ΠΝΕΥΜΟΝΙΤΙΣ ΑΠΟ ΥΠΕΡΕΥΑΙΣΘΗΣΙΑ

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ΟΡΙΣΜΟΣ

Η πνευμονίτιδα από υπερευαισθησία *Hypersensitivity pneumonitis (HP),* ή εξωγενής αλλεργική κυψελιδίτιδα *(extrinsic allergic alveolitis)*, είναι πολύπλοκο σύνδρομο που ποικίλει σε ένταση, κλινική παρουσίαση και πορεία, και είναι απότοκο διεγερμένης ανοσολογικής απάντησης σε μεγάλη ποικιλία οργανικών σωματιδίων.

- **Μπορεί να καταλήξει σε *πνεύμονα τελικού σταδίου και θάνατο.***

ΑΙΤΙΟΛΟΓΙΑ ΤΗΣ HP

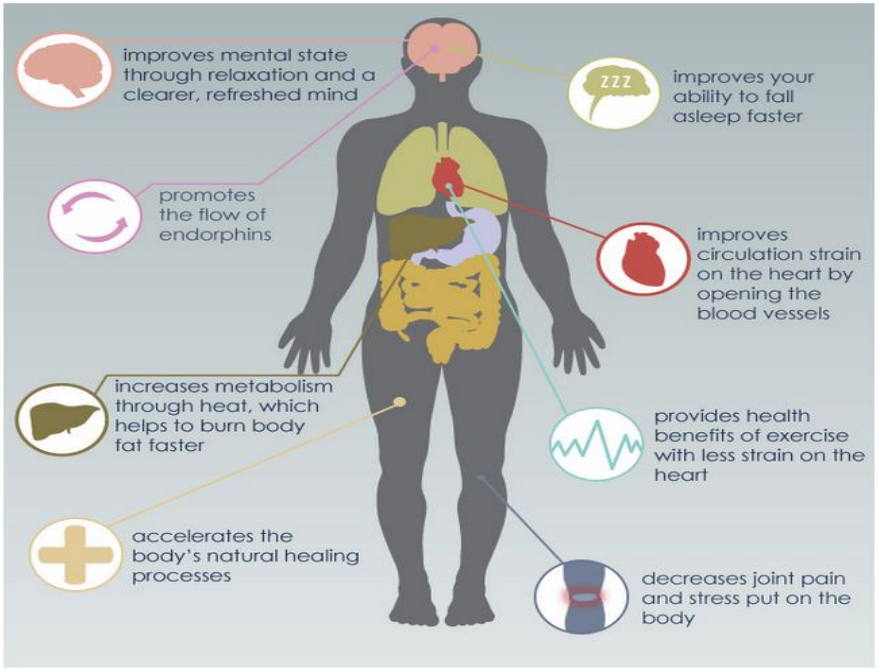
>300 αερογενή αντιγόνα, όπως:

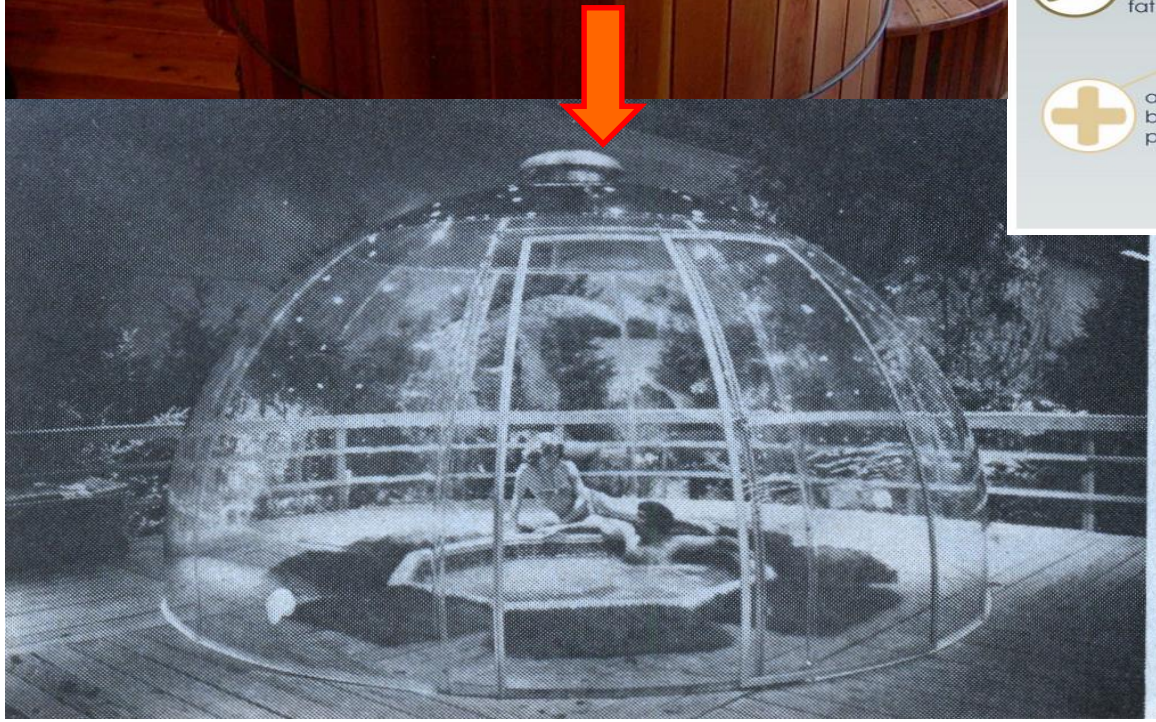
- ***αγροτική σκόνη***
- ***bioaerosols,***
- ***Μικροοργανισμοί (fungal, bacterial, or protozoal),***
- ***ανόργανα χημικά***
- ***φάρμακα***

THE
FINE
BEDDING
COMPANY
Goose Feather
& Down Duvet

© Alamy

Health Benefits of Hot Tubs





Hot-tub dome

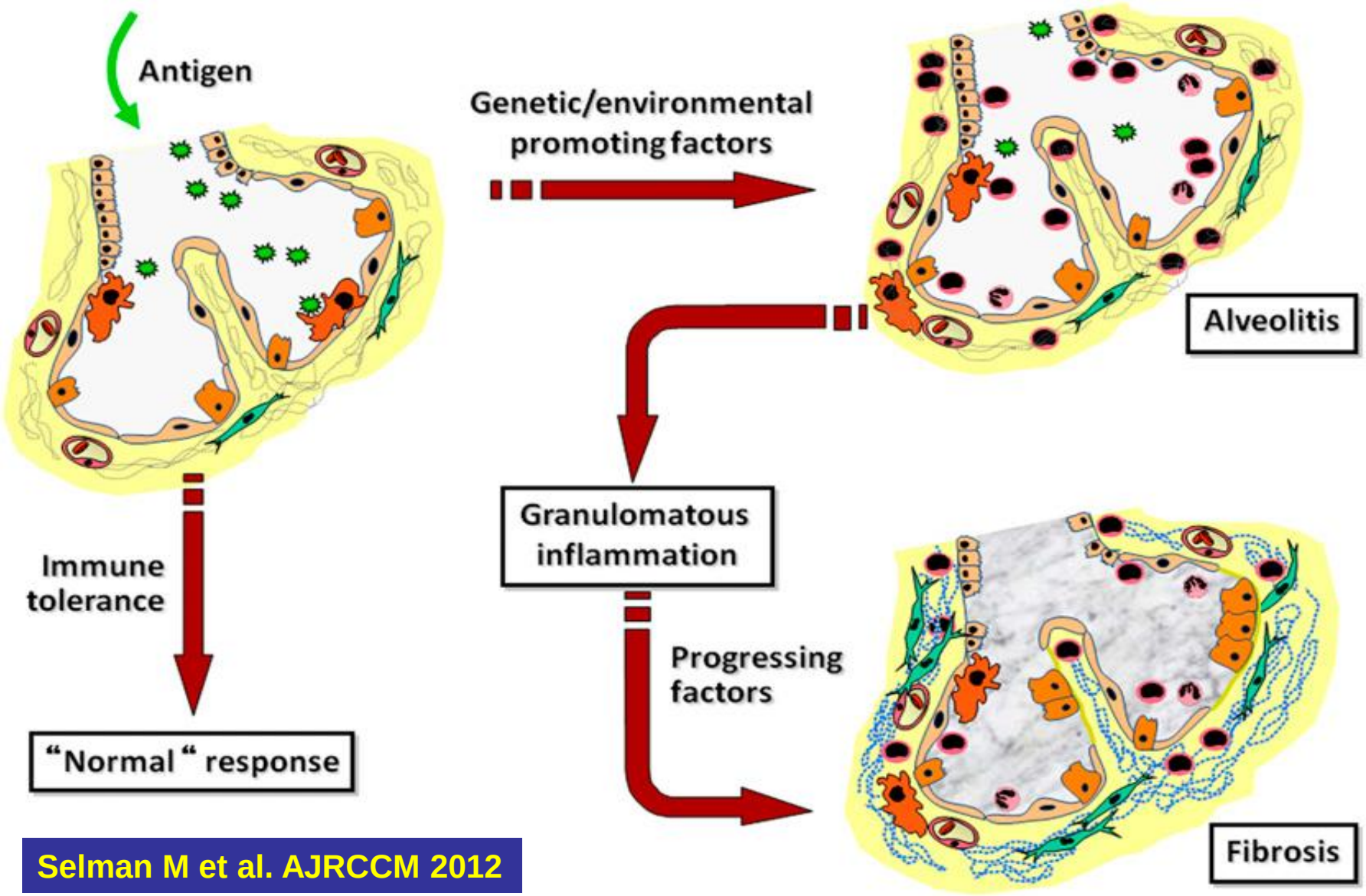
Hot tubs and whirlpools might use less energy if they were covered with this 14-ft.-dia. plastic dome. Its 10 side panels and four top panels are formed of ⅛-in.-thick Uvex. Solarium, Inc. (2901 John, Troy, Mich. 48084) makes the free-standing structure.

ΠΑΘΟΓΕΝΕΙΑ ΤΗΣ HP

- **Υπόθεση διπλής προσβολής (two-hit hypothesis):**
- **<u>1η προσβολή</u>: γενετική ευαισθησία *(genetic susceptibility)* ή περιβαλλοντικοί παράγοντες που αυξάνουν τον κίνδυνο εκδήλωσης της HP μετά την**
- **<u>2η προσβολή:</u> έκθεση στο αντιγόνο.**

