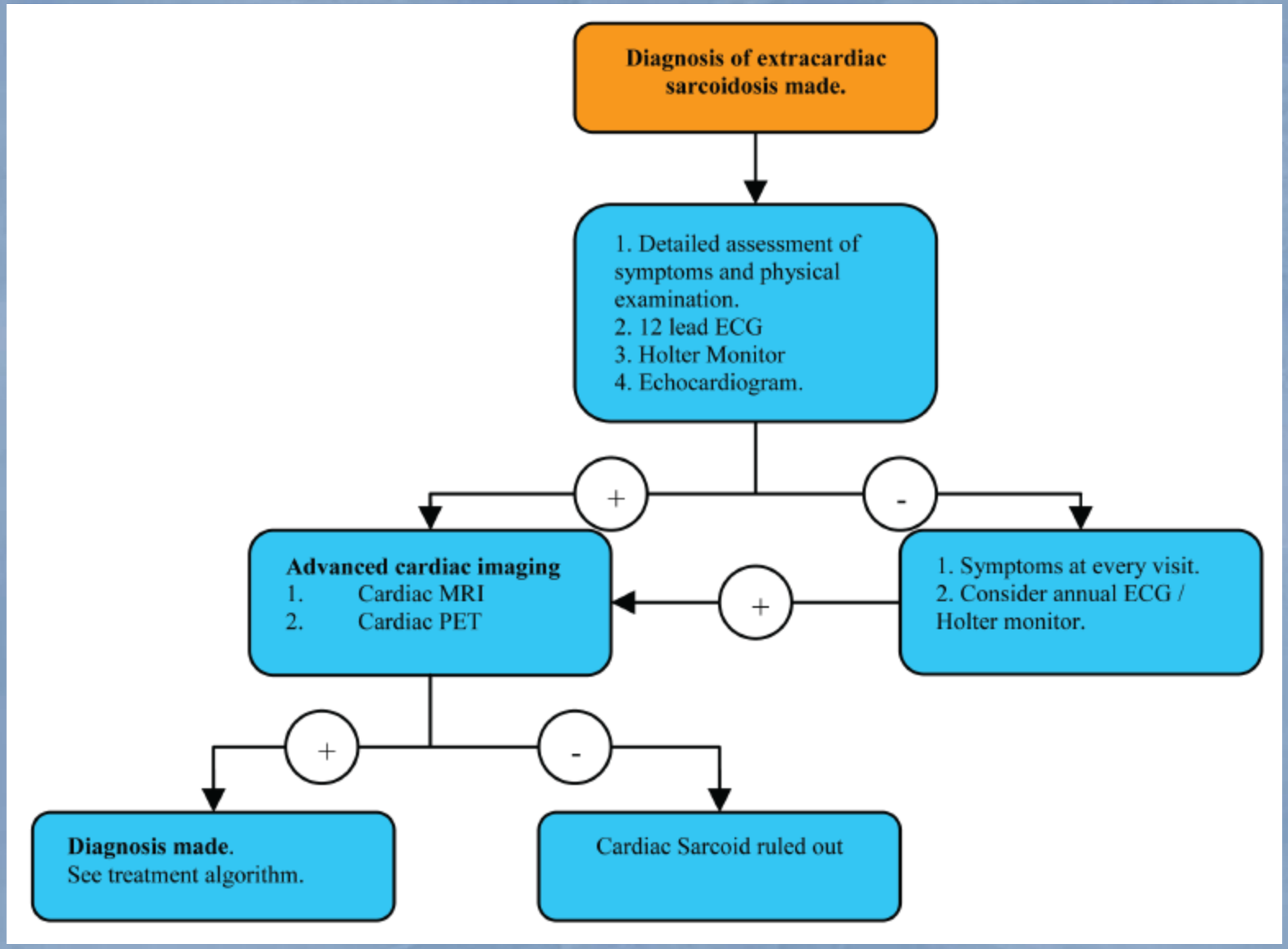
There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological Diagnosis from Myocardial Tissue
   CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
2. Clinical Diagnosis from Invasive and Non-Invasive Studies:
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis
   and
   b) One or more of following is present
   - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
   - Unexplained reduced LVEF (<40%)
   - Unexplained sustained (spontaneous or induced) VT
   - Mobitz type II 2nd degree heart block or 3rd degree heart block
   - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
   - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
   - Positive gallium uptake (in a pattern consistent with CS)

   and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded

*In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.[33]

