2020.09.12

ILD School 2020

Chronic Hypersensitivity Pneumonitis

The New Diagnostic Criteria and Treatment

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Hypersensitivity Pneumonia

Definition

- Typically results from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals

- Inflammatory and/or fibrotic disease affecting the lung parenchyme and small airways

Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

Classification of HP

	Acute	Subacute	Chronic
Factors	Frequency, intensity, duration of exposure and host/other factors		
Onset	2-9 hours (Onset) 6-24 hours (Peak) Hours to days (Last)	Gradual (over days and weeks)	Insidious (over months)
Symptoms	Influenza-like Sx (fever, chills, sweating, myalgias, lassitude, headache, nausea, cough, dyspnea)	Cough, dyspnea (may progress to severe dyspnea with cyanosis)	Cough, exertional dyspnea fatigue, weight loss
HRCT	Multifocal and diffuse GGO	Multifocal and diffuse GGO Centrilobular nodules Air-trapping	Features of subacute HP Presence of fibrosis (reticular opacities, bronchiectasis)
Pathology	Peribronchial inflammation Interstitial and intra-alveolar inflammation	Chronic peribronchiolar lymphocytic inflammation Poorly formed non-necrotizing granuloma Focal organizing pneumonia	Chronic fibrosis (may resemble UIP or NSIP pattern)
BAL	Increased neutrophils Lymphocytosis (24-72 hr)	Lymphocytosis CD4/CD8 < 1	Lymphocytosis CD4/CD8: variable

Richerson HB *et al*. *J Allergy Clin Immunol*. 1989; 84
Broaddus VC et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. 2016

Guidelines for Evaluation of HP

- **Clinical history**
  - ✓ Symptoms (fever, chill, sweating, myalgia, headache, cough etc.)
  - ✓ Environmental exposure

- **Radiologic evaluation (Chest radiography)**
  - ✓ Acute phase: Poorly-defined diffuse uniform nodularity
  - ✓ Chronic phase: Interstitial infiltrates (accentuated linear elements)

- **Pulmonary function**
  - ✓ Typically restrictive pattern (Decreased compliance, Low DLco)

- **Serum antibody (Inciting Antigen)**
  - ✓ Important part of diagnostic evaluation
  - ✓ Serum precipitin reactions
  - ✓ “Simple” marker for exposure
  - ✓ Caution: Not available for many antigens or possibility for false-negative

Richerson HB *et al*. *J Allergy Clin Immunol*. 1989; 84

Guidelines for Evaluation of HP

- **Additional potential aids**
  - ✓ General laboratory tests
  - ✓ In-vitro tests for cell-mediated immunity (Not available)
  - ✓ Skin testing (Not commercially available)
  - ✓ Inhalation challenge (No standardized Ag or techniques)
  - ✓ Bronchoalveolar lavage
    - ➢ Lymphocytosis, Decreased CD4/CD8 ratio
    - ➢ Insufficient information to evaluate efficacy
  - ✓ Lung biopsy
    - ➢ May be indicated in patients without sufficient clinical criteria
    - ➢ Open lung biopsy > TBLB
    - ➢ Distinctive features (plasma cells and lymphocytes accumulation in alveolar space, granuloma formation, bronchiolitis etc.)
  - ✓ Therapeutic trial (Antigen avoidance)

Richerson HB *et al*. *J Allergy Clin Immunol*. 1989; 84

Difficulties in Diagnosis of HP

- **Clinical history / Lung function**
  - ✓ Nonspecific symptoms and signs (esp. chronic HP)

- **Inciting antigen**
  - ✓ Numerous antigens
  - ✓ Absence of confirmatory method for antigen identification
  - ✓ Absence of validated questionnaires
  - ✓ Variability in performances of serum IgG test (not confirmatory)
  - → Low rate of antigen identification (40%~70%)

- **Radiologic evaluation**
  - ✓ Resemblance to other ILDs (IPF, NSIP etc.)
  - ✓ Low agreement rate [(κ=0.27) compared to IPF(κ=0.46)]

Fernandez Perez ER *et al*. *Chest*. 2013; 144(5)
Varone F et al. *Lung*. 2020; 198
Morell F *et al*. *Lancet Respir Med*. 2013; 1(9)
Nunes H *et al*. *Eur Respir J*. 2015; 45(3)
Walsh SL et al. *Lancet Respir Med*. 2016; 5(4)