Selman M et al. AJRCCM 2012

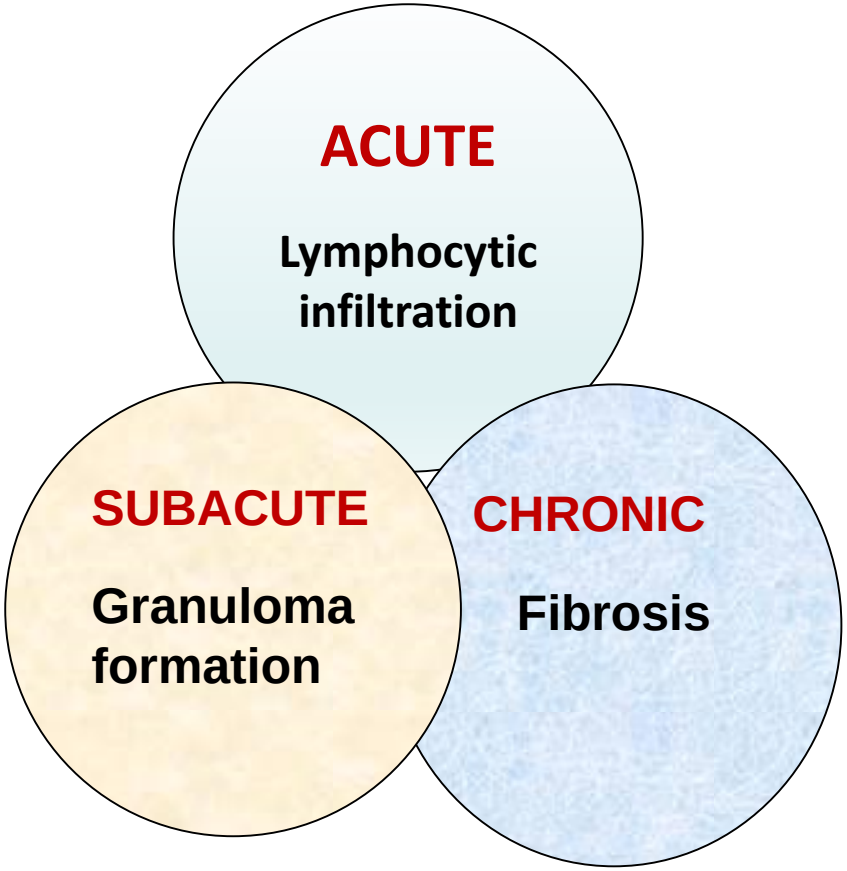
PATHOGENESIS OF HP



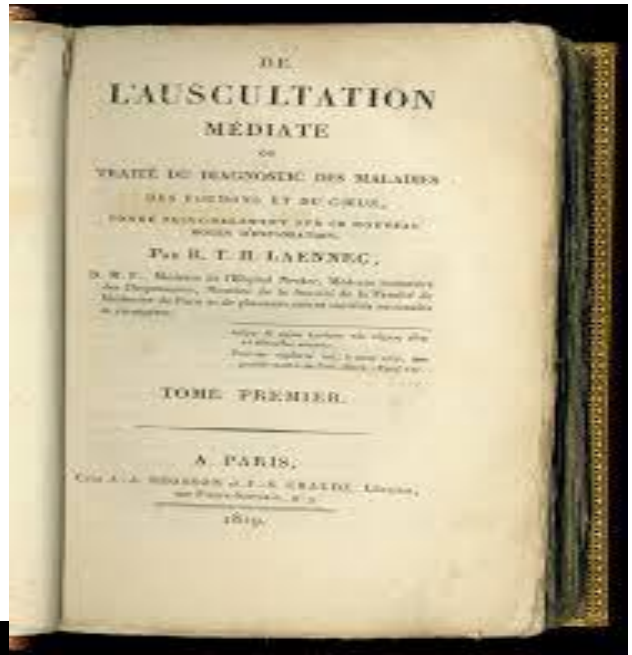
Selman M et al. AJRCCM 2012

HP PATHOGENESIS

- Immunopathogenesis in 3 phases
- Only 5-10% of exposed develop HP
- Most have normal harmless IgG response
- Recent RTI can precipitate the pathological process



Τελοεισπνευστικοί λεπτοί μη μουσικοί ρόγχοι στις βάσεις + κριγμοί (squeaks*).



Προκαλούνται από την απότομη διάνοιξη από τον εισπνεόμενο αέρα, των μικρών βρόγχων, που τα τοιχώματά τους έχουν αποφραχθεί από οίδημα, ενώ στους μεγάλους βρόγχους οφείλονται στη ρήξη πολύ ξηρών, παχύρρευστων φυσαλίδων.

* a short, very high cry or sound

Telomeropathy in Chronic Hypersensitivity Pneumonitis

Am J Respir Crit Care Med. 2019 Nov 1;200(9):1086-1087.

Demosthenes Bouros, MD, PhD, Argyrios Tzouvelekis, MD, PhD,

Rare Protein-Altering Telomere-related Gene Variants in Patients with Chronic Hypersensitivity Pneumonitis.

16 of 144 patients (11.1%) in the discovery cohort and 17 of 209 patients (8.1%) in the replication cohort.

[Am J Respir Crit Care Med. 2019, *Nov 1;200(9):1154-1163*

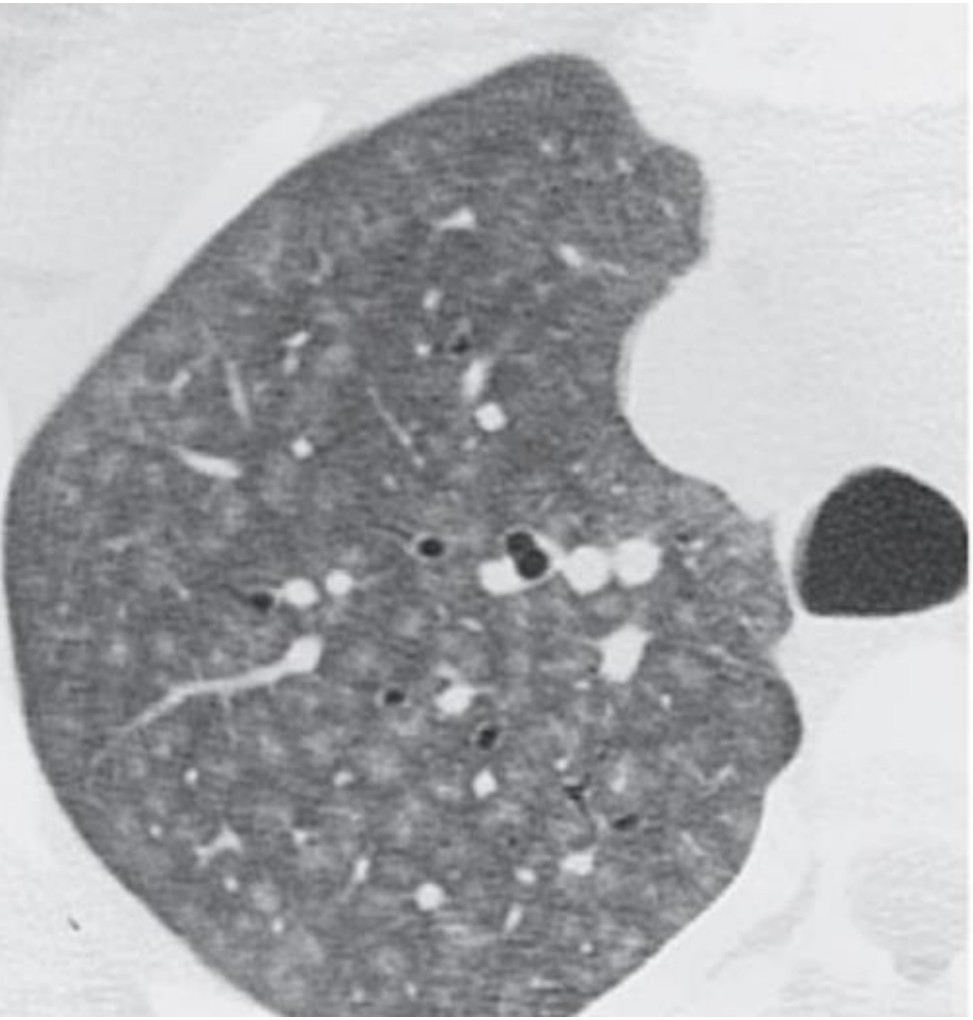
HRCT ΟΞΕΙΑΣ ΦΑΣΕΩΣ HP

- **Βλάβες δίκην γαλακτοχρόου υάλου (GGO).**
- **Παγίδευση αέρα *(air-trapping)* *σε δευτερογενή λοβίδια*.**
- **HRCT σε εκπνοή είναι πολύ χρήσιμη!**