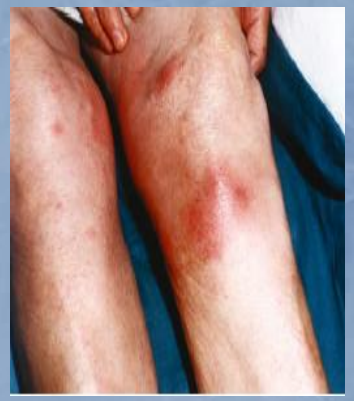
Birnie DH, *et al. Heart Rhythm 2014*



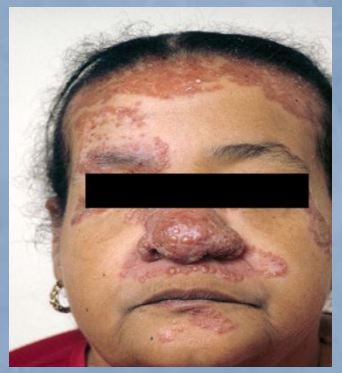
Evanchan P, *et al. JICRM 2013*

Cutaneous Involvement

Although not life-threatening, but can be emotionally devastating and are divided into two categories: specific and **nonspecific.**



- **Erythema nodosum may occur.**
- **Lupus pernio is the most specific associated cutaneous lesion.**
- **Violaceous rash is often seen on the cheeks or nose.**
- **Osseous involvement may be present.**
- **Maculopapular plaques are possible**.



- **Lupus pernio** is more common in women than in men and is associated with chronic disease and extrapulmonary involvement.

- **Erythema nodosum** occurs in about 10% of patients with sarcoidosis and usually lasts for about 3 weeks.

- **Biopsy specimens of erythema nodosum lesions** show nonspecific septal panniculitis, which **neither confirms nor negates the diagnosis of sarcoidosis**.

Marchell RM, *et al. Semin Respir Crit Care Med 2010*

Ophthalmologic Complications

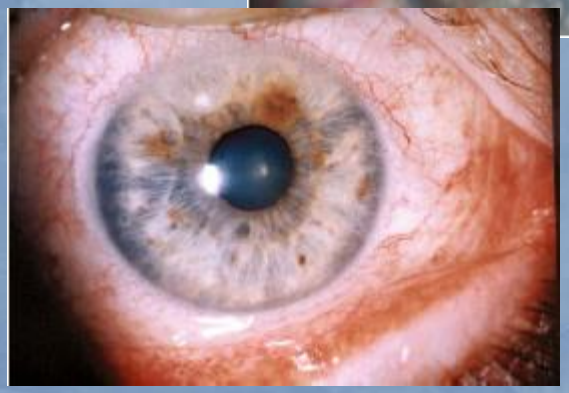
- The eye and adnexa are involved in 25 -80%
- Anterior or posterior granulomatous uveitis, Optic neuritis.
- Conjunctival lesions and scleral plaques may also be noted.
- Ocular involvement may lead to blindness if untreated.

This necessitating routine slit-lamp and funduscopic examination

- **Anterior uveitis**

Is the most common manifestation

Chronic anterior uveitis, with insidious symptoms leading to glaucoma and vision loss, is more common than acute anterior uveitis.



- **Posterior uveitis:**

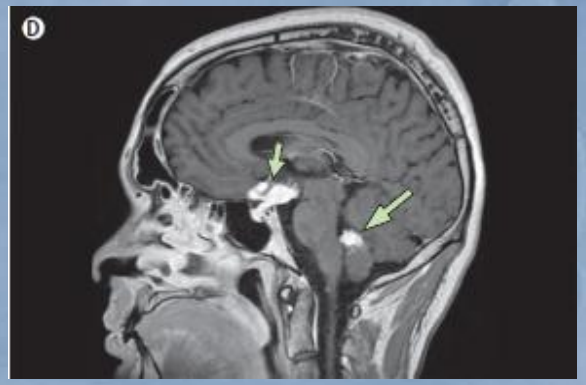
If suspected fluorescence angiography

Baughman RP, *et al. Semin Respir Crit Care Med 2010*

Neurologic Involvement

CNS is involved in up to 25% of patients with sarcoidosis who undergo autopsy, but only 10% of all patients with sarcoidosis present with neurologic symptoms.