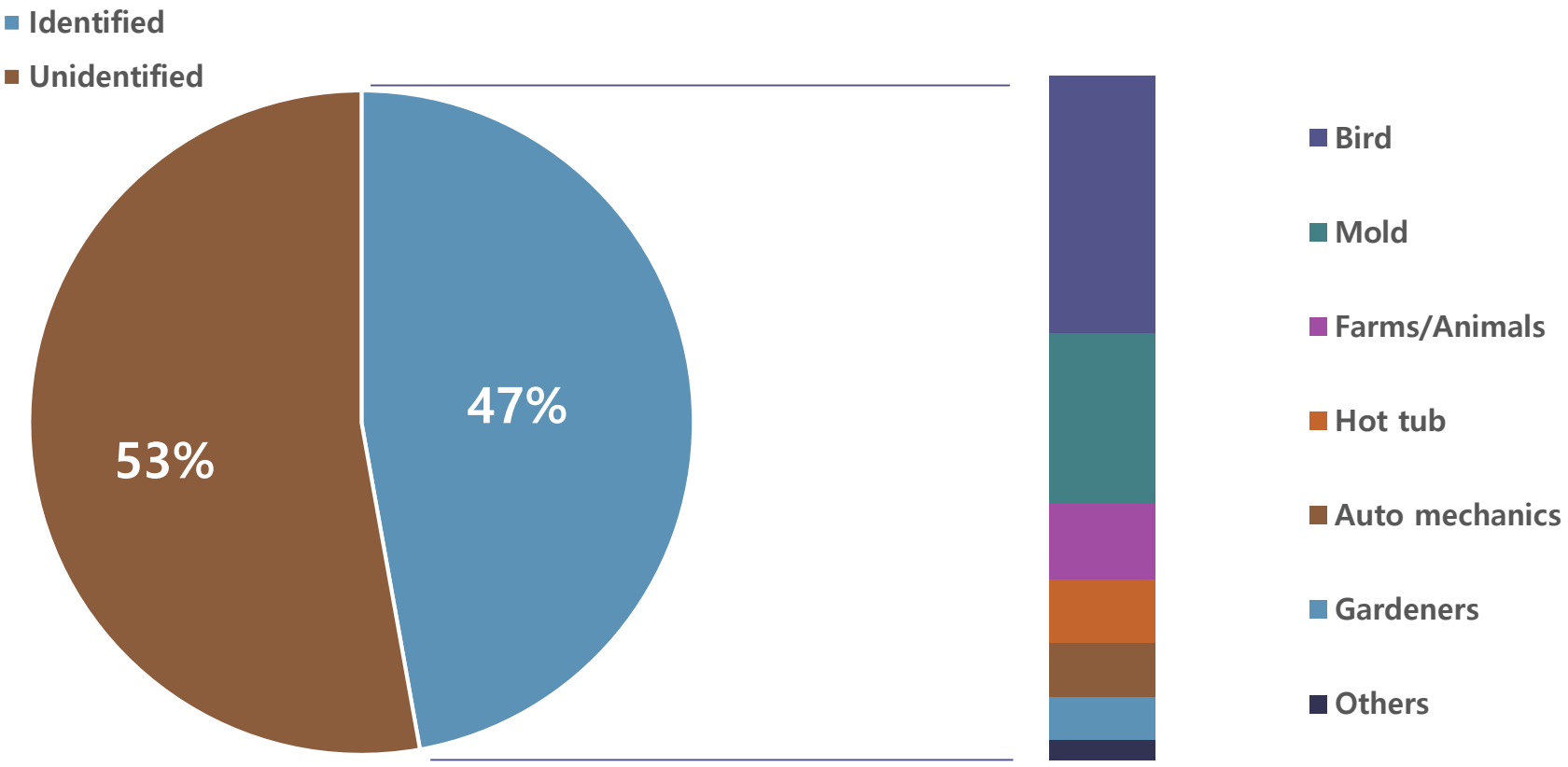
Known Sources of HP

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	*Saccharopolyspora rectivirgula*	Moldy hay, grain, silage
Ventilation pneumonitis; humidifier lung; air conditioner lung	*Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca*	Contaminated forced-air systems; water reservoirs
Bagassosis	*T. vulgaris*	Moldy sugarcane (i.e., bagasse)
Mushroom worker's lung	*T. sacchari*	Moldy mushroom compost
Enoki mushroom worker's lung (Japan)	*Penicillium citrinum*	Moldy mushroom compost
Suberosis	*Thermoactinomyces viridis, Aspergillus fumigatus, Penicillium frequentans, Penicillium glabrum*	Moldy cork
Detergent lung; washing powder lung	*Bacillus subtilis* enzymes	Detergents (during processing or use)
Malt worker's lung	*Aspergillus fumigatus, Aspergillus clavatus*	Moldy barley
Sequoiosis	*Graphium, Pullularia, and Trichoderma* spp., *Aureobasidium pullulans*	Moldy wood dust
Maple bark stripper's lung	*Cryptostroma corticale*	Moldy maple bark
Cheese washer's lung	*Penicillium casei, A. clavatus*	Moldy cheese
Woodworker's lung	*Alternaria* spp., wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Hardwood worker's lung	*Paecilomyces*	Kiln-dried wood
Paprika slicer's lung	*Mucor stolonifer*	Moldy paprika pods
Sauna taker's lung	*Aureobasidium* spp., other sources	Contaminated sauna water
Familial HP	*B. subtilis*	Contaminated wood dust in walls
Wood trimmer's lung	*Rhizopus* spp., *Mucor* spp.	Contaminated wood trimmings
Composter's lung	*T. vulgaris, Aspergillus*	Compost
Basement shower HP	*Epicoccum nigrum*	Mold on unventilated shower
Hot tub lung	*Mycobacterium avium complex*	Hot tub mists; mold on ceiling
Wine maker's lung	*Botrytis cinerea*	Mold on grapes
Woodsman's disease	*Penicillium* spp.	Oak and maple trees
Thatched roof lung	*Saccharomonospora viridis*	Dead grasses and leaves
Tobacco grower's lung	*Aspergillus* spp.	Tobacco plants
Potato riddler's lung	*Thermophilic actinomycetes, S. rectivirgula, T. vulgaris, Aspergillus* spp.	Moldy hay around potatoes
Summer-type pneumonitis	*Trichosporon cutaneum*	Contaminated old houses
Dry rot lung	*Merulius lacrymans*	Rotten wood
Stipatosis	*Aspergillus fumigatus; T. actinomycetes*	Esparto dust
Machine operator's lung	*Mycobacterium immunogenum; Pseudomonas fluorescens*	Aerosolized metalworking fluid
Residential provoked pneumonitis Amebae	*Aureobasidium pullulans*	Residential exposure
Humidifier lung	*Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani, Bacillus* sp., others	Contaminated water from home humidifier, ultrasonic misting fountains
Shower curtain disease	*Phoma violacea*	Moldy shower curtain
Animal proteins		
Pigeon breeder's or pigeon fancier's disease	Avian droppings, feathers, serum	Parakeets, budgerigars, pigeons, chickens, turkeys
Pituitary snuff taker's lung	Pituitary snuff	Bovine and porcine pituitary proteins
Fish meal worker's lung	Fish meal	Fish meal dust
Bat lung	Bat serum protein	Bat droppings
Furrier's lung	Animal fur dust	Animal pelts
Animal handler's lung; laboratory worker's lung	Rats, gerbils	Urine, serum, pelts, proteins
Insect proteins		
Miller's lung	*Sitophilus granarius* (i.e., wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

Selman M *et al*. *Am J Respir Crit Care Med*. 2012; 186(4)

Low Identification Rate of Antigen

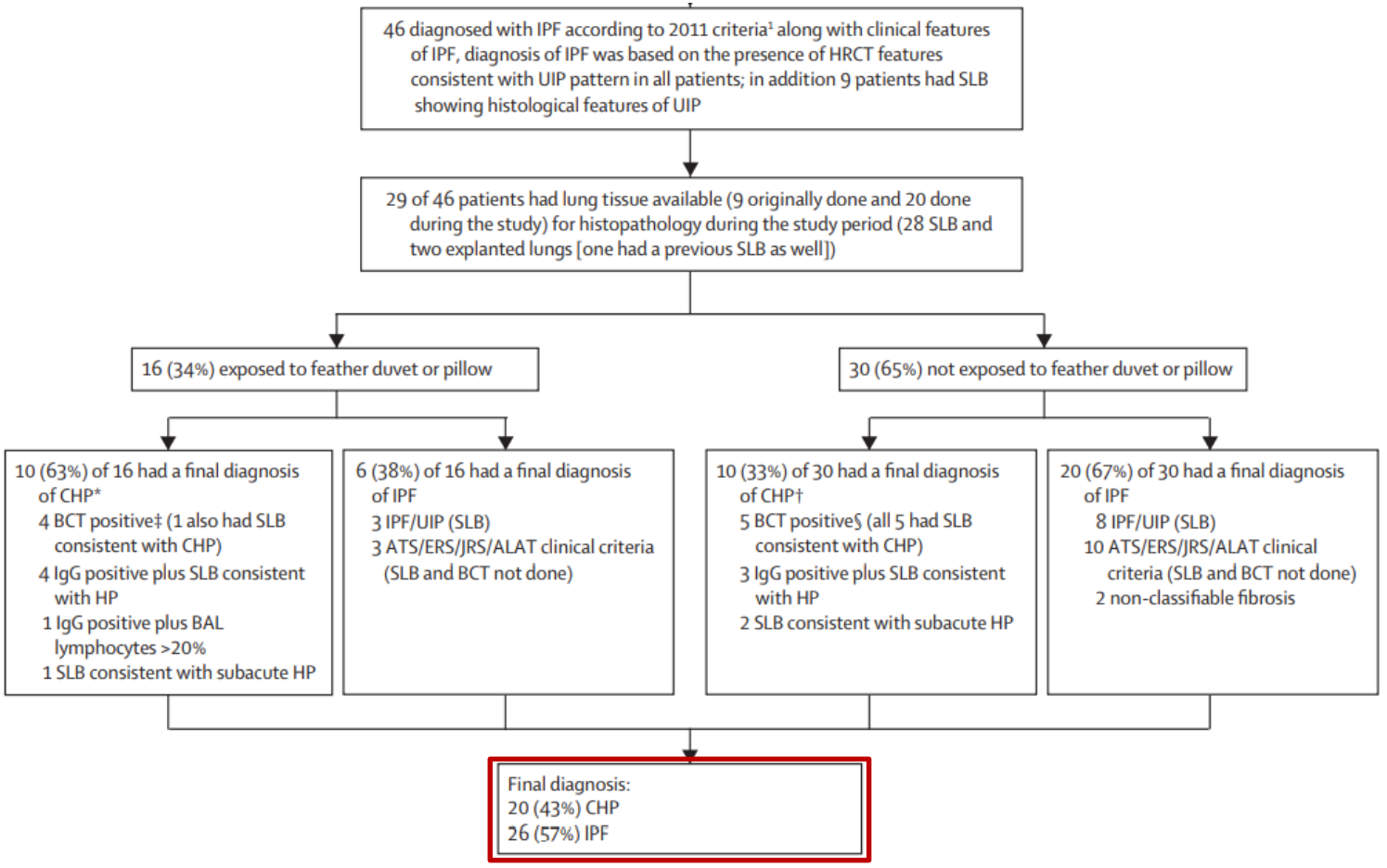
- 142 HP patients from ILD single center cohort (National Jewish MRC)
- Inciting Ag (Known cause of HP/Serum precipitant antibodies and Chronological plausibility)



Fernandez-Perez ER *et al*. *Chest*. 2013; 144(5)

Chronic HP (UIP pattern)

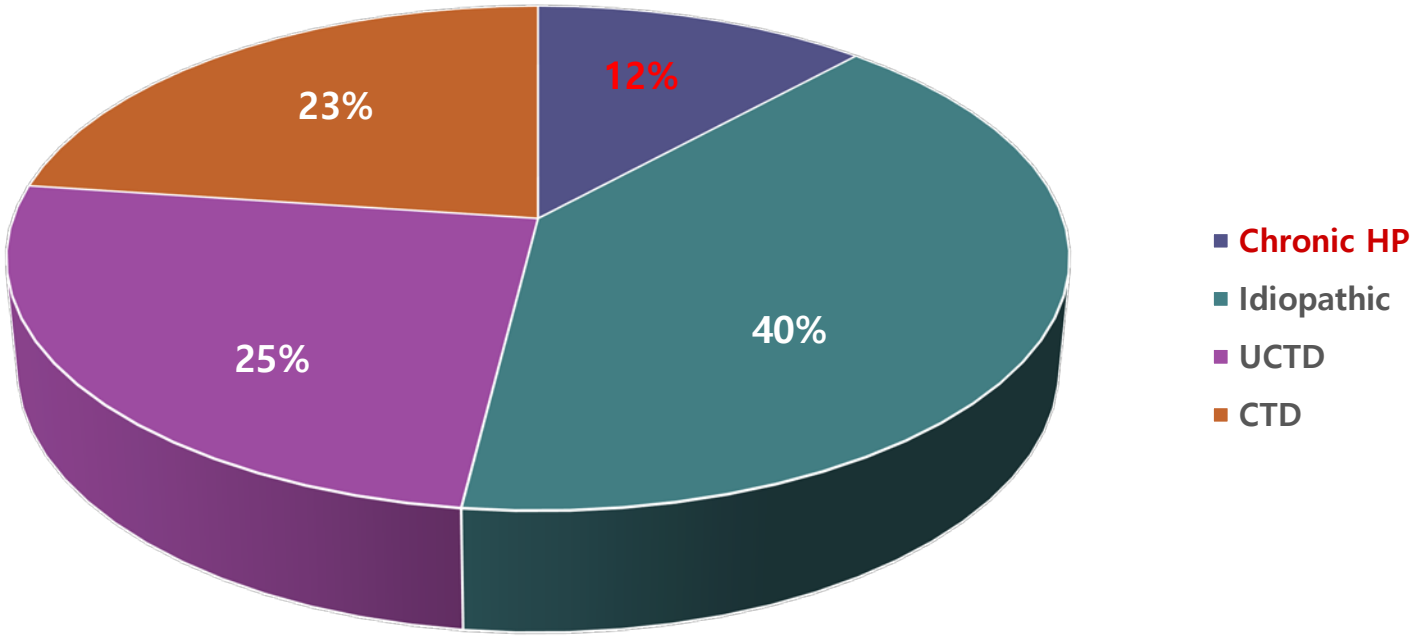
- 46 consecutive IPF patients, prospectively followed (Spain)
- Uniform questionnaire, specific IgG test, BAL, bronchial challenge tests