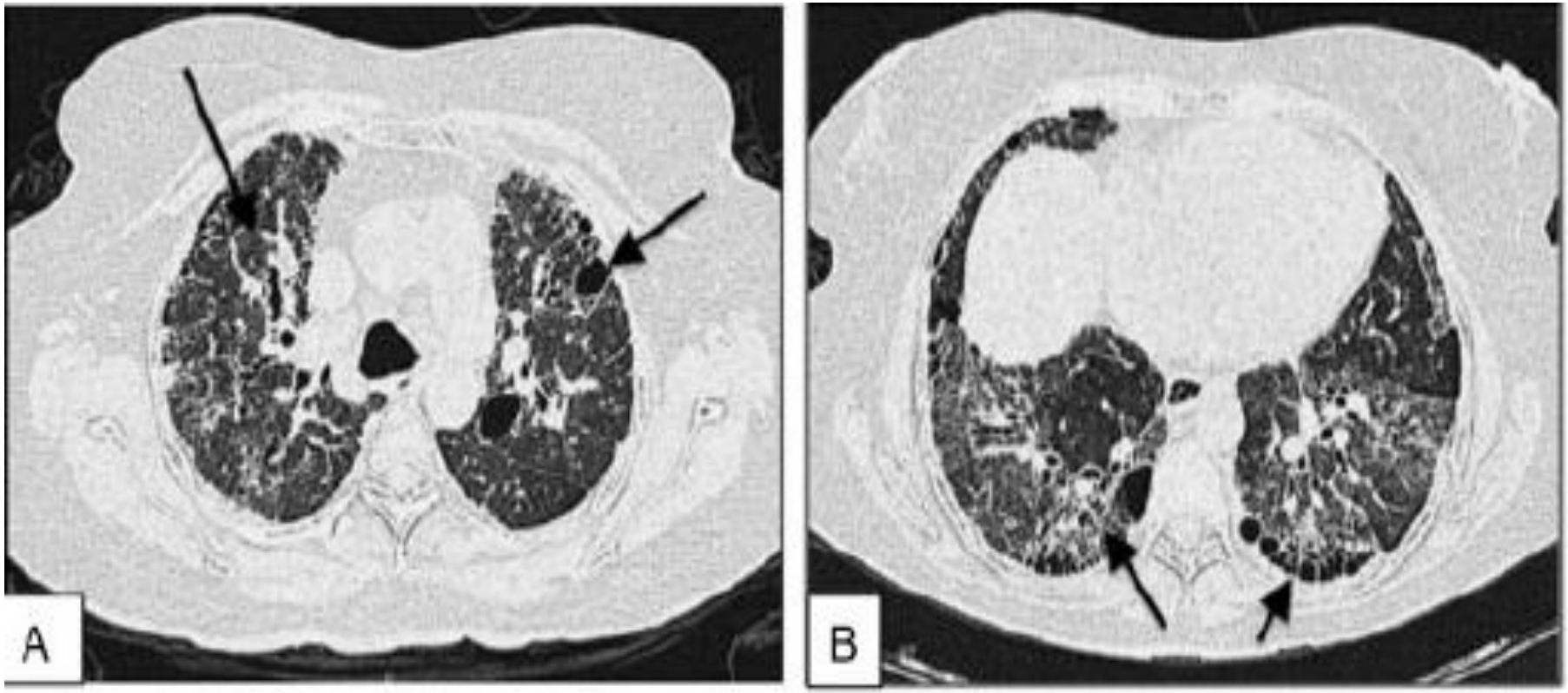
- *Courtesy of Paul Stark, MD.*

HRCT ΥΠΟΞΕΙΑΣ ΦΑΣΕΩΣ HP

- **Πολλαπλά βοτρυδιακά οζίδια (acinar nodules) *(<5mm)* σε όλο τον πνεύμονα.**



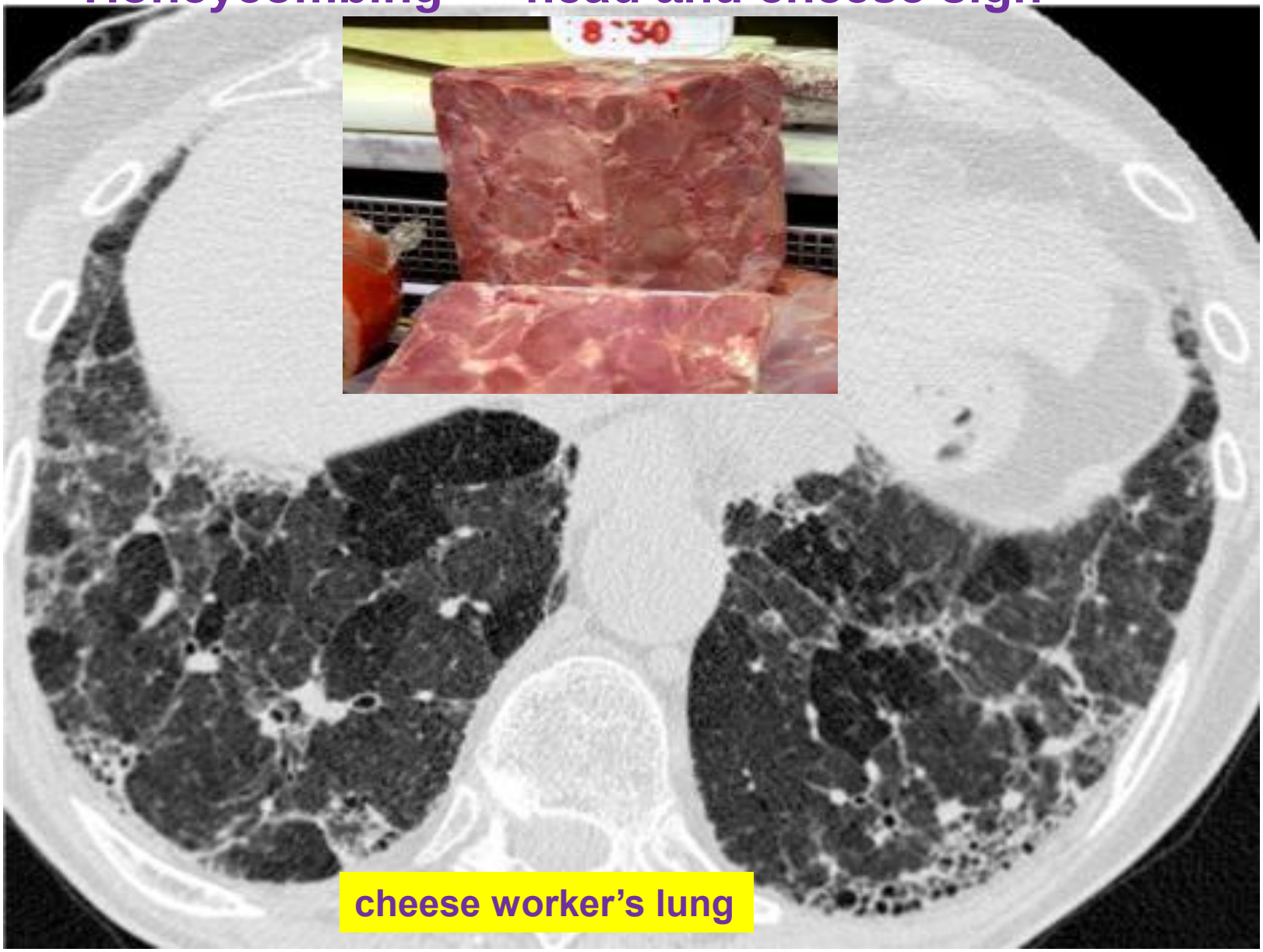
HRCT ΧΡΟΝΙΑΣ ΦΑΣΕΩΣ HP



- **Εικόνα UIP (εκτεταμένες δικτυωτές σκιάσεις, βρογχεκτασίες εξ έλξεως και κηρήθρα).**
- ***Selman and Buendia-Roldan. Sem Respir Crit Care Med 2012***

HRCT 45χρονου γεωργού, μη καπνιστού, με δύσπνοια III/IV, και ξηρό βήχα από εξαμήνου, με πληκροδακτυλία, MMP (Velcro)+ κριγμούς (squeaks). BALF Λ=40%.

Honeycombing + “head and cheese sign”



cheese worker’s lung

Upper lobe predominant honeycombing

HRCT in HP

- ✓ The presence of mosaic attenuation was present in 51% of IPF patients
- ✓ The "headcheese sign" is a highly specific radiologic finding for fibrotic HP

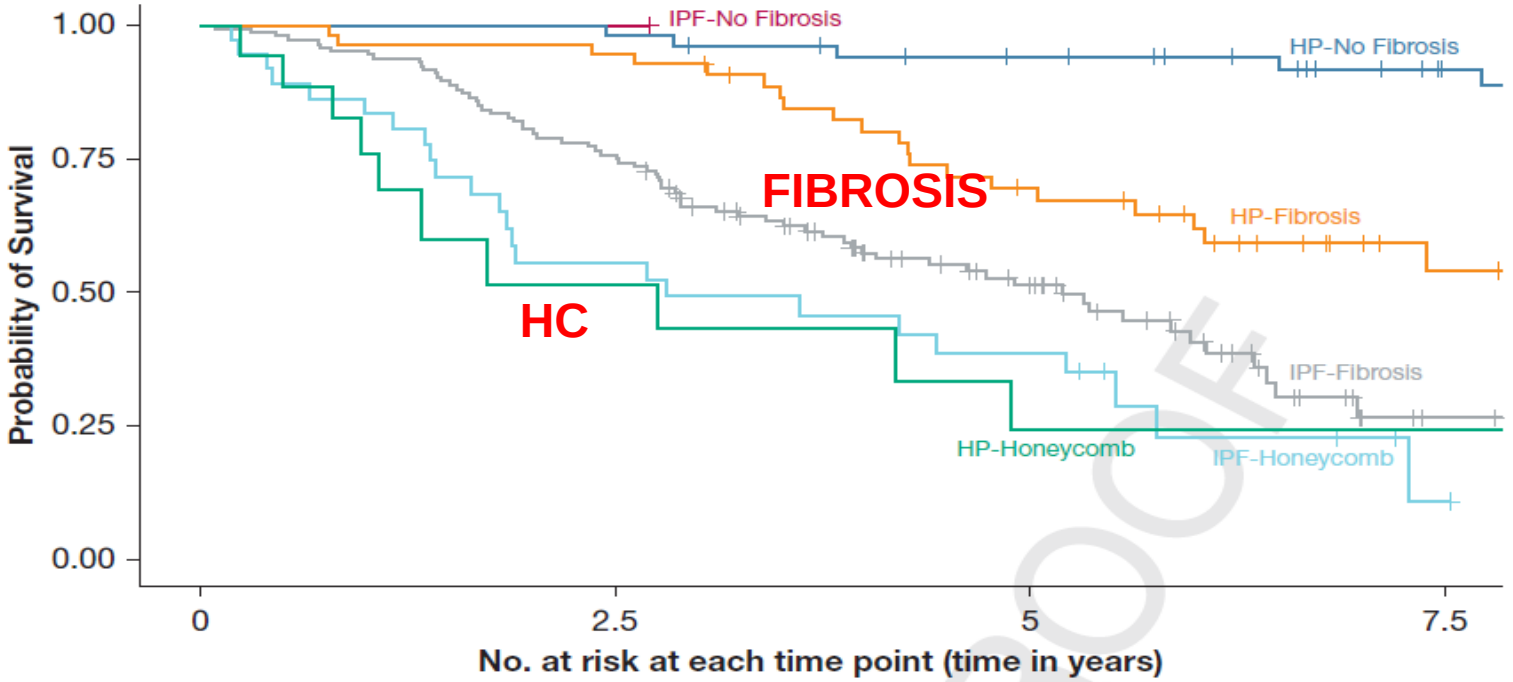
Barnett J, et al. ERJ 2019

Hypersensitivity Pneumonitis

Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory

Margaret L. Salisbury, MD; Tian Gu, MS; Susan Murray, ScD; Barry H. Gross, MD; Aamer Chughtai, MBBS; Mohamed Sayyouh, MBBCh; Ella A. Kazerooni, MD; Jeffrey L. Myers, MD; Amir Lagstein, MD; Kristine E. Konopka, MD;