Sarcoidosis can affect any part of the neuroaxis.
Neurosarcoidosis may appear in an acute explosive fashion or as a slow chronic illness



most common presentations

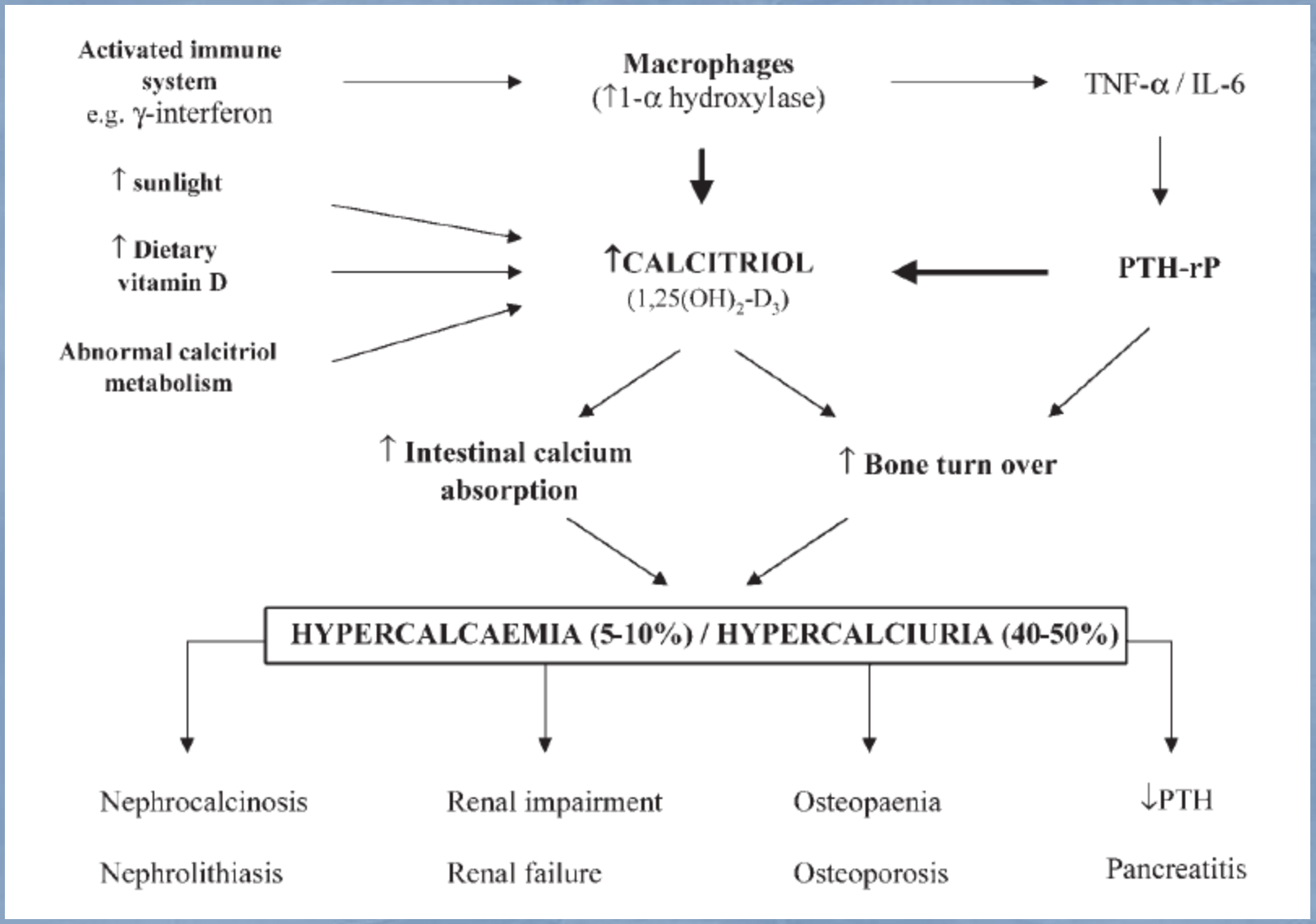
- cranial nerve palsies
- brain and spinal cord intraparenchymal lesions
- leptomeningeal infiltration
- peripheral neuropathies.