Morell F *et al*. *Lancet Respir Med*. 2013; 1(9)

Chronic HP (NSIP pattern)

- 127 pathologically-proven NSIP patients
- Multicenter retrospective study in France



Nunes H *et al*. *Eur Respir J*. 2015; 45(3)

Low Agreement rate in HRCT

- 70 ILD patients (IPF, NSIP, CTD-ILD, HP)
- Multicenter MDTM of ILD patients

	Clinicians (κ)		Radiologists (κ)		Pathologists (κ)		MDTM (κ)	
	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)	Total (n=70)	No biopsy (n=48)
Overall total	0·45	0·50	0·33	0·31	0·31	..	0·50	0·57
Idiopathic pulmonary fibrosis total	0·59	0·71	0·46	0·42	0·46	..	0·60	0·70
Non-specific interstitial pneumonia total	0·19	0·19	0·25	0·25	0·23	..	0·25	0·25
Connective tissue disease-related interstitial lung disease total	0·57	0·62	0·10	0·11	0·22	..	0·64	0·73
Hypersensitivity pneumonitis total	0·25	0·38	0·27	0·22	0·20	..	0·24	0·31

MDTM=multidisciplinary team meeting.

Walsh SL *et al*. *Lancet Respir Med*. 2016; 5(4)

Difficulties in Diagnosis HP

- **Bronchoalveolar lavage (BAL)**
  - ✓ Lymphocytosis
    - ➢ Usually >30-40% in acute HP / May be lower in chronic HP (>20%)
    - ➢ May be elevated in sarcoidosis, NSIP, or OP
  - ✓ CD4/CD8 ratio
    - ➢ CD4/CD8 ratio < 1 in acute HP
    - ➢ CD4/CD8 ratio: variable in chronic HP

  → Diagnostic value is not determined

- **Histopathology**
  - ✓ Typical histopathology (diffuse interstitial inflammation, chronic bronchiolitis, granulomas)
  - ✓ Modality: TBLB/TBLC vs. SLB
  - ✓ Complications (May not be possible for all patients)

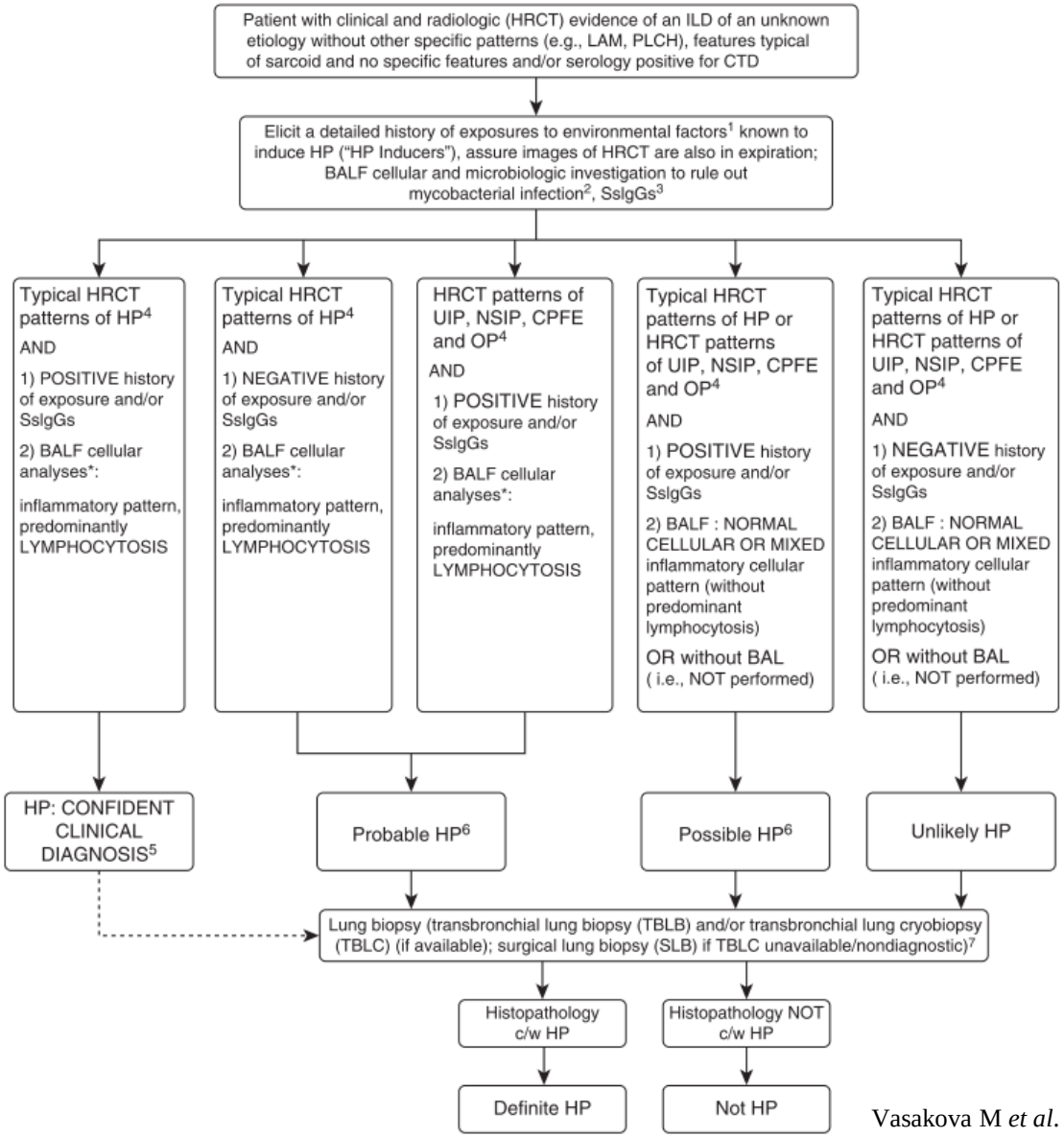
Soumagne T *et al*. *Exp Rev Respir Med*. 2018; 12(6)
Meyer KC *et al*. *Am J Respir Crit Care Med*. 2012; 185
Ohshimo S *et al*. *Am J Respir Crit Care Med*. 2009; 179
Myers JL *et al*. *Mold Pathol*. 2012; 25(1)
Grunes D. *J Clin Pathol*. 2013; 66

Demand for New Guidelines of HP

- **Need for new diagnostic guidelines**
  - Practical guideline which can be readily applicable to clinical practice
  - Uniform diagnostic guideline for data interpretation and future research