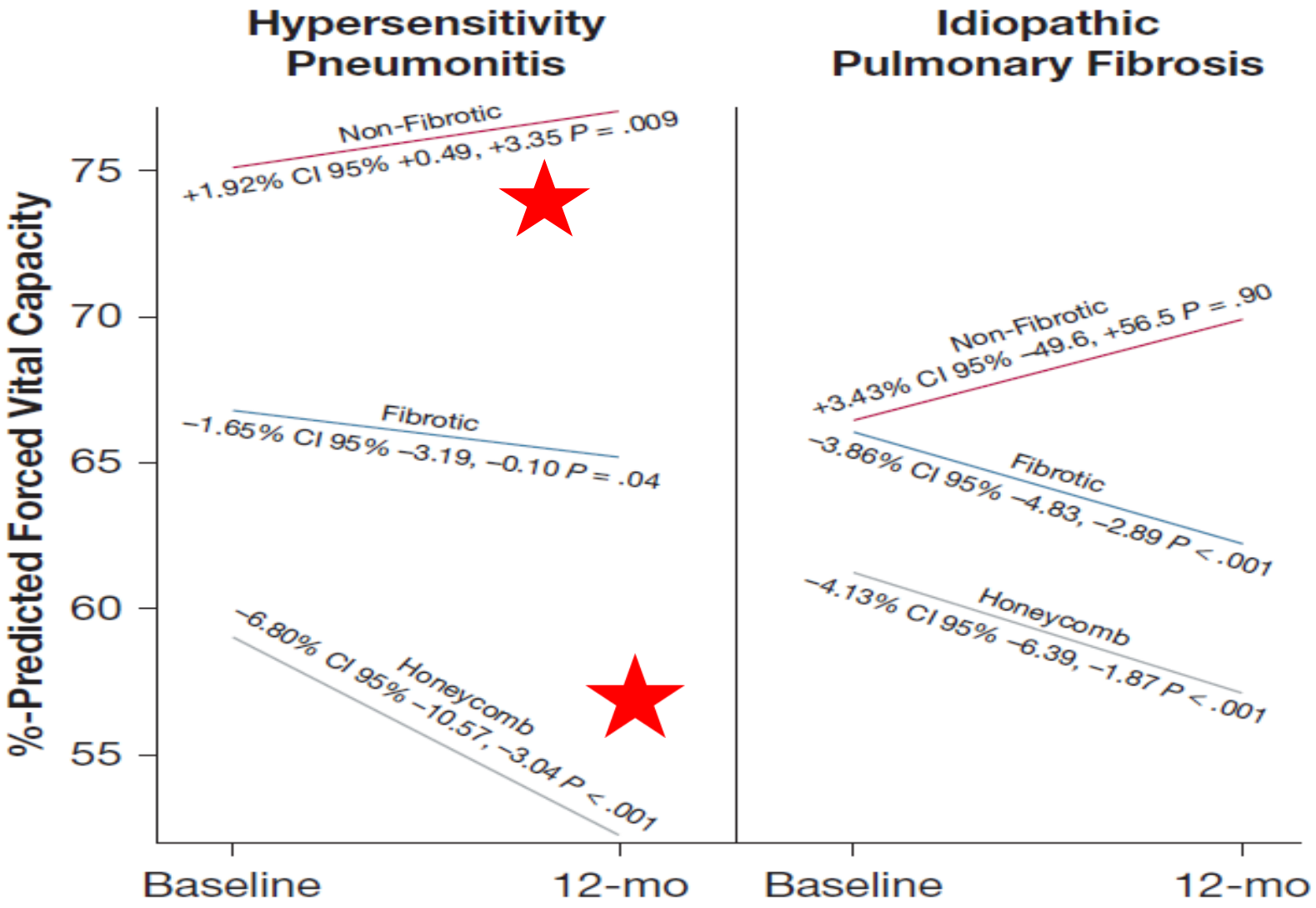
CHEST 2019



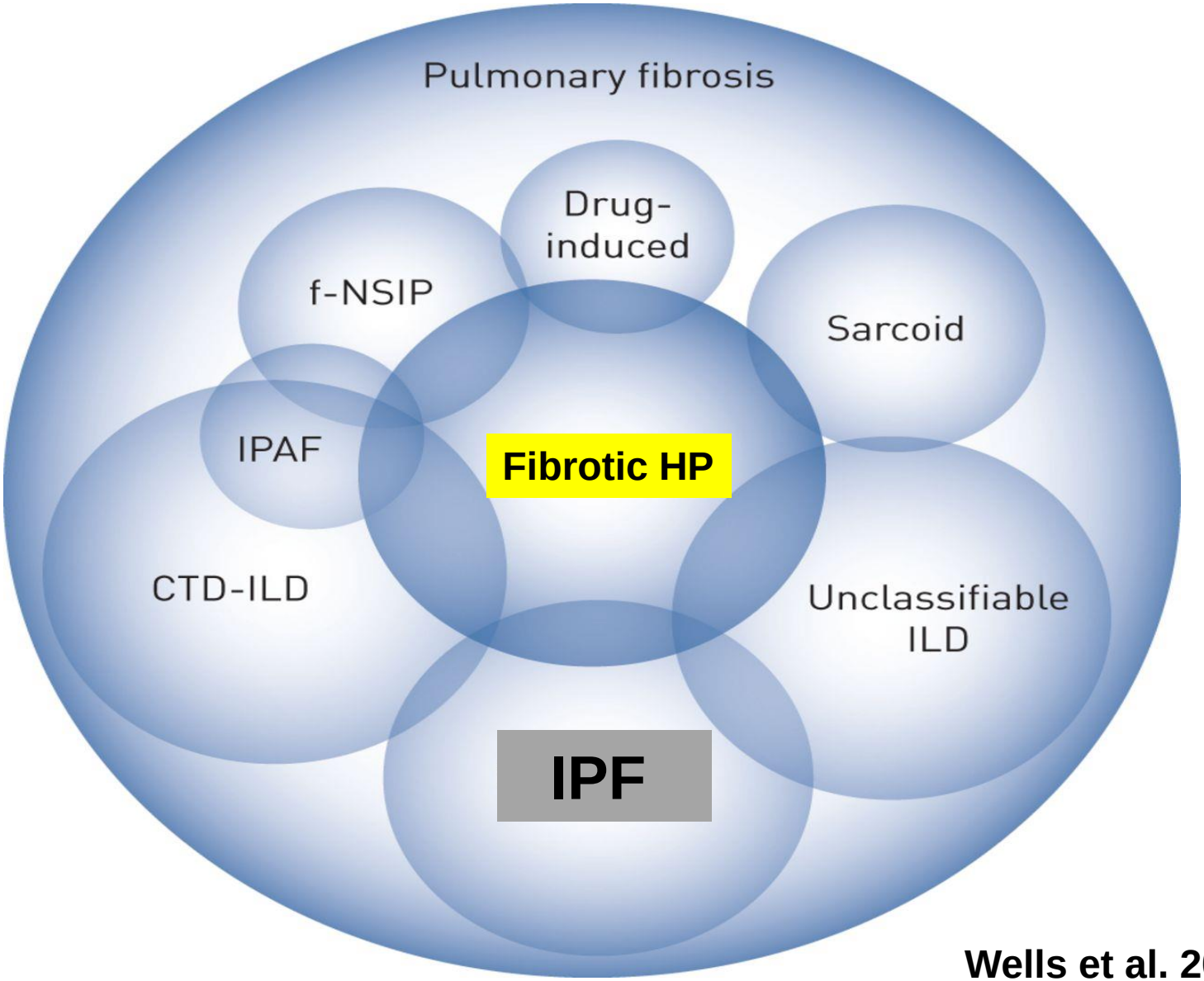
IPF-No Fibrosis	1	1	0	0
HP-No Fibrosis	60	59	53	41
IPF-Fibrosis	122	89	40	5
HP-Fibrosis	45	42	27	11
IPF-Honeycomb	29	14	9	1
HP-Honeycomb	12	5	2	2

D PROOF

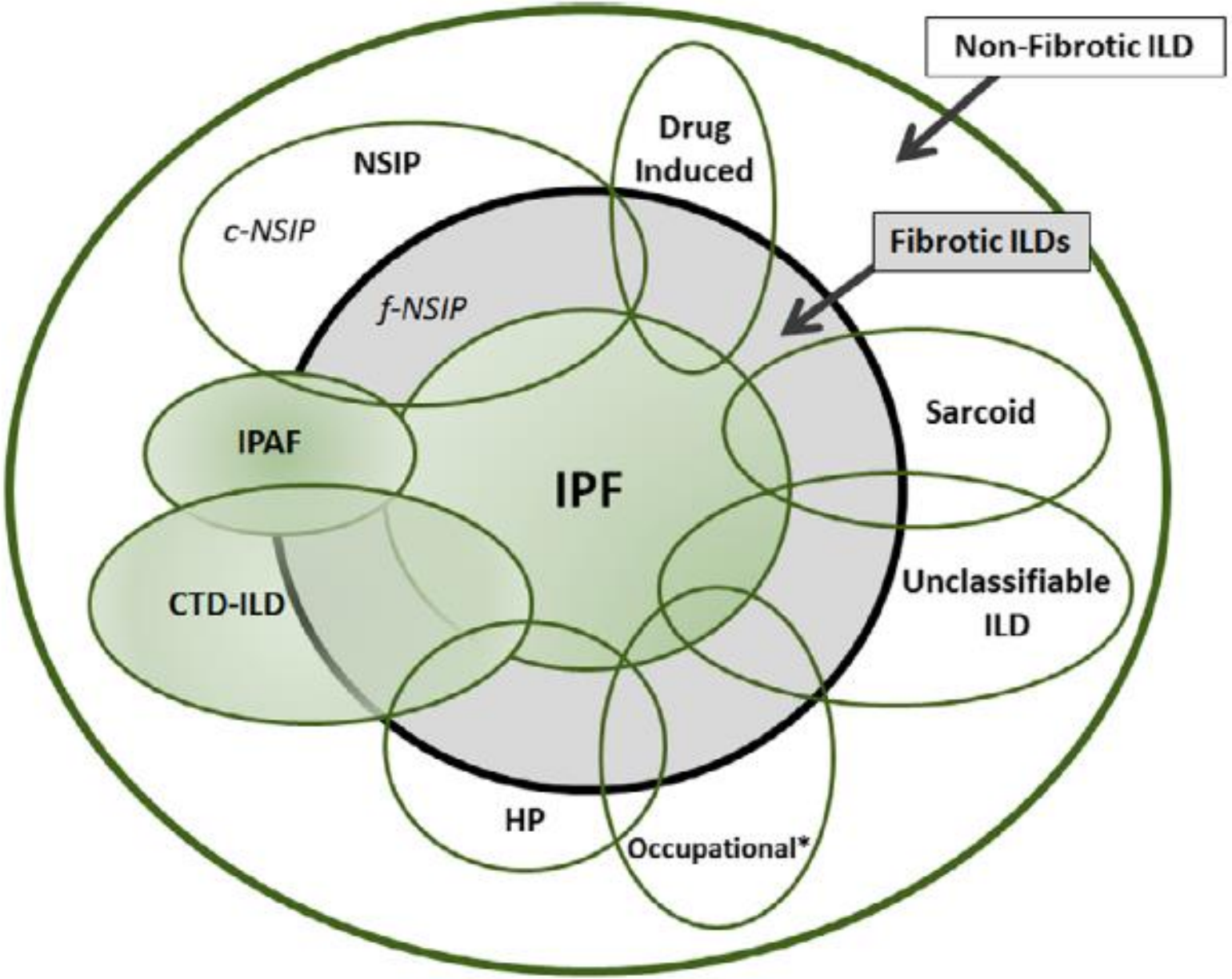
Patients with HP without radiologic fibrosis have significant increase in FVC %, whereas all other groups had a significant decrease



ΕΠΙΚΑΛΥΨΗ ΧΡΟΝΙΩΝ ΙΝΩΤΙΚΩΝ ΠΝΕΥΜΟΝΟΠΑΘΕΙΩΝ



Wells et al. 2018



* Including asbestosis, silicosis, pneumoconiosis

Inter-MDT agreement in the setting of diffuse lung disease

IPF Kappa=060

Hypersensitivity pneumonitis

Kappa = 0.24

<0.4 = poor,

0.4-0.6 = satisfactory,

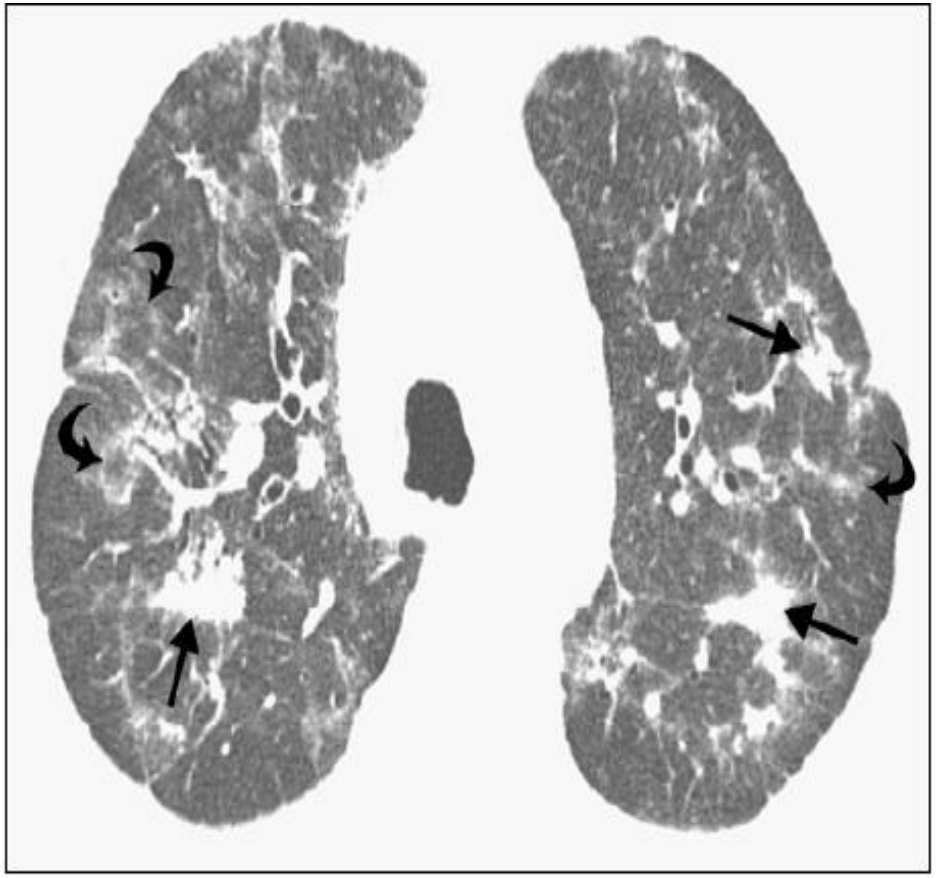
0.6-0.8 = good,

>0.8 = excellent

Walsh SL et al, Lancet Resp Med 2016: in press

HP ΚΑΙ ΣΥΝΟΣΗΡΟΤΗΤΕΣ

Fig. 17—44-year-old man with chronic hypersensitivity pneumonitis (farmer's lung). High-resolution CT image shows bilateral ground-glass opacities and centrilobular emphysema. Patient was lifelong nonsmoker. (Courtesy of Dr. Yvon Cormier, Quebec, Canada)



HP and organizing pneumonia.
Courtesy of Silva I, et al.

BRONCHOALVEOLR LAVAGE IN HP

- **Αυξημένος αριθμός (ολικός και %) λεμφοκυττάρων, T cells, mast cells.**
- **Και σε ασυμπτωματικούς ασθενείς.**
- **Φυσιολογικός αριθμός λεμφοκυττάρων αποκλείει την HP, εκτός από υπολειμματική νόσο.**
- **CD4:CD8 -ΔΕΝ ΣΥΝΙΣΤΑΤΑΙ!.**

  [Range according to the type of causative antigen, the clinical status, smoking habit, etc].