Depending on the location of the granulomas in the neuroaxis, the symptomatology reflects the neuroanatomical structures compromised. This means that potentially any neurological symptom and sign can be seen in patients with neurosarcoidosis.

- Magnetic resonance imaging (MRI), FDG-PET
- May ultimately require a tissue biopsy to reach a definitive conclusion

Vargas DL, *et al. Semin Respir Crit Care Med 2010*

Calcium and Vitamin D in Sarcoidosis: How to Assess and Manage

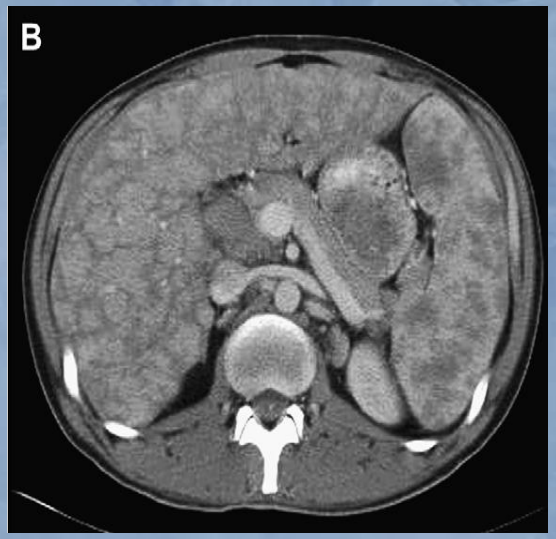


Isolated hypercalciuria alone is not an indication for prednisone therapy

Burke RR, *et al. Semin Respir Crit Care Med 2010*

Liver and Spleen Involvement

- 10% of all patients with sarcoidosis have elevated serum aminotransferase and alkaline phosphatase levels.
- Detection of hepatic and splenic lesions on CT is described in 5% and 15% of patients.



- A cholestatic syndrome characterized by pruritus and jaundice, hepatic failure, or portal hypertension can develop (liver involvement is usually clinically silent).
- 60% of patients with hepatic manifestations have constitutional symptoms such as fever, night sweats, anorexia, and weight loss.
- Portal hypertension and cirrhosis leading to liver failure occur in only 1% of patients with sarcoidosis.

Ebert E, *et al. Am J Gastroenterol 2008*

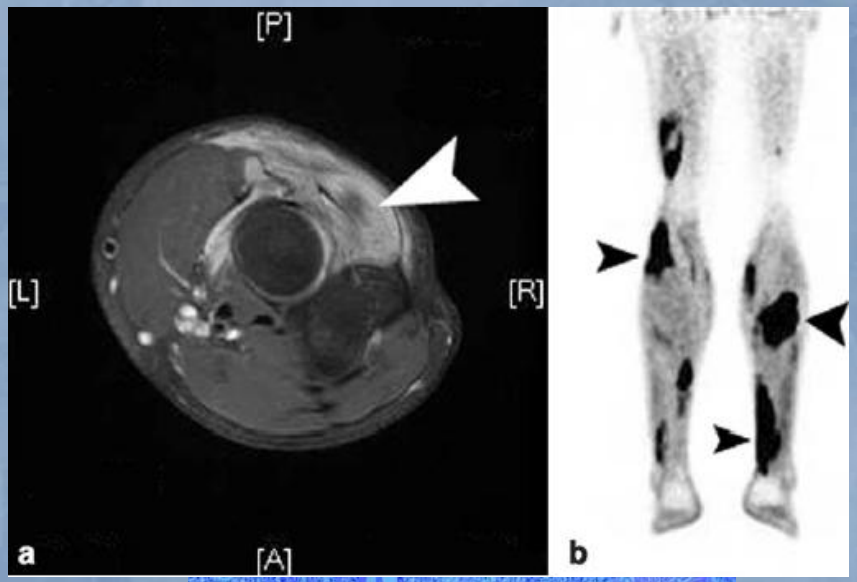
Rheumatol Int
DOI 10.1007/s00296-009-0989-1