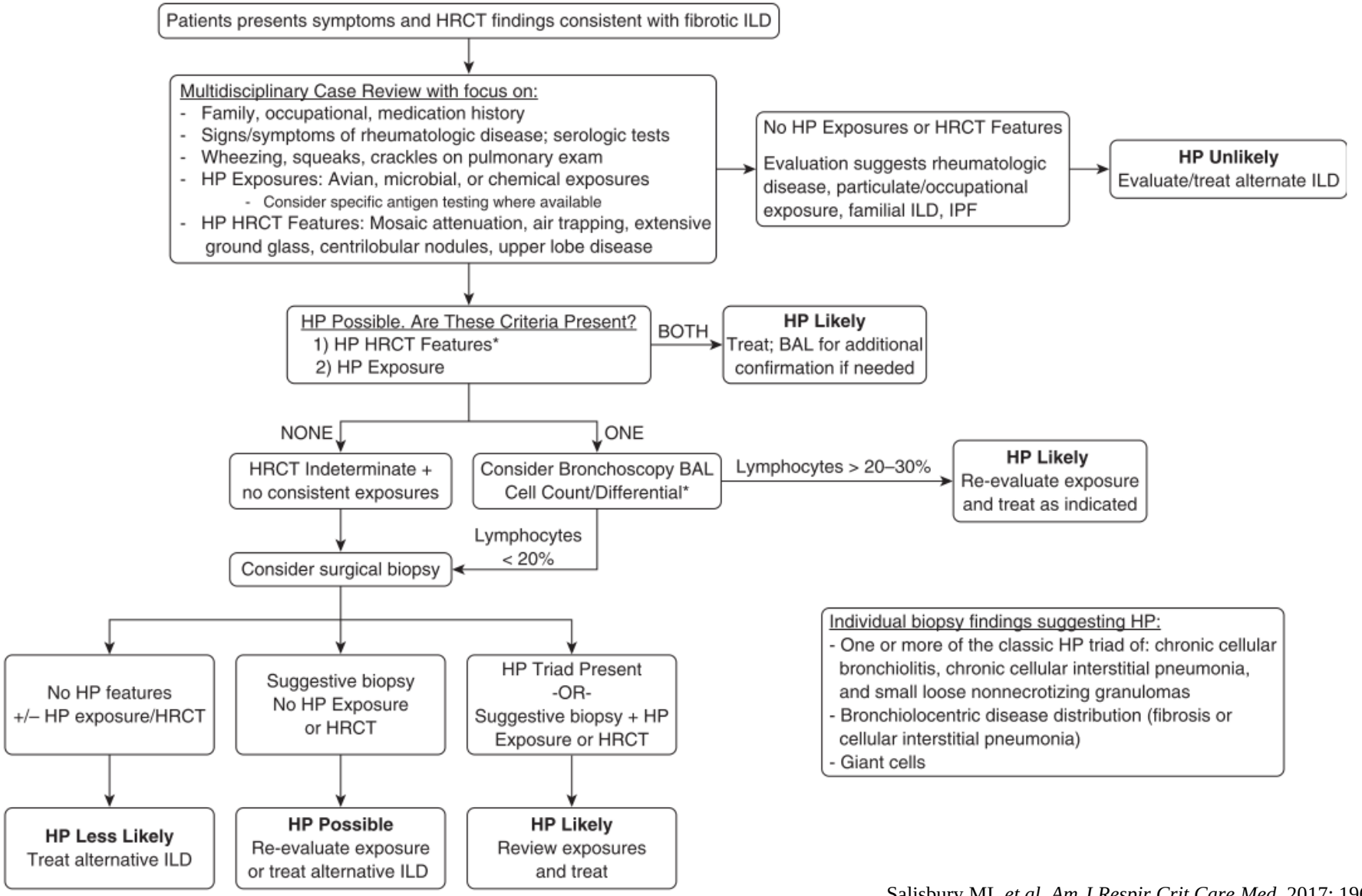
- **Suggested diagnostic algorithms**
  - Hypersensitivity pneumonitis: Perspectives in diagnosis and management (Vasakova M et al. *AJRCCM*. 2017)
  - Diagnosis and treatment of fibrotic hypersensitivity pneumonitis. Where we stand and where we need to go (Salisbury ML et al. *AJRCCM*. 2017)
  - Hypersensitivity pneumonitis. A perspective from members of the pulmonary pathology society (Miller R et al. *Arch Pathol Lab Med*. 2018)
  - Identification of diagnostic criteria for chronic hypersensitivity pneumonitis: An international modified Delphi survey (Morriset J et al. *AJRCCM*. 2018)

Diagnostic Algorithm for HP (Vasakova et al.)



Vasakova M *et al*. *Am J Respir Crit Care Med*. 2017; 196(6)

Diagnostic Algorithm for HP (Salisbury et al.)



Salisbury ML *et al*. *Am J Respir Crit Care Med*. 2017; 196(6)

Diagnostic Criteria of HP (Miller et al.)

Criteria	Specifics
1. Exposure to offending agent	A. Exposure history B. Aerobiologic or microbiologic investigations of the environment confirming presence of the agent C. Presence of specific IgG Ab against the identified agent
2. Clinical, radiographic, physiologic findings compatible with HP	A. Respiratory Sx/signs appearing/worsening after antigen exposure B. Reticular, nodular, or GGO on Chest CT/X-ray C. Altered spirometry and/or lung volumes, reduced DLco, altered gas exchange
3. BAL with lymphocytosis	A. Low CD4/CD8 ratio B. Specific immune response to the Ag by lymphocyte transformation testing
4. Positive inhalation challenge test	A. Re-exposure to environment B. Inhalation challenge to suspected Ag
5. Compatible pathology	A. Vague/poorly formed granulomas B. Mononuclear cell infiltrates

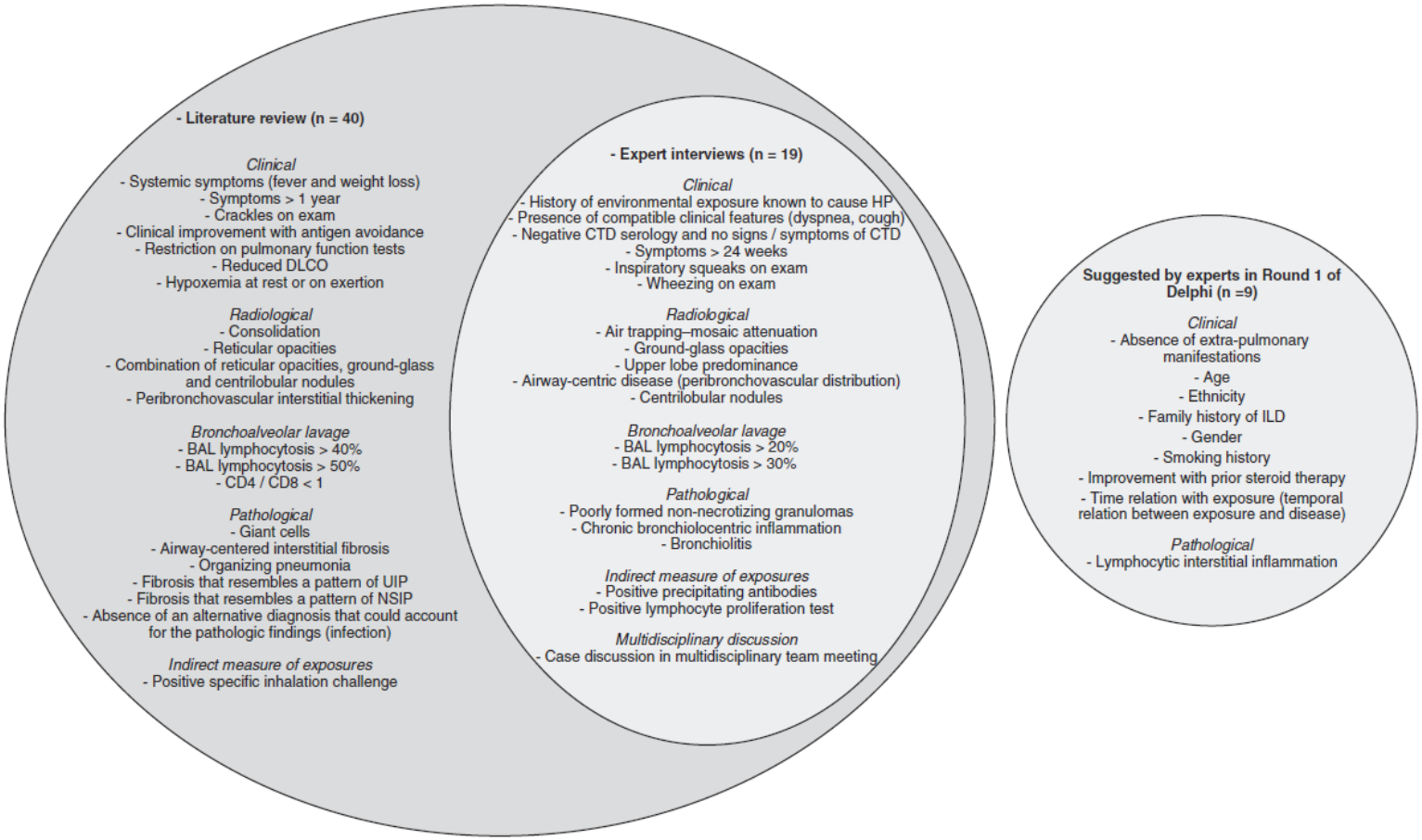
Criteria 1,2,3 / 1,2,4A / 1,2A,3,5 / 2,3,5 → Definite