- **Οξεία προσβολή = αυξημένος αριθμός ουδετεροφίλων και λεμφοκυττάρων.**

EUROPEAN RESPIRATORY *journal*

Diagnostic value of BAL lymphocytosis in patients with indeterminate for UIP imaging pattern

Eur Respir J 2019;

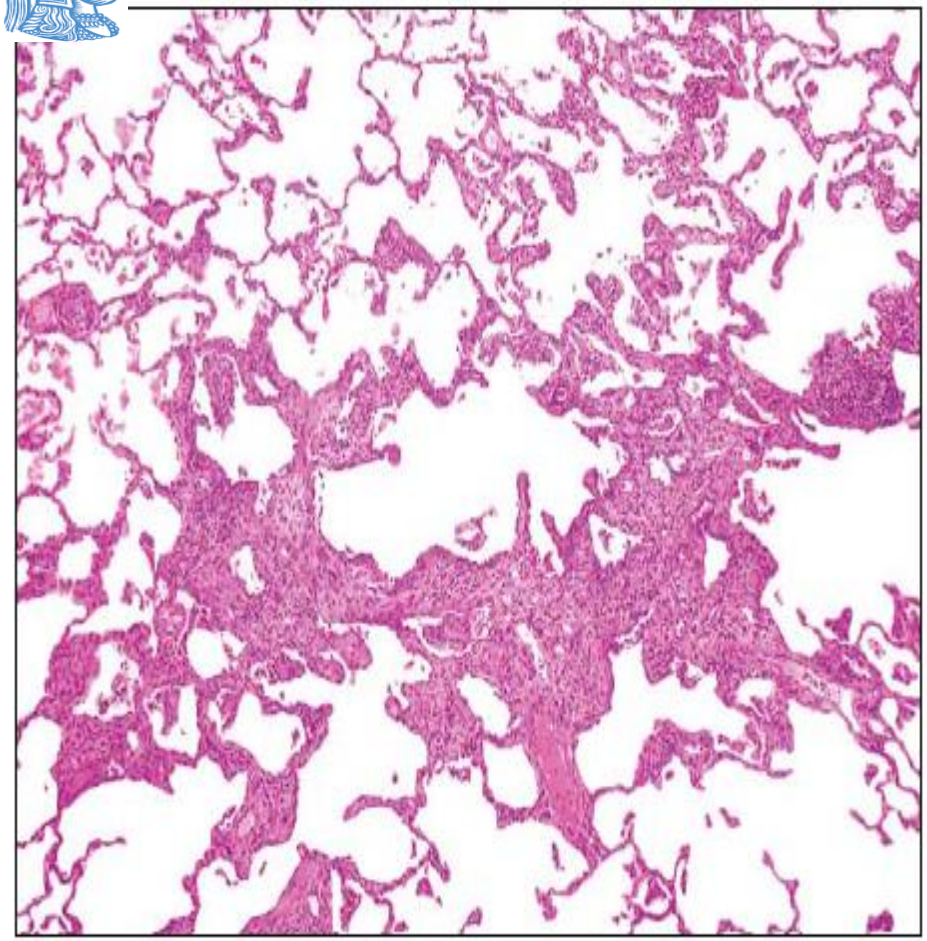
Vasilios Tzilas, Argyrios Tzouvelekis, Evangelos Bouros, Thodoris Karampitsakos, Maria Ntasiou, Mattheos Katsaras, Ulrich Costabel, Athol Wells, Demosthenes Bouros

Diagnostic value of BALF

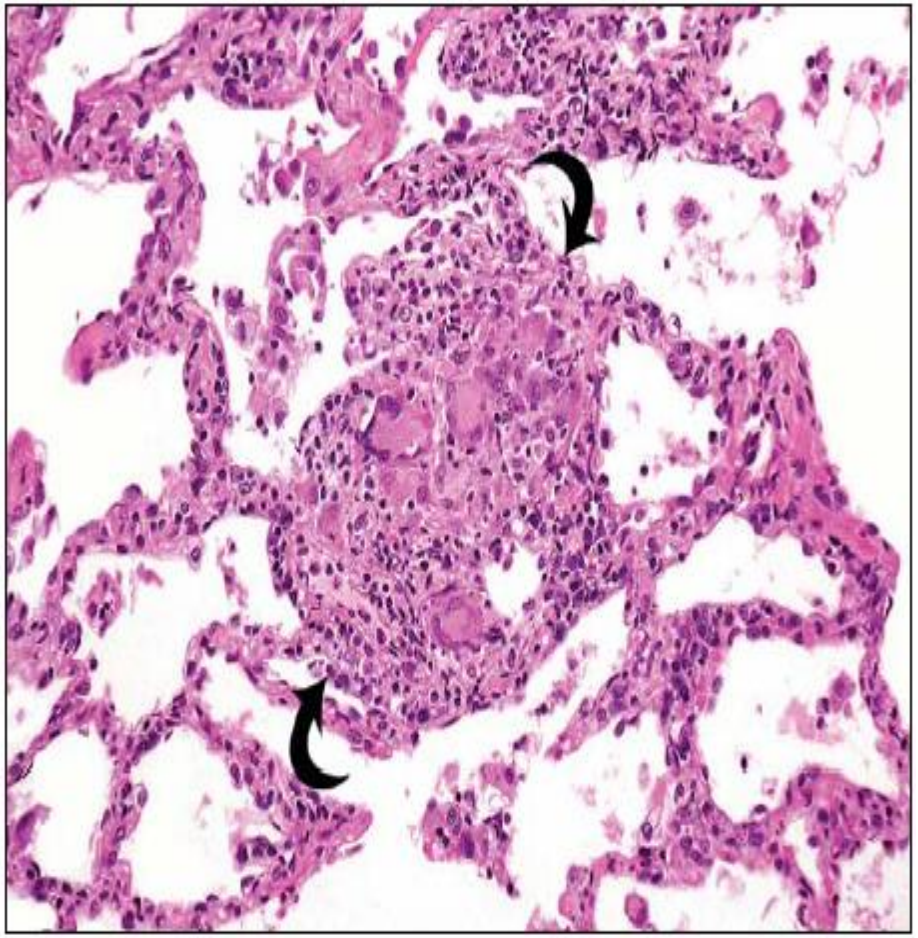
Reevaluation of patients driven by BALF results, led to a change in diagnosis in 14 patients (14.7%). In the majority of these cases (11/14, 78.6%) the initial diagnosis was altered from IPF to HP. In the remaining cases, the initial diagnosis was changed from Unclassifiable fibrosis to HP, from IPF to and from NSIP to HP. Interestingly, identification of a previously unidentified inciting agent occurred in seven patients.

4 κύρια ιστολογικά χαρακτηριστικά

1. **Διήθηση διαμέσου ιστού από μονοπύρηνα**
2. **Μικρά, ασαφή μη νεκρωτικά κοκκιώματα *(non caseating granulomas)*- απουσία στο ~1/3 των περιπτώσεων.**
3. **Βρογχιολίτιδα, συχνά παρόμοια με την αποφρακτική (ΒΟ), *περιβρογχιολικά, λεμφοκυτταρική.***
4. **Διάμεση ίνωση/ ομοία με την UIP.**



A



B

Fig. 1—35-year-old woman with subacute hypersensitivity pneumonitis (bird fancier's lung).

A, Photomicrograph of histopathologic specimen obtained at surgical lung biopsy shows moderate, diffuse, bronchiolocentric chronic lymphocytic inflammatory infiltrate. (H and E, ×60)

B, Magnified view of different area from **A** shows poorly formed granuloma (*arrows*) and chronic interstitial inflammatory infiltrate. (H and E, ×200)

AJR 2007; 188:334–344

Ο ΡΟΛΟΣ ΤΩΝ ΙΖΗΜΑΤΙΝΩΝ ΚΑΙ ΤΗΣ ΠΡΟΚΛΗΣΗΣ

- **Πρέπει να διενεργούνται (serum IgG ab) σε έκθεση σε γνωστό αντιγόνο.**
- **Ψευδώς αρνητικές σε χρόνιες περιπτώσεις.**
- **Η παρουσία τους σημαίνει έκθεση και ανοσολογική απάντηση**

(μέχρι 50% σε ασυμπτωματικούς pigeon breeders and 2–10% σε ασυμπτωματικούς αγρότες).

- **Πρόκληση με εισπνεόμενο αντιγόνο- μόνο σε ειδικά κέντρα.**

ΔΙΑΚΡΙΣΗ HP ΑΠΟ ΑΛΛΕΣ ΔΠ

- **<u>Συχνά συγχέονται</u> με άλλες διάμεσες πνευμονοπάθειες και *αντίθετα*, εκτός αν είναι εμφανής η έκθεση!**

- **> 30% δεν έχουν αναγνωρίσιμη έκθεση!**

- ***(AJRCCM 188,2013)***

ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ IPF ΚΑΙ ΙΝΩΤΙΚΗΣ HP

Features	Fibrotic HP	IPF
Demographics		
Sex	No difference	More frequent in men
Smoking	Protective	Risk factor
Age	No predilection	More frequent > 55 years
Clinical symptoms/history		
Clubbing	Often	Often
Squeaks	Typical	Absent
Bibasal crackles	Frequent	Frequent
Systemic disease features (fever, joint pains, fatigue)	Often	Absent
Exposure to antigens	Frequent	Rare
Positive precipitins	Frequent	Rare

HRCT ΣΕ IPF ΚΑΙ ΙΝΩΤΙΚΗ HP

Imaging (CT)	HP	IPF
Distribution	Upper lobe predominance	Peripheral, predominantly basal
Mosaic attenuation	Frequent	Absent/Limited
Nodules	Frequent	Absent
Interlobular septal thickening	Often	Absent/Limited
Honeycombing	Often	Frequent (typical for UIP pattern)
Bronchocentricity	Frequent	Absent
Discrete cysts	Often	Absent
Consolidation	Rare	Absent

ΜΙΚΡΟΣΚΟΠΙΚΑ ΕΥΡΗΜΑΤΑ ΣΕ IPF ΚΑΙ HP

	HP	IPF
Bronchoalveolar lavage (BAL) ★	Lymphocytosis > 25–30%	Lymphocytosis < 20%
Histological		
Fibroblast foci	Often	Frequent
Granulomas/giant cells/Schaumann bodies	Frequent	Rare
Organizing pneumonia	Rare	Rare
Honeycombing	Often	Frequent
Paraseptal subpleural distribution	Often	Frequent
Bronchocentricity	Frequent	Absent

ΘΕΡΑΠΕΙΑ HP

- **Αποφυγή του αντιγόνου**
  - **Πολύ σημαντική**
  - **συνήθως η πάθηση υποχωρεί**
  - **Αποφυγή ευαισθητοποίησης άλλων ατόμων**
  - **Δεν είναι πάντα δυνατή / αποτελεσματική**
  - **Το αντιγόνο των πτηνών μπορεί να παραμένει και 6 μήνες στο σπίτι μετά την απομάκρυνση των πτηνών *(βιολογικός καθαρισμός).***