SHORT COMMUNICATION

The many faces of sarcoidosis: asymptomatic muscle mass mimicking giant-cell tumor

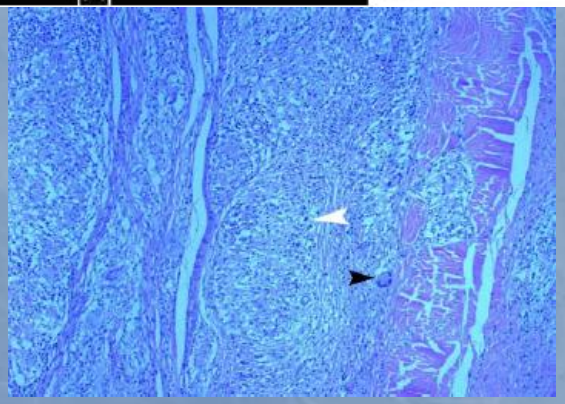
Likurgos Kolilekas · Christina Triantafillidou · Effrosyni Manali · Dimitra Rontogianni · Sophia Chatziioannou · Spyros Papiris

Although symptomatic sarcoid myositis is rarely encountered (<5%), muscle involvement is common in sarcoidosis and muscle biopsy in asymptomatic patients reveals granulomas in 50–80% of cases.



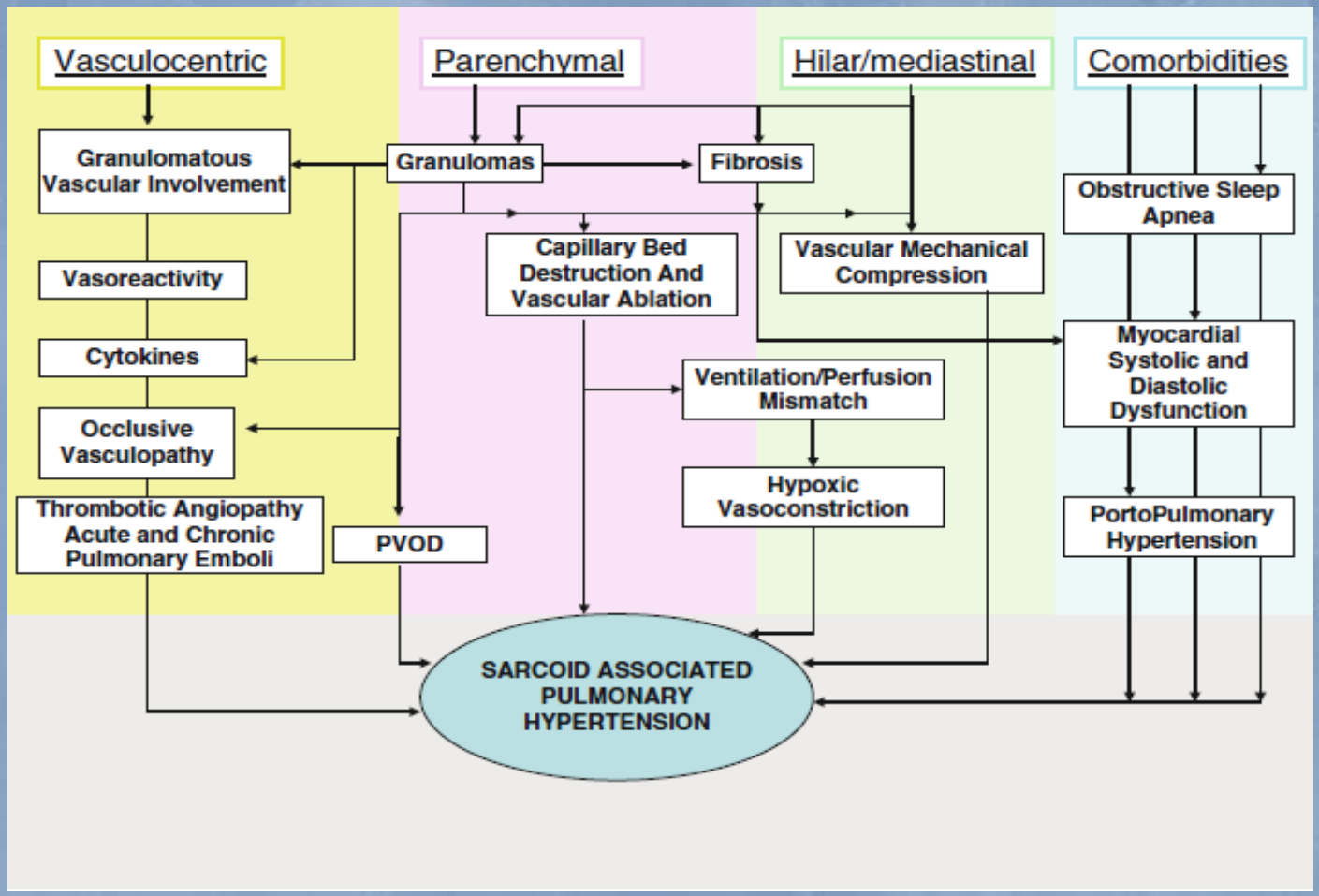
Three types of muscle sarcoidosis:

- chronic myopathy
- acute myositis
- nodular or tumorous type



Sarcoidosis-Associated Pulmonary Hypertension and Lung Transplantation for Sarcoidosis

Michael Y. Shino, MD[1] Joseph P. Lynch III, MD[1] Michael C. Fishbein, MD[2] Charles McGraw, M
Jared Oyama, MD[4] John A. Belperio, MD[1] Rajan Saggar, MD[1]



PH is a significant complication of sarcoidosis, occurring in ~ 6 to > 20% of cases, and markedly increases mortality among these patients.

Shino M, *et al. Semin Respir Crit Care Med 2014*

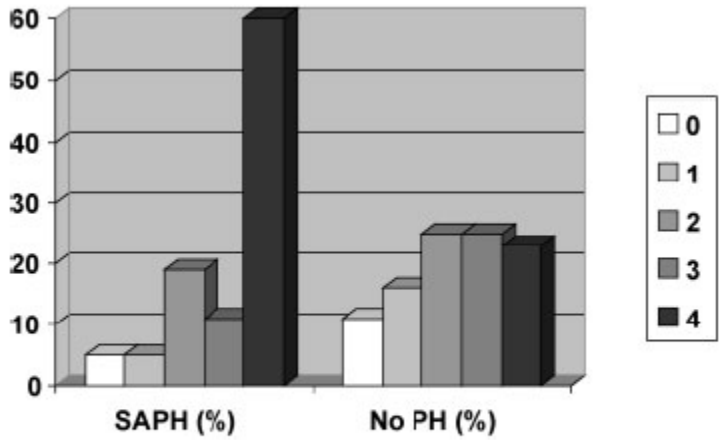


Figure 1 Radiographic staging in sarcoidosis-associated pulmonary hypertension compared with patients with sarcoidosis without pulmonary hypertension.[7]