Criteria 1,2A,3 → Probable

Criteria 1,3A → Subclinical

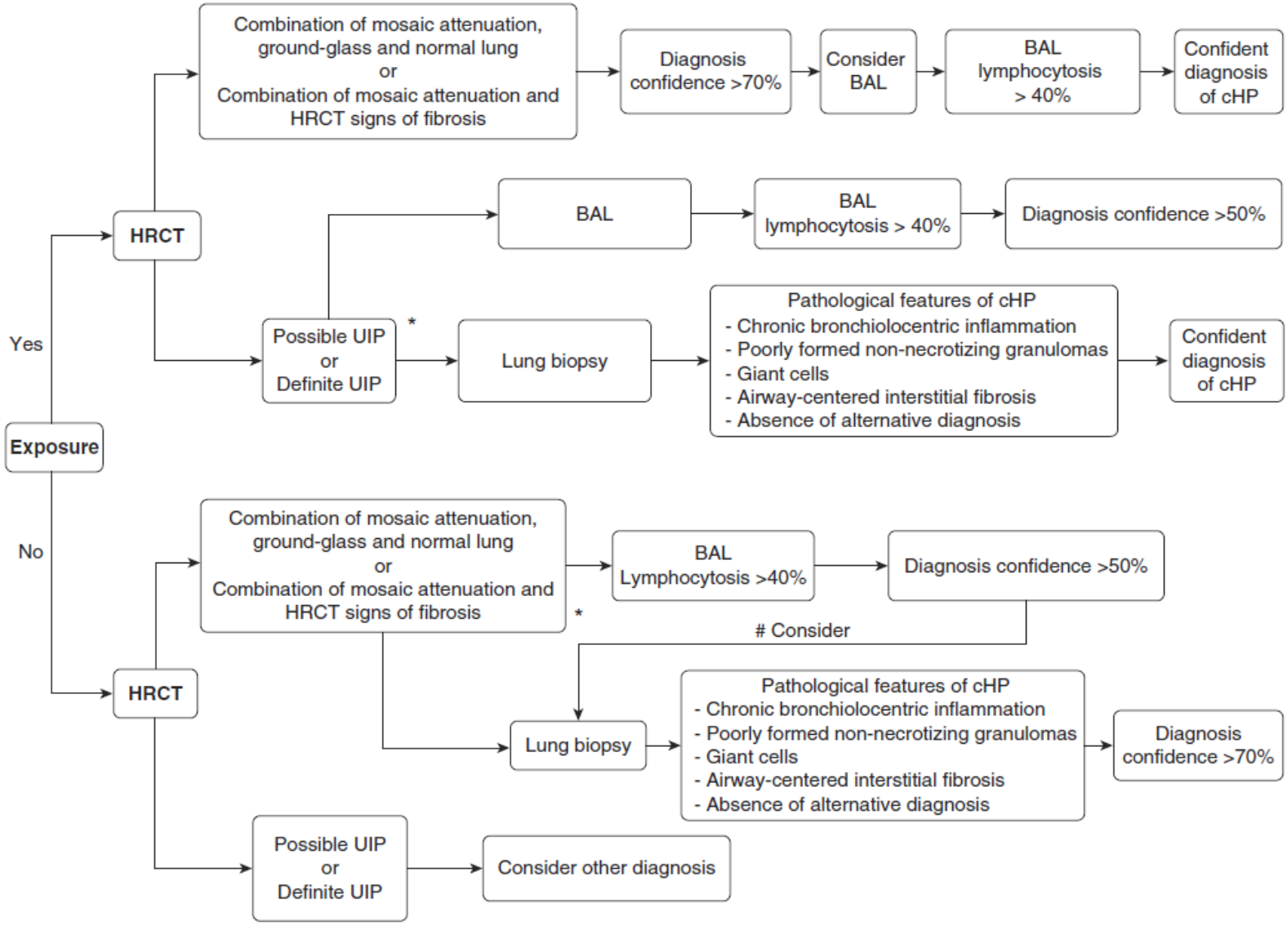
Miller R *et al*. *Arch Pathol Lab Med*. 2018; 142

Diagnostic Criteria of HP (Morriset et al.)
- Diagnostic Items -



Morriset J *et al*. *Am J Respir Crit Care Med*. 2018; 197(8)

Diagnostic Criteria of HP (Morriset et al.)
- Diagnostic Algorithm -



Morriset J *et al*. *Am J Respir Crit Care Med*. 2018; 197(8)

Diagnosis of HP in Adults
An Official ATS/JRS/ALAT Clinical Practice Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

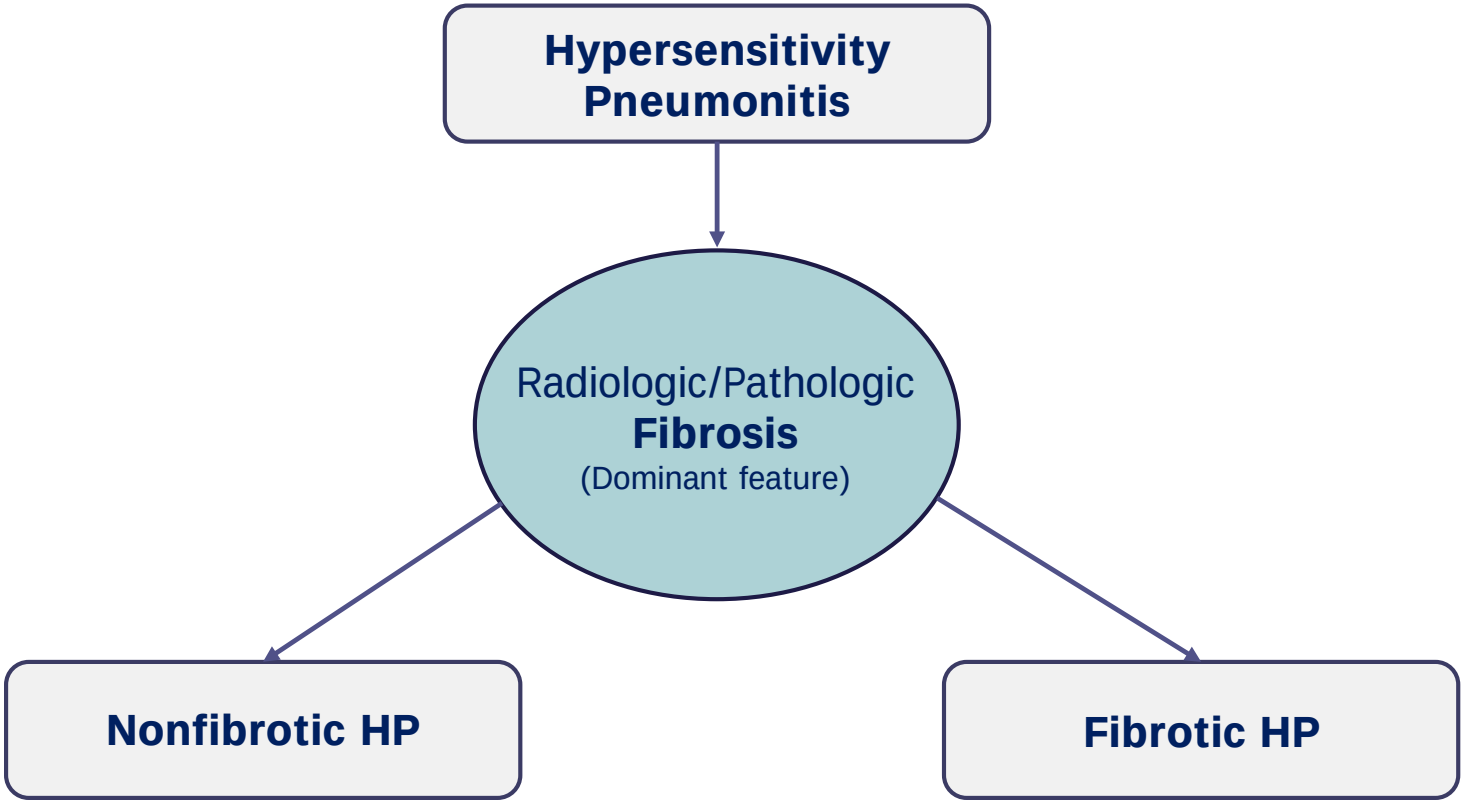
Diagnosis of Hypersensitivity Pneumonitis in Adults
An Official ATS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson, Jeffrey L. Myers, Michael Kreuter, Martina Vasakova, Elena Bargagli, Jonathan H. Chung, Bridget F. Collins, Elisabeth Bendstrup, Hassan A. Chami, Abigail T. Chua, Tamera J. Corte, Jean-Charles Dalphin†, Sonye K. Danoff, Javier Diaz-Mendoza, Abhijit Duggal, Ryoko Egashira, Thomas Ewing, Mridu Gulati, Yoshikazu Inoue, Alex R. Jenkins, Kerri A. Johannson, Takeshi Johkoh, Maximiliano Tamae-Kakazu, Masanori Kitaichi, Shandra L. Knight, Dirk Koschel, David J. Lederer, Yolanda Mageto, Lisa A. Maier, Carlos Matiz, Ferran Morell, Andrew G. Nicholson, Setu Patolia, Carlos A. Pereira, Elisabetta A. Renzoni, Margaret L. Salisbury, Moises Selman, Simon L. F. Walsh, Wim A. Wuyts, and Kevin C. Wilson; on behalf of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin† (June 2, 1956–October 17, 2019)