TREATMENT OF HP

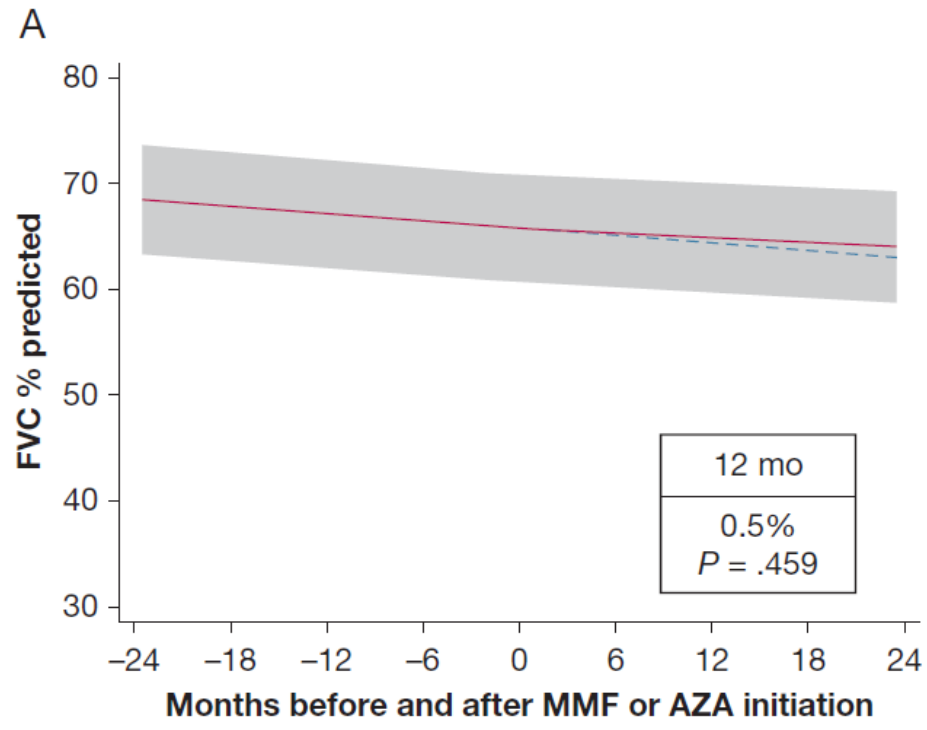
Κορτικοειδή – AZA- MMF

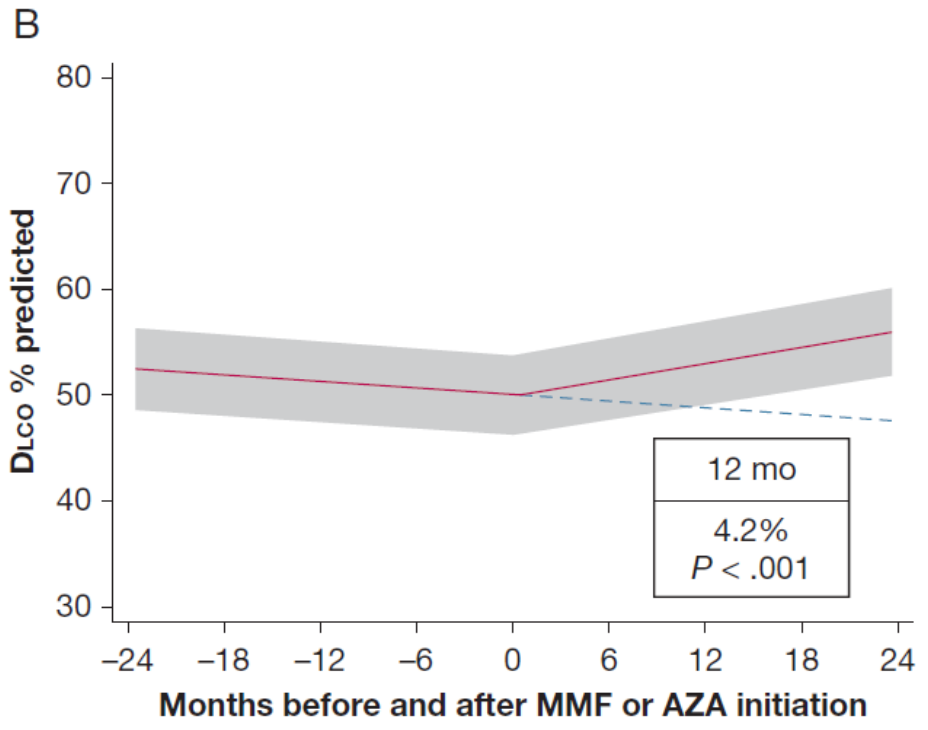
- **Επιταχύνει την αρχική αποδρομή σε βαριά ασθενείς**
- **Έναρξη 20 mg/d (< 60 mg/d), συντήρηση**
- **10-15 mg/d**
- **Η μακροχρόνια πορεία δεν αλλάζει..**

Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis

CONCLUSIONS: Treatment with MMF or AZA is associated with improvements in DLCO in patients with cHP. Prospective randomized trials are needed to validate their effectiveness for cHP.

CHEST 2017; 151(3):619-625





TREATMENT OF HP

ANTIFIBROTICS?

- **Pirfenidone/Nintedanib in chronic HP?**
  - ***INBUILT TRIAL. NEJM 2019***

LUNG TRANSPLANTATION…

Table 1. Treatment Strategies in Hypersensitivity Pneumonia

Inflammatory Features* Present

- Environmental evaluation and antigen remediation
- Consider a trial of immunosuppression. Watchful waiting is also an option in stable and/or mild disease, or if an antigen is identified and removed
- Suggested immunosuppressive regimen†:
  1. Corticosteroids (0.5–1 mg/kg daily prednisone equivalent) ± cytotoxic agent‡§
     a. Taper prednisone to 20 mg daily in the first 3 mo
     b. Close interval monitoring of FEV_1, FVC, and D_{LCO} (consider every 1–2 mo initially)
  2. Taper corticosteroid to <20 mg daily when pulmonary function plateaus (presuming initial improvement)
     a. Interval pulmonary function every 3–4 mo. Consider HRCT at 3–6 mo
     b. If disease worsens during steroid taper, consider cytotoxic agent (if not already initiated). Evaluate for infection or reintroduction of antigen, as indicated

Ο ΟΡΙΣΜΟΣ ΤΟΥ ‘ΕΜΠΕΙΡΟΓΝΩΜΟΝΑ’

A person who is very knowledgeable about or skillful in a particular area.

Cambridge Dictionary

‘An expert is a man who has stopped thinking - he knows!’
Frank Lloyd Wright

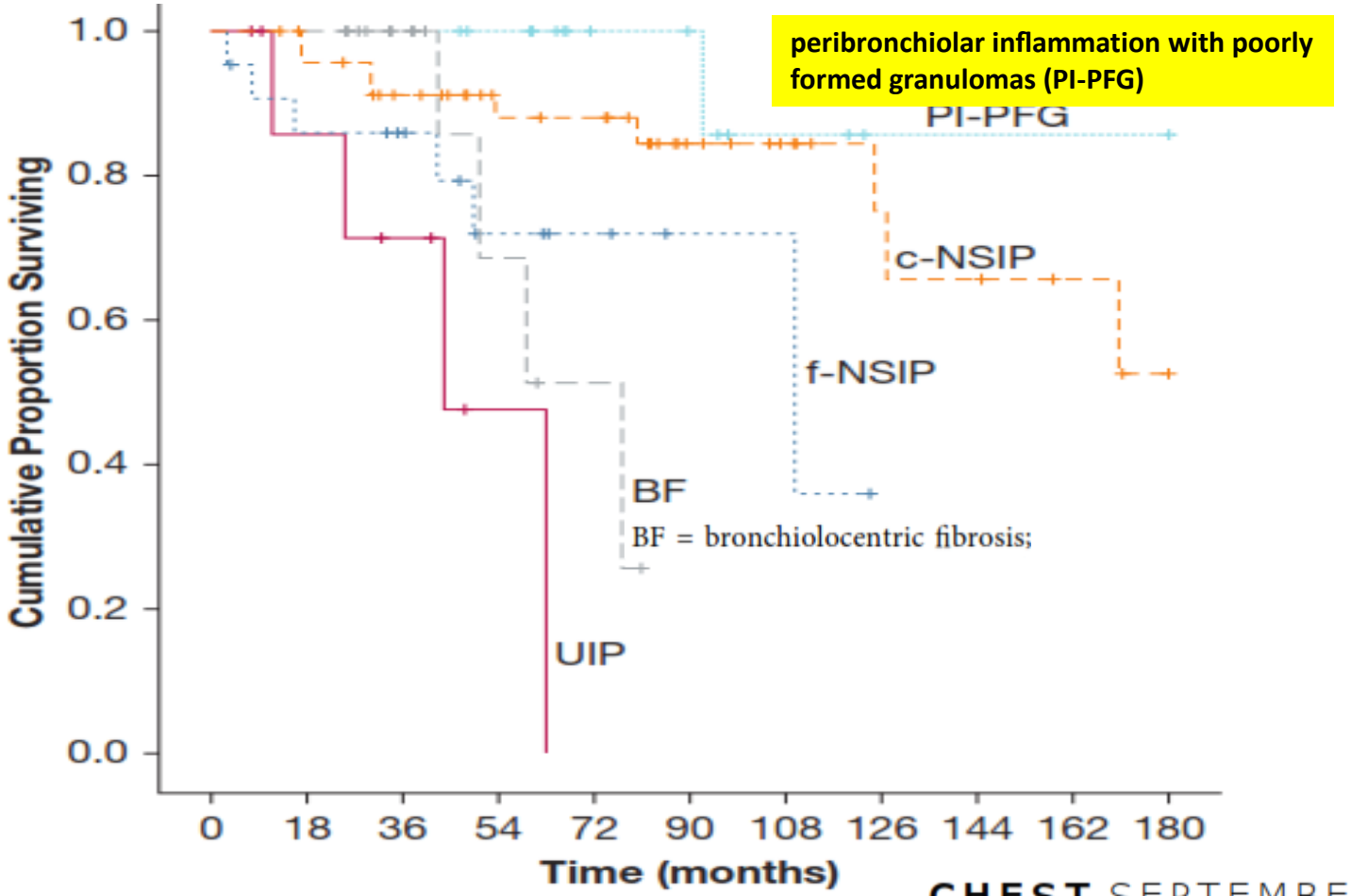
‘An expert is somebody who is more than 50 miles from home, has no responsibility for implementing the advice he gives, and shows slides’
Edwin Meese III

ΠΡΟΓΝΩΣΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ HP

1. Η διάρκεια και η ένταση της έκθεσης
2. Οι ιστολογικές βλάβες (OP, cellular NSIP vs. fibrotic NSIP or a UIP-like pattern)
3. Η παρουσίαση (acute, subacute, or chronic HP)
4. Η πληκτροδακτυλία (χειρότερη πρόγνωση)
5. Οι ηλικιωμένοι είναι λιγότερο πιθανό να βελτιωθούν.
6. Ούτε οι PFTs ούτε η CXR κατά την διάγνωση δεν σχετίζονται με την πρόγνωση.
7. Τα HRCT πρότυπα μπορεί να είναι προγνωστικά της χρονίας HP.

Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis

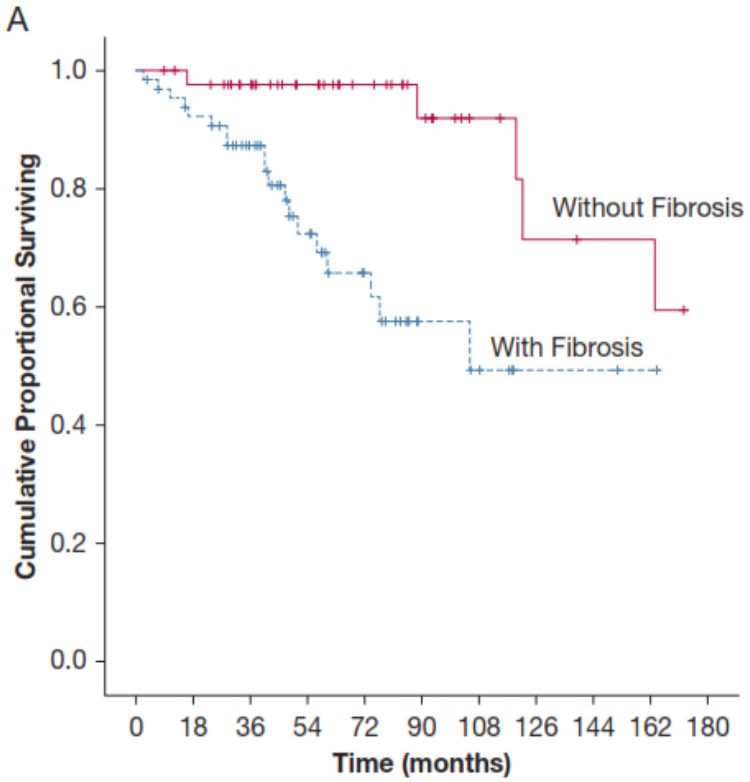
Ping Wang, MD; Kirk D. Jones, MD; Anatoly Urisman, MD; Brett M. Elicker, MD; Thomas Urbania, MD; Kerri A. Johannson, MD; Deborah Assayag, MD; Joyce Lee, MD; Paul J. Wolters, MD; Harold R. Collard, MD; and Laura L. Koth, MD