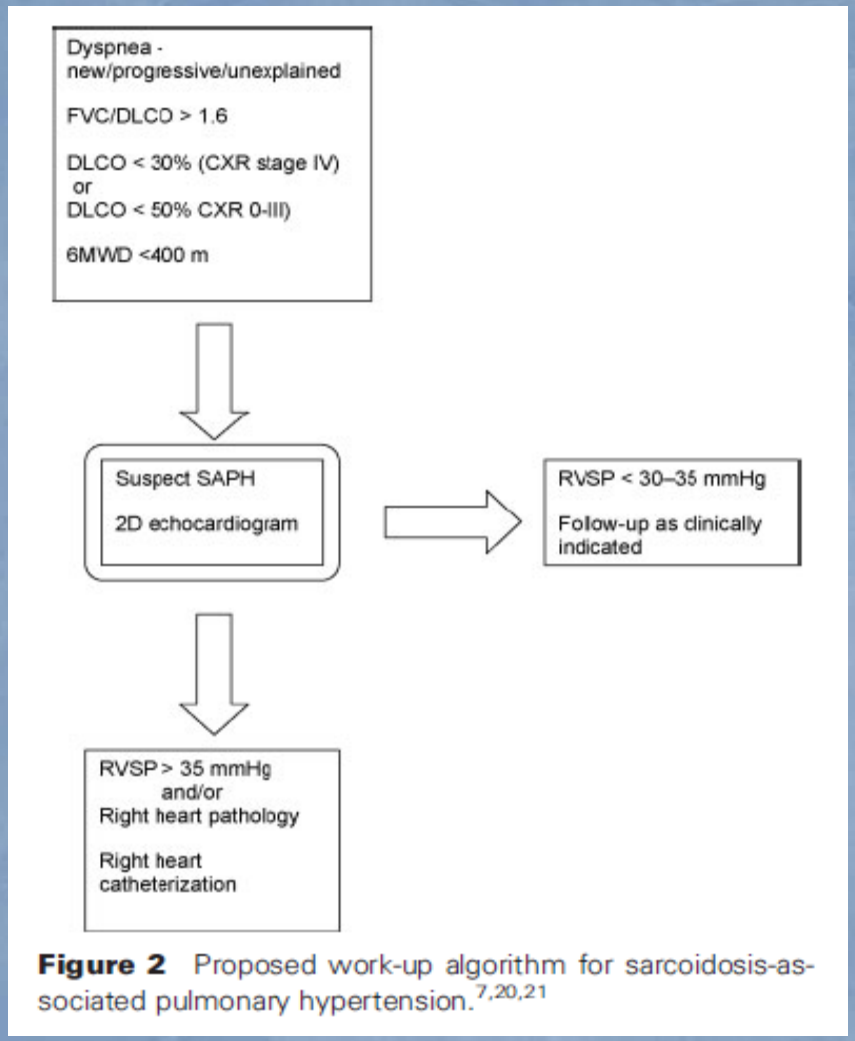


Figure 2 Proposed work-up algorithm for sarcoidosis-associated pulmonary hypertension.[7,20,21]

Palmero V, *et al. Semin Respir Crit Care Med 2010*

Table 1 Summary of outcomes after PH-targeted therapy for SAPH

Author	Year	Treatment	*N*	Major outcomes	Adverse effects
Preston et al[15]	2001	iNO	8	↓ mPAP 18%, ↓ PVR 31%, ↑ CO 12%	Ø Adverse events
Preston et al[15]	2001	IV EPO	6	Ø mPAP, ↓ PVR 25%, ↑ CO 25%	Ø Adverse events
Fisher et al[67]	2006	IV EPO	7	↓ mPAP 21%, ↓ PVR 45%, ↑ CO 44%, ↑ WHO class 1–2	↓ Pao_2 in 3/7 with one death
Baughman et al[70]	2009	Inhaled iloprost	15	↓ mPAP 15%, ↓ PVR 14%, ↑ 6 MWD 12%, ↑ QOL	↓ Pao_2 in 2/15 (mild)
Milman et al[5]	2008	Sildenafil	12	↓ mPAP 19%, ↓ PVR 48%, ↑ CO 36%, Ø 6 MWD	Ø Adverse events
Baughman et al[73]	2013	Bosentan in RCT	35	↓ mPAP 11%, ↓ PVR 28%, Ø 6 MWD, WHO class or QOL	Ø Adverse events
Barnett et al[33]	2009	IV EPO, sildenafil, bosentan	22	↓ mPAP 20%, ↓ PVR 39%, ↑ 6 MWD	Ø Adverse events
Judson et al[74]	2011	Ambrisentan	21	Ø 6 MWD, DL_{CO}, QOL or dyspnea scores	Increased edema and dyspnea

The pathophysiology of PH in sarcoidosis is complex and multifactorial making the optimal management of SAPH controversial.

Specific PH therapy is not routinely recommended in SAPH as there are no successful placebo controlled trials, although there is limited data to suggest that endothelin receptor antagonists and phosphodiesterase-5 inhibitors may be useful.

Lung transplantation (LT) is a viable therapeutic option for sarcoid patients with severe pulmonary fibrocystic sarcoidosis or SAPH refractory to medical therapy.

Shino M, *et al. Semin Respir Crit Care Med 2014*

Ευχαριστώ