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX MAY 2020

New Classification of HP



Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

HRCT Pattern of HP

Nonfibrotic		
Typical HP	**Compatible with HP**	**Indeterminate**
- Parenchymal 1) GGO 2) Mosaic attenuation **- Small airway** 1) Ill-defined, centrilobular nodules 2) Air trapping **- Distribution** 1) Diffuse	**- Parenchymal** 1) Uniform and subtle GGOs 2) Airspace consolidation 3) Lung cysts **- Distribution** 1) Diffuse	N/A
Fibrotic		
Typical HP	**Compatible with HP**	**Indeterminate**
- Lung fibrosis 1) Irregular linear opacities/coarse reticulation with lung distortion 2) Traction BE/HC (No predominate) **- Distribution (Lung fibrosis)** 1) Random both axially or craniocaudally 2) Mid lung zone-predominant or relatively spared in the lower lung zone **- Small airway** 1) Ill-defined, centrilobular nodules, GGO 2) Mosaic attenuation, three-density pattern, and/or air trapping	**- Variant lung fibrosis** 1) UIP pattern 2) Extensive GGOs c subtle fibrosis **- Distribution (Variant)** 1) Axial: Peribronchovascular, subpleural 2) Craniocaudal: Upper lung zones **- Small airway** 1) Ill-defined, centrilobular nodules and/or GGOs 2) Three-density pattern, air trapping	1) UIP pattern 2) Probable UIP 3) Indeterminate UIP pattern 4) Fibrotic NSIP pattern 5) Organizing pneumonia-like pattern 6) Truly indeterminate HRCT pattern

Histopathologic Criteria (Nonfibrotic HP)

HP	Probable HP	Indeterminate for HP
Nonfibrotic HP (cellular HP) Typical histopathological features of nonfibrotic HP; at least one biopsy site showing all three of the following features: 1. Cellular interstitial pneumonia • Bronchiolocentric (airway-centered) • Cellular NSIP-like pattern • Lymphocyte-predominant 2. Cellular bronchiolitis • Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers • ±Organizing pneumonia pattern with Masson bodies • ±Foamy macrophages in terminal air spaces 3. Poorly formed nonnecrotizing granulomas† • Loose clusters of epithelioid cells and/or multinucleated giant cells ± intracytoplasmic inclusions • Situated in peribronchiolar interstitium, terminal air spaces, and/or organizing pneumonia (Masson bodies) *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	Both of the following features (*1* and *2* from first column) in at least one biopsy site: 1. Cellular interstitial pneumonia • Bronchiolocentric (airway-centered) • Cellular NSIP-like pattern • Lymphocyte-predominant 2. Cellular bronchiolitis • Lymphocyte-predominant (lymphs > plasma cells) with no more than focal peribronchiolar lymphoid aggregates with germinal centers • ±Organizing pneumonia pattern with Masson bodies • ±Foamy macrophages in terminal air spaces *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	At least one biopsy site showing one of the following: • *1* or *2* from the first column • Selected IIP patterns ○ Cellular NSIP pattern ○ Organizing pneumonia pattern ○ Peribronchiolar metaplasia *without* other features to suggest fibrotic HP *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates

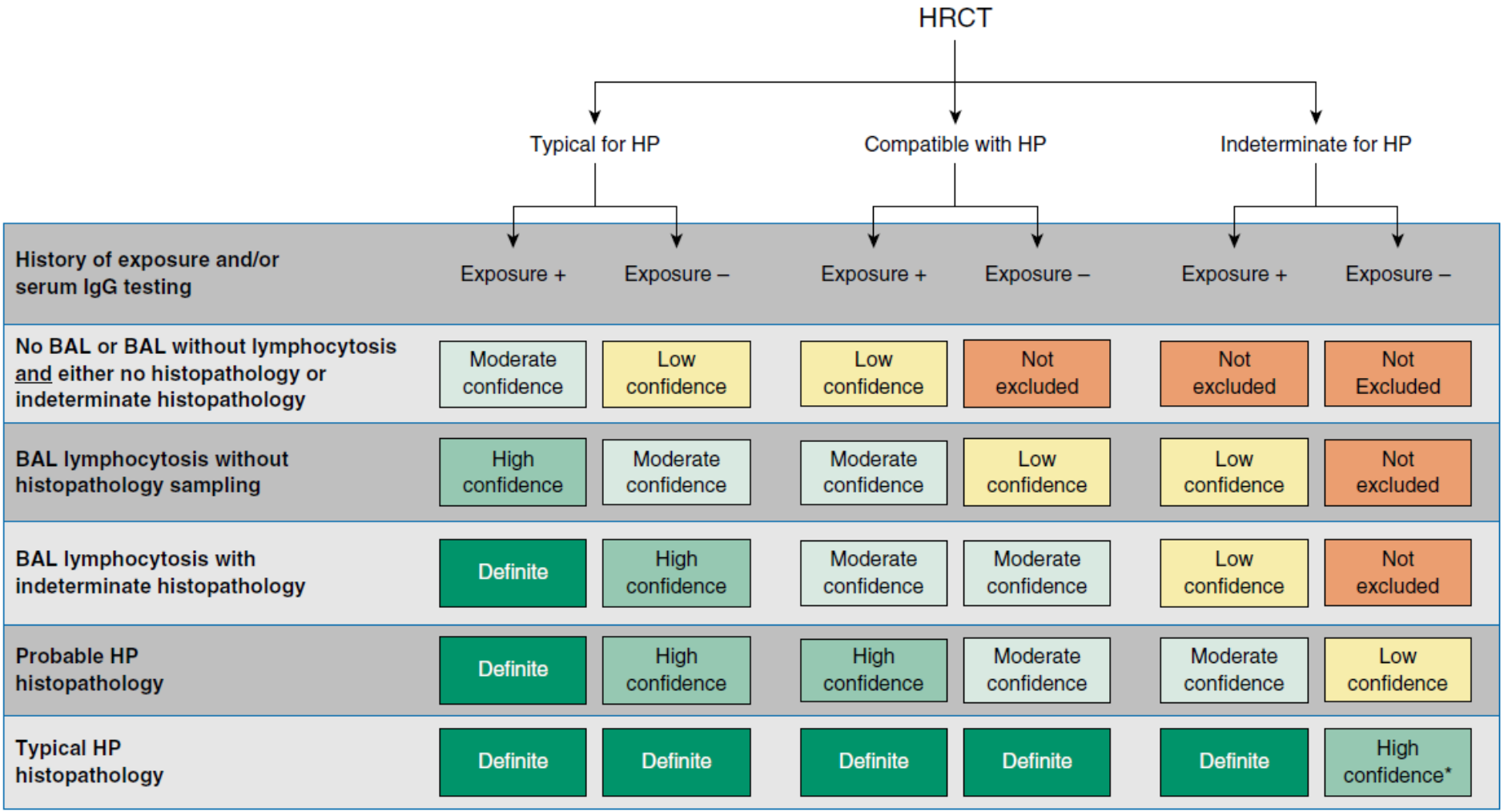
Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

Histopathologic Criteria (Fibrotic HP)

HP	Probable HP	Indeterminate for HP
Fibrotic HP[‡] Typical histopathological features of fibrotic HP; *1* or *2 and 3* in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± subpleural honeycombing • Fibrotic NSIP-like[§] pattern 2. Airway-centered fibrosis • ±Peribronchiolar metaplasia • ±Bridging fibrosis[‖] 3. Poorly formed nonnecrotizing granulomas[†] ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	Both of the following features (*1* or *2* from first column) in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± subpleural honeycombing • Fibrotic NSIP-like pattern 2. Airway-centered fibrosis • ±Peribronchiolar metaplasia • ±Bridging fibrosis[‖] ±Cellular interstitial pneumonia ±Organizing pneumonia pattern ±Cellular bronchiolitis *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	Either one of the following features in at least one biopsy site: 1. Chronic fibrosing interstitial pneumonia • Architectural distortion, fibroblast foci ± honeycombing • Fibrotic NSIP-like pattern ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern *and* Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates

Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

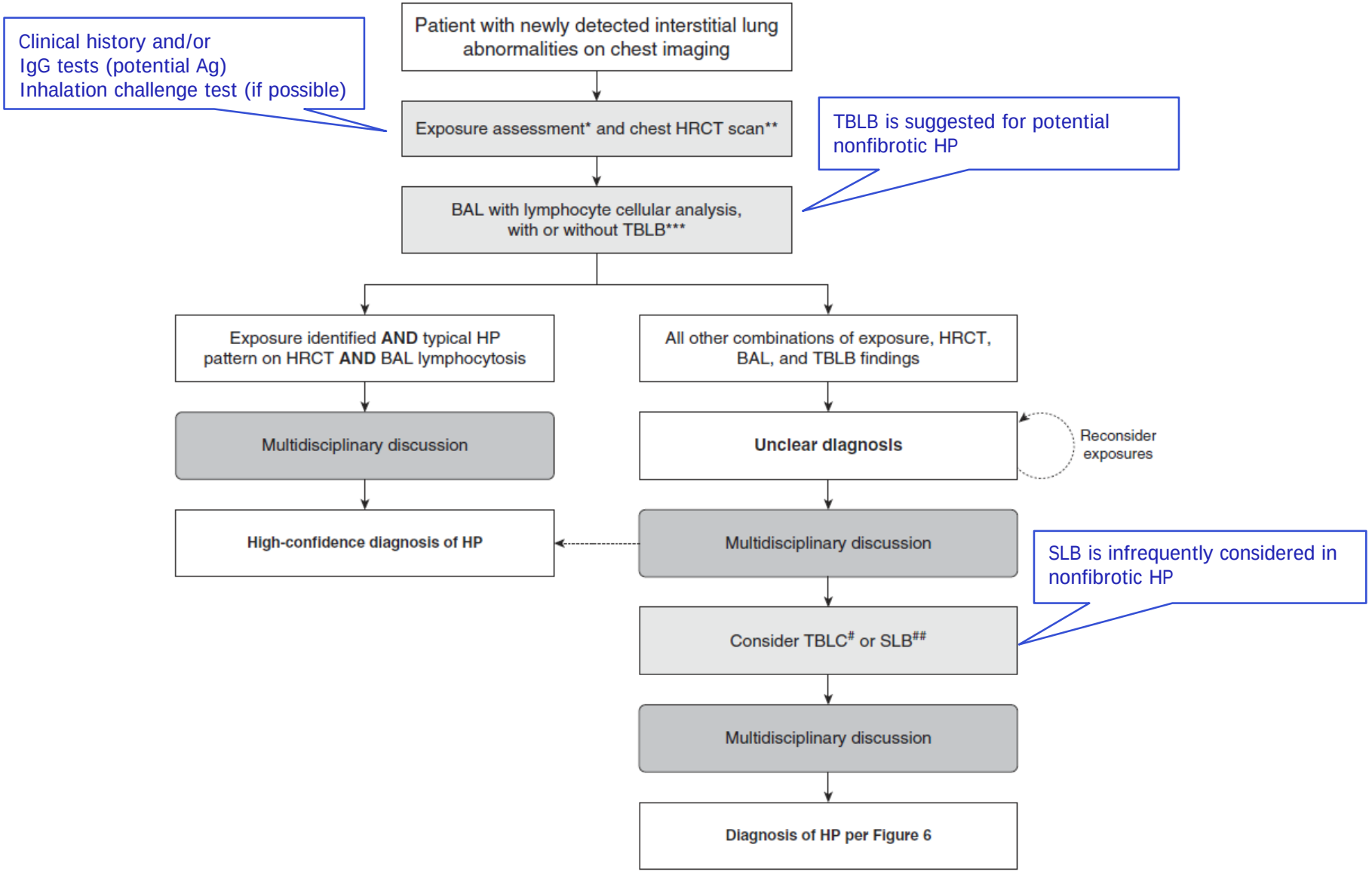
Diagnosis of HP (Combination of Evaluation)



All confidence levels are subject to multidisciplinary discussion. *Confidence may increase to "definite" if the pathologist's conclusion persists after reevaluation in the context of additional clinical information or an expert second opinion on histopathology.

Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

Diagnosis of HP (MDD)



Raghu G *et al*. *Am J Respir Crit Care Med*. 2020; 202(3)

Summary of Recommendations for Tests

	Non-fibrotic HP	Fibrotic HP
Questionnaire	No recommendations for or against (Thorough history for potential exposures and sources)	No recommendations for or against (Thorough history for potential exposures and sources)
Serum IgG testing	Suggestion (very low confidence)	Suggestion (very low confidence)
BAL Lymphocyte analysis	Recommendation (very low confidence)	Suggestion (very low confidence)
TBLB	Suggestion (very low confidence)	No recommendations for or against
TBLC	No recommendations for or against	Suggestion (very low confidence)
SLB	Suggestion, only when all other diagnostic testing has not yielded Dx (very low confidence)	Suggestion, only when all other diagnostic testing has not yielded Dx (very low confidence)

Raghu G *et al. Am J Respir Crit Care Med.* 2020; 202(3)

BAL Lymphocytes for HP

	Fibrotic HP vs. IPF		Non-fibrotic HP vs. IPF		Fibrotic HP vs. sarcoidosis		Non-fibrotic HP vs. sarcoidosis	
Lymphocyte	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
> 20 %	69%	61%	95%	61%	69%	26%	95%	26%
> 30 %	55%	80%	88%	80%	55%	43%	88%	43%
> 40 %	41%	93%	76%	93%	41%	61%	76%	61%
AUC	AUC 0.54 (95% CI 0.51 – 0.58)		AUC 0.75 (95% CI 0.71 – 0.78)		AUC 0.44 (95% CI 0.41 – 0.47)		AUC 0.71 (95% CI 0.67 – 0.74)	
N	1238		1202		2565		2529	

Patolia S *et al*. *Annals ATS*. 2020; Article in press

Treatment of HP

- **Avoidance of antigen**
  - ✓ Initial step of treatment (RCT is not available)
  - ✓ Improvement of lung function (DLco)
  - ✓ Identification of Ag is associated with survival
  - ✓ Unidentified Ag / Unavoidable Ag or unwillingness to avoid (occupational etc.)

- **Corticosteroid**
  - ✓ Improvement of lung function (DLco) and early resolution of symptoms
  - ✓ Improvement in radiological extent
  - ✓ No RCT is available
  - ✓ Optimal dose and duration is not known

Cormier Y *et al*. *Can Respir J*. 1994; 1(4)
Miyazaki Y et al. *Expert Rev Clin Immunol*. 2016; 12(9)
Varone F *et al*. *Lung*. 2020; 198(3)

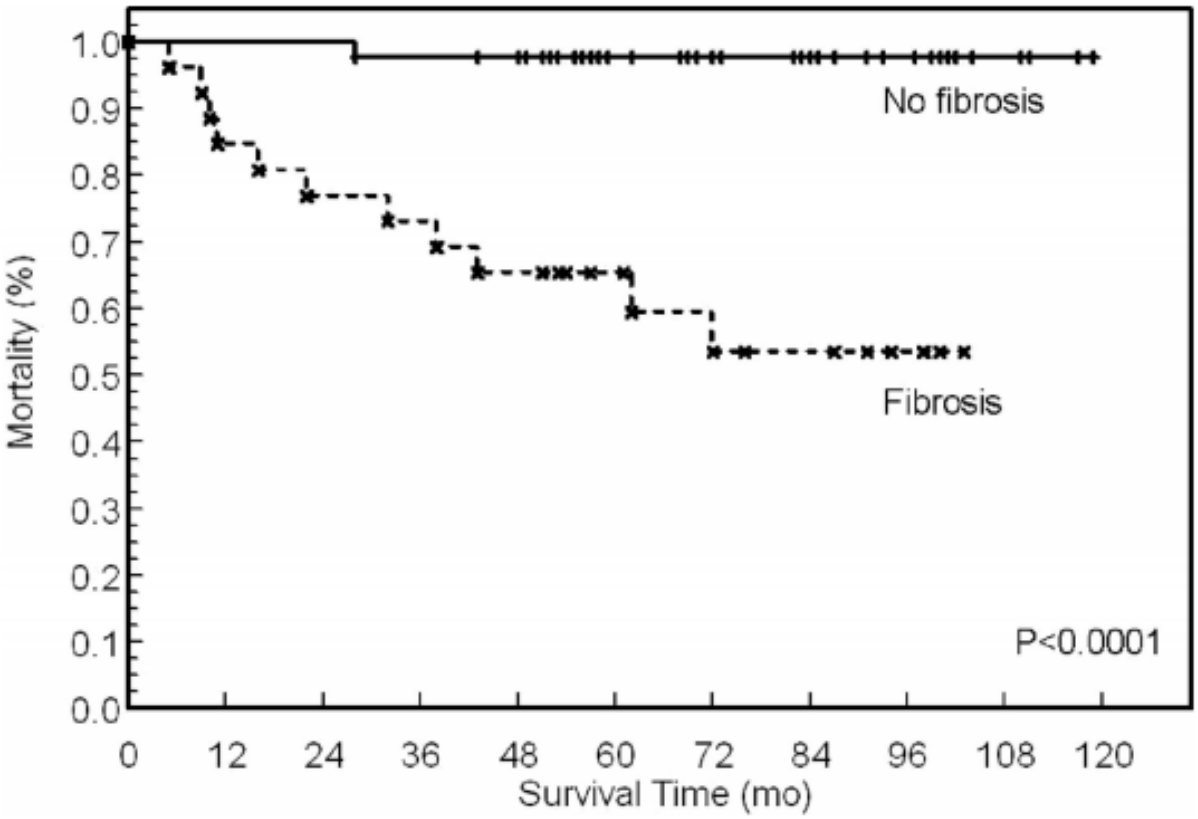
Prognosis of HP
- Fibrosis matters (HRCT) -

- 69 consecutive HP patients (26 Fibrotic, 43 Nonfibrotic)
- Single center retrospective study
- Fibrosis: Irregular linear opacities, Traction BE, or HC in HRCT