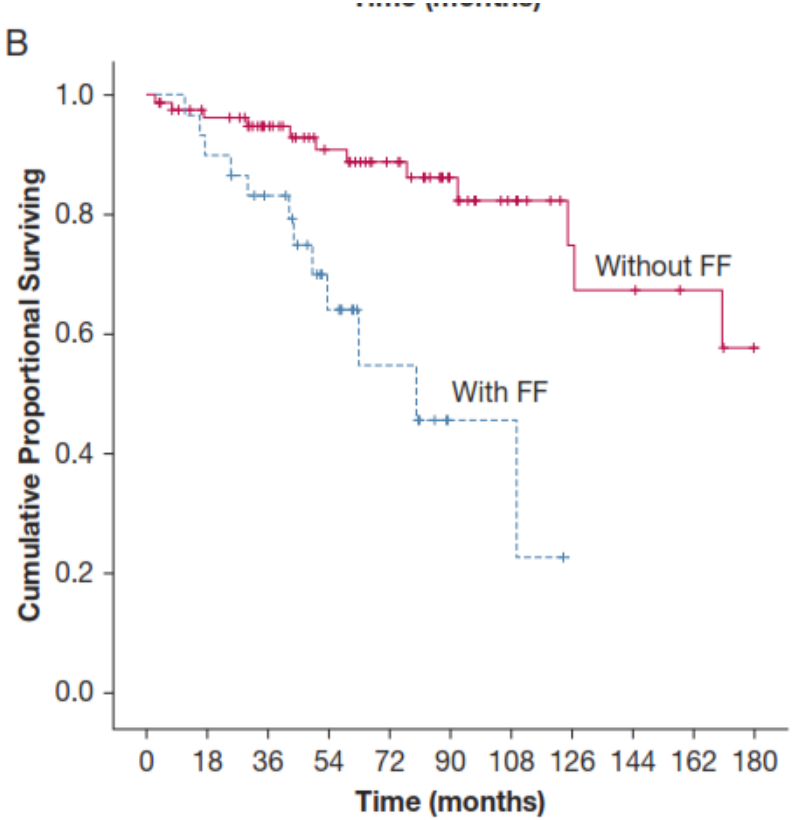


CHEST SEPTEMBER 2017

Pathologic Findings and Prognosis in a Large Prospective Cohort of Chronic Hypersensitivity Pneumonitis

CHEST SEPTEMBER 2017





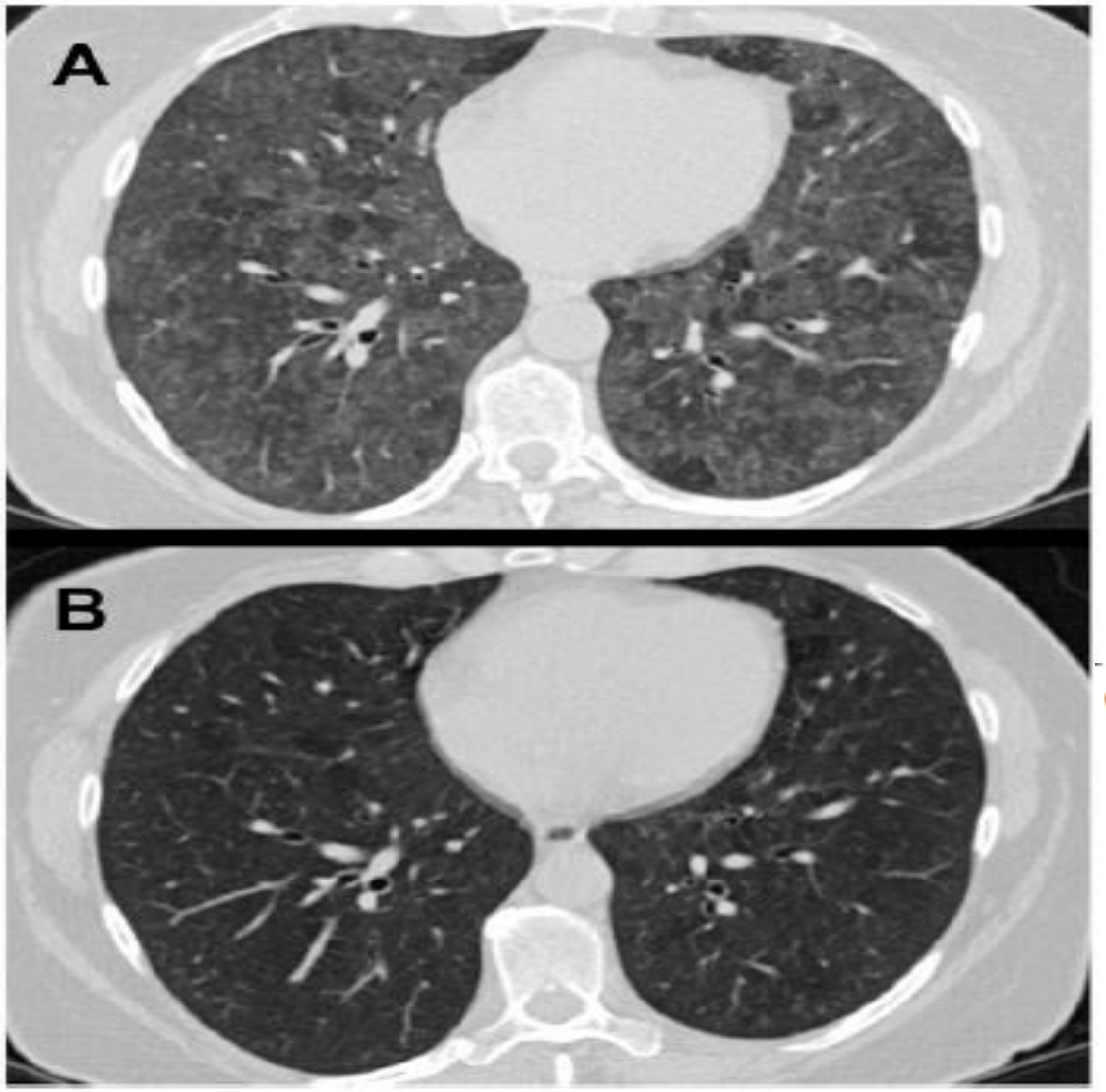
FF=Fibroblastic foci

ΜΕΣΗ ΕΠΙΒΙΩΣΗ

TABLE 1] Selected Studies Reporting Median Survival in Chronic HP According to Pathologic Pattern

Series	Pathologic Pattern/Median Survival			Comments
	UIP	Fibrotic NSIP	Centrilobular Fibrosis Only	
Ohtani et al[3]	50 mo	50 mo		• Bird exposures
Churg et al[2]	36 mo	36 mo	144 mo	• Mixed exposures
Gaxiola et al[4]	40 mo			• Bird exposures
Takemura et al[5]	80% survival at 100 mo			• Mixed exposures • UIP comparison group; median survival, 100 mo
Chiba et al[6]	27 mo if > 2.2 fibroblast foci/cm^2 70% survival at 100 mo if < 2.2 fibroblast foci/cm^2			• Bird exposures • Amounts of HRCT reticulation, honeycombing, traction bronchiectasis higher in cases with > 2.2 fibroblast foci/cm^2
Wang et al[1]	40 mo	108 mo	60 mo	• Mixed exposures

COMPLETE RESOLUTION



CHEST 2012; 142(1):208–217

FIGURE 1. A, High-resolution CT scan of a patient with hot tub lung: patchy bilateral ground-glass opacities with poorly defined small centrilobular nodules. B, Same patient, 6 weeks following exposure withdrawal, showing full radiologic recovery.

PROGRESS TO FIBROSIS

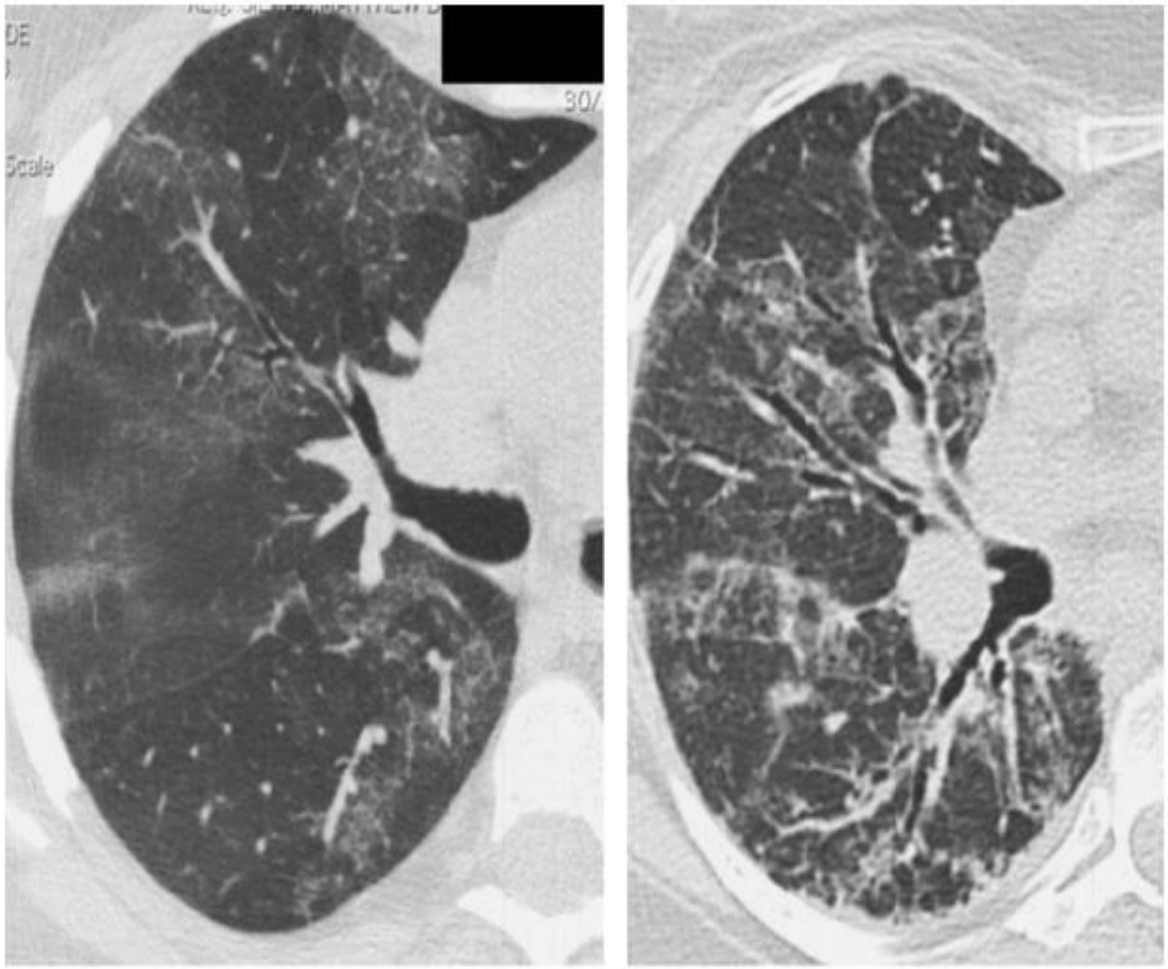
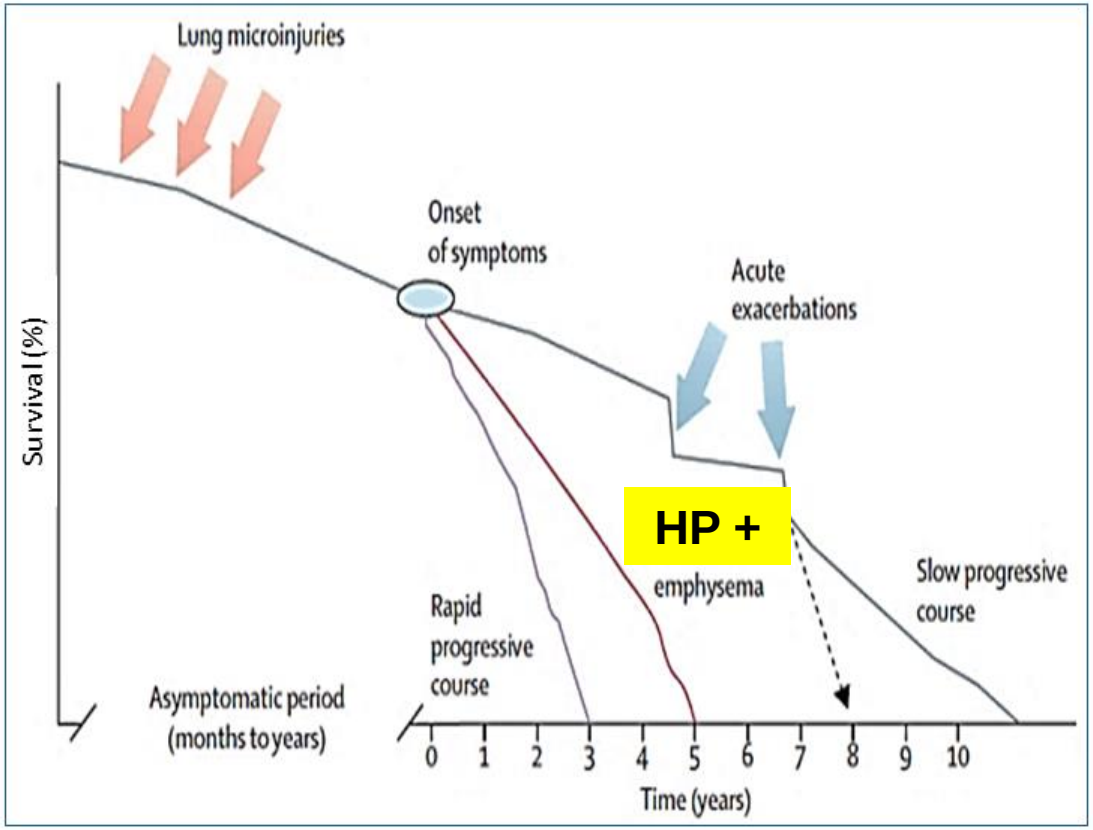


Figure 13. Progression of insidious hypersensitivity pneumonitis to fibrosis. **(a)** Axial high-resolution CT image of the right lung at the takeoff of the right middle lobe bronchus shows patchy ground-glass opacity. **(b)** Axial high-resolution CT image obtained at a similar level 3 years later demonstrates a predominantly reticular abnormality with associated traction bronchiectasis, findings suggestive of fibrosis.

The Course o HP is Variable



King TE Jr, et al. *Lancet*. 2011;378(9807):1949-1961.

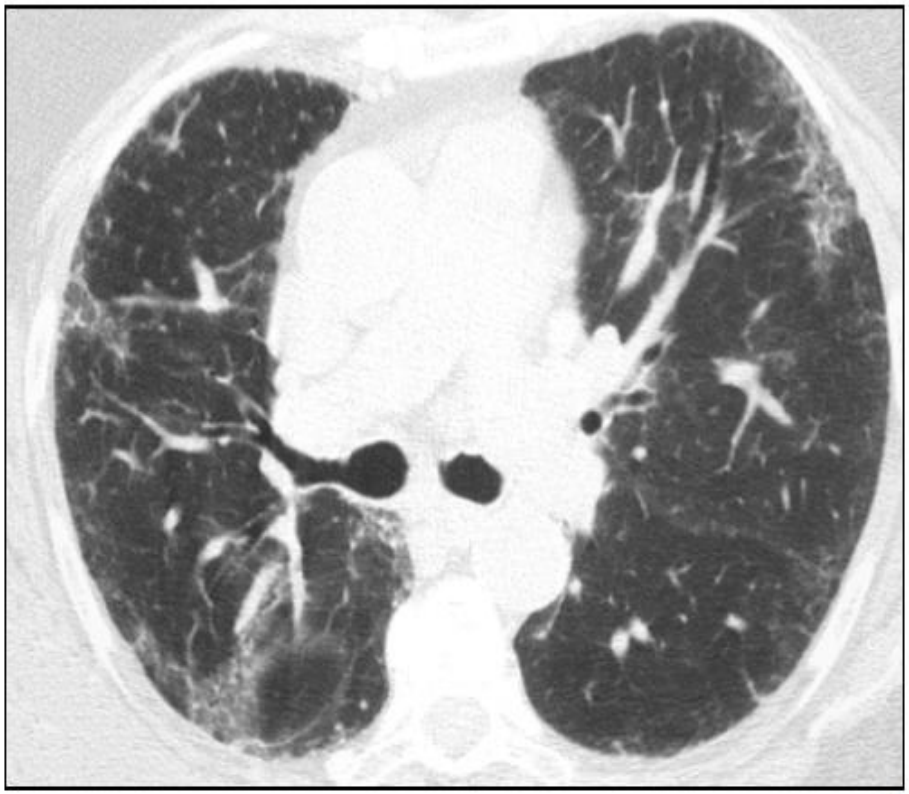
ACUTE EXACERBATIONS OF HP

Seems to occur mainly in:

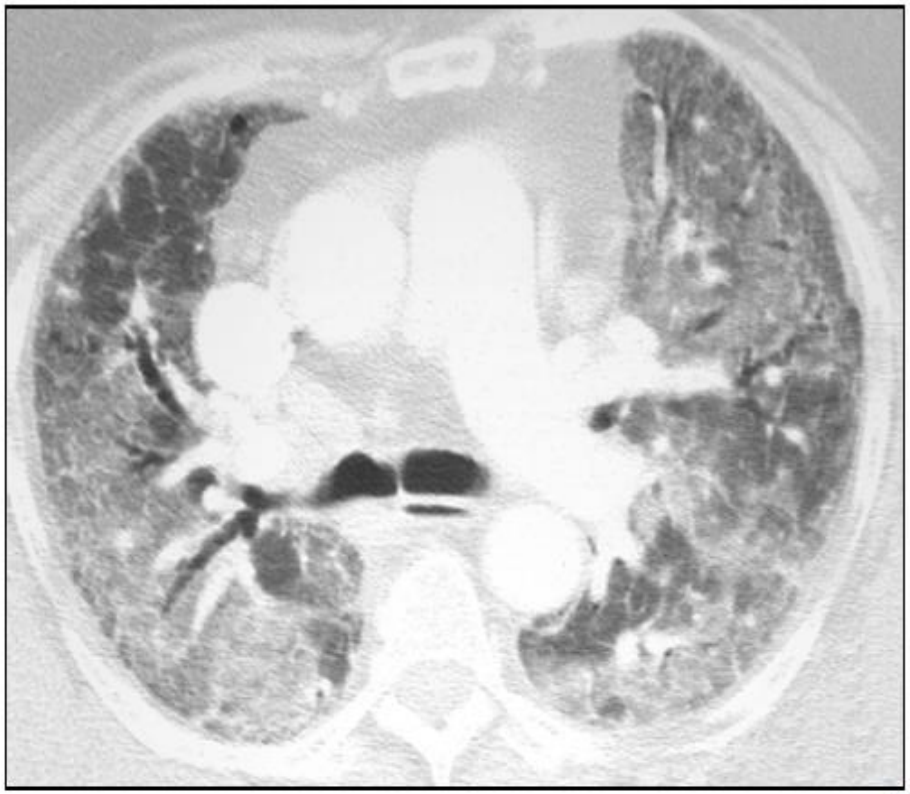
- *male smokers*
- ***BALF:*** *fewer lymphocytes and increased neutrophils*
- *with advanced fibrosis on HRCT*
- *worse pulmonary* **function**

Pathology: DAD+OP

ΠΑΡΟΞΥΝΣΗ HP ΜΕΤΑ ΑΠΟ 7 ΧΡΟΝΙΑ.



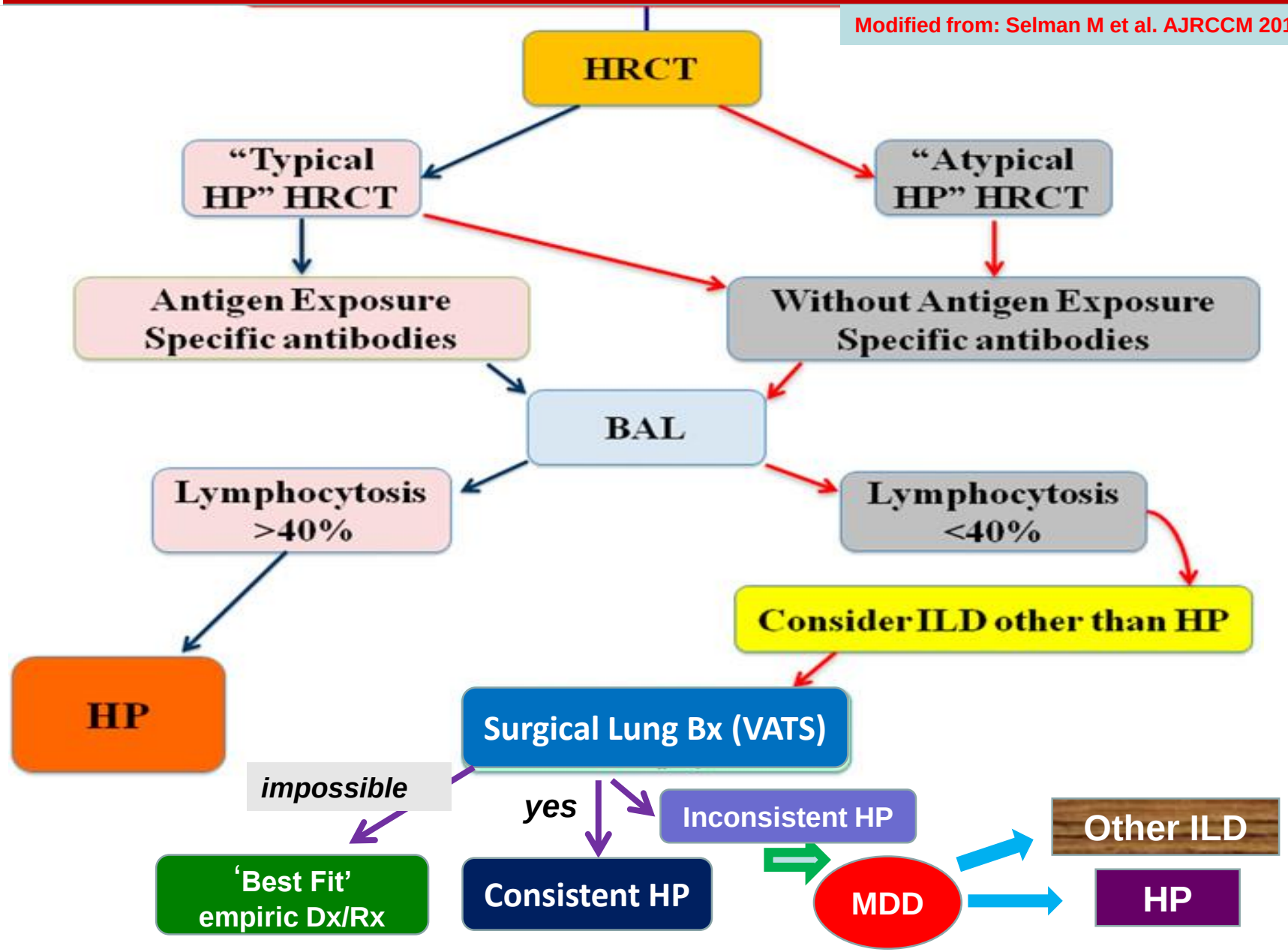
A



B

DIAGNOSTIC ALGORITHM OF HP

Modified from: Selman M et al. AJRCCM 2012



Google University of Medicine

This certifies that Dr: _____ *on recommendation of the faculty of the Google University of Medicine has conferred the degree of:*

Internet Doctor of Medicine

Who has honorably fulfilled all the requirements prescribed by the university for that degree.

President

Director

Date