Characteristics	All Patients (n = 69)	Fibrotic Patients (n = 26)	Nonfibrotic Patients (n = 43)	p Value
Age, yr	54 ± 14	60 ± 12	50 ± 14	0.003†
Female gender	44 (64)	17 (65)	27 (63)	0.827
Symptom duration, mo‡	13 (4–43)	25 (11–76)	7 (3–38)	0.006†
Ever smoker	31 (45)	9 (35)	22 (51)	0.178
Antigen identified	52 (75)	20 (77)	32 (74)	0.814
Avian antigen	24 (35)	13 (50)	11 (26)	0.040†
Deceased	12 (17)	11 (42)	1 (2)	0.0001†
Physical findings				
Crackles	45 (65)	21 (81)	24 (56)	0.031†
Finger clubbing	3 (4)	2 (8)	1 (2)	0.298
HRCT findings				
Ground-glass opacities	46 (67)	17 (65)	29 (67)	0.861
Centrilobular nodules	22 (32)	7 (27)	15 (35)	0.488
Mosaic pattern	39 (57)	13 (50)	26 (60)	0.396
Irregular linear opacities	26 (38)	26 (100)		
Honeycombing	5 (7)	5 (19)		
Traction bronchiectasis	13 (19)	13 (50)		
Lung physiology‖				
Total lung capacity, %§	80 ± 19	68 ± 13	86 ± 18	0.0005†
Residual volume, %§	105 ± 52	84 ± 26	115 ± 58	0.038†
FVC, %§	65 ± 18	58 ± 18	70 ± 17	0.008†
FEV_1/FVC ratio	81 ± 9	83 ± 8	79 ± 10	0.140
Diffusing lung capacity, %§	60 ± 17	50 ± 17	66 ± 14	0.0001†
Resting oxygen saturation, %	94 ± 3	93 ± 3	94 ± 3	0.094
Therapy				
Systemic glucocorticoids	52 (75)	21 (81)	31 (72)	0.566
Supplemental oxygen	15 (22)	7 (27)	8 (19)	0.219

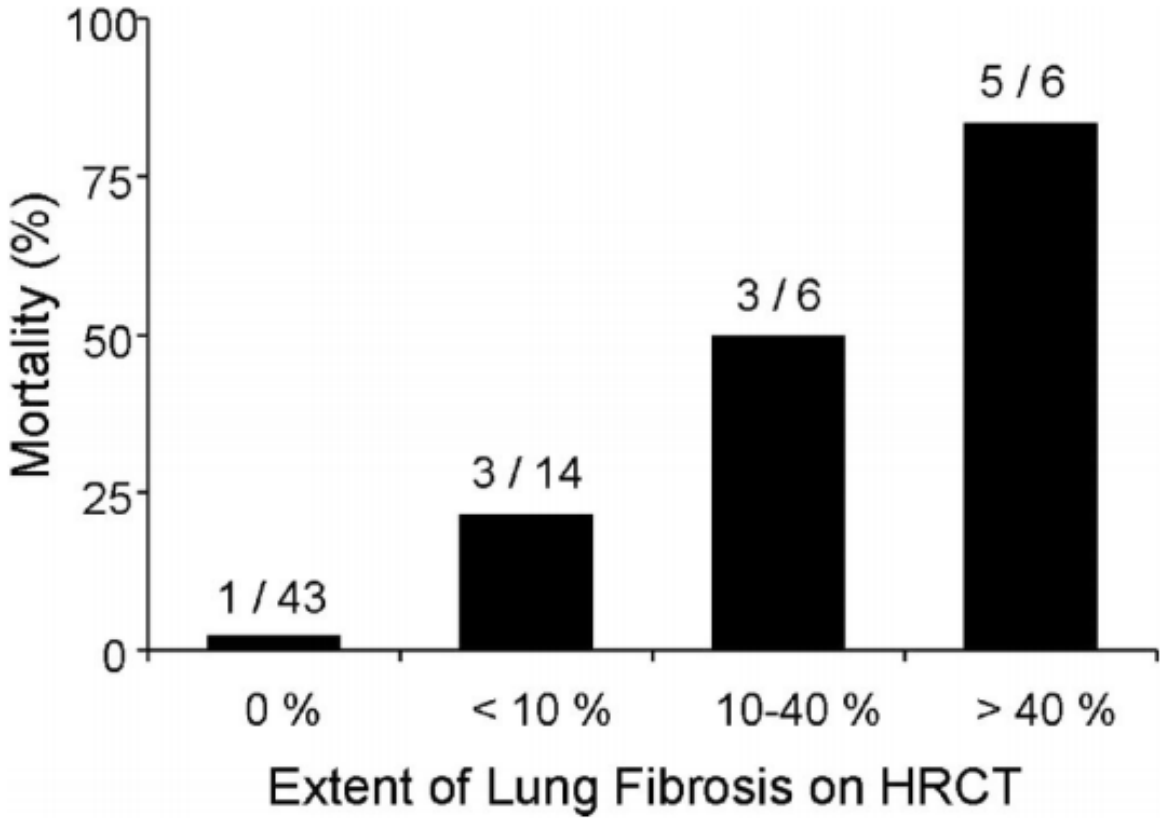
Hanak V *et al*. *Chest*. 2008; 134

Prognosis of HP
- Fibrosis matters (HRCT) -



Hanak V *et al*. *Chest*. 2008; 134

Prognosis of HP
- Fibrosis matters (HRCT) -



Hanak V *et al*. *Chest*. 2008; 134

Prognosis of HP
- Fibrosis matters (Pathology) -

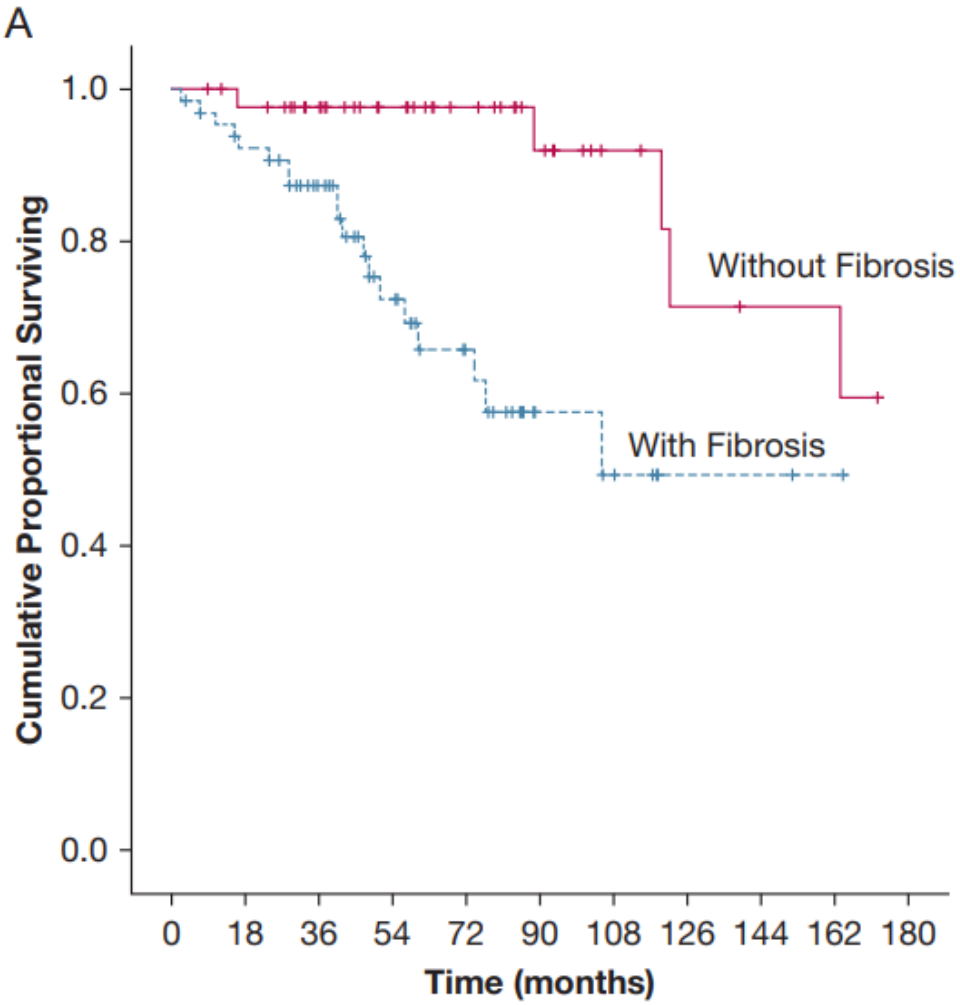
- 119 pathologically-proven Chronic HP patients
- Single center longitudinal cohort (UCSF)

Variable	c-NSIP (n = 49)	f-NSIP (n = 22)	UIP (n = 7)	PI-PFG (n = 22)	BF (n = 10)	*P* Value
Age, y	57 ± 12	62 ± 10	63 ± 10	62 ± 11	60 ± 9	.487
Male sex	17 (34.7)	9 (40.9)	3 (42.9)	6 (27.3)	3 (30.0)	.883
Ex-smoker	22 (44.9)	9 (40.9)	3 (42.9)	12 (54.5)	4 (40.0)	.918
Dyspnea score[a]	10 ± 5	12 ± 6	7 ± 5	10 ± 5	10 ± 6	.511
Pulmonary function						
FEV_1,% predicted[b]	69 ± 18	73 ± 19	80 ± 22	83 ± 21	73 ± 15	.141
FVC,% predicted[c]	66 ± 17	66 ± 15	72 ± 19	78 ± 21	67 ± 21	.154
FEV_1/FVC ratio[d]	82 ± 9	84 ± 6	86 ± 6	80 ± 5	82 ± 8	.313
D_{LCO},% predicted[e]	48 ± 14	50 ± 15	55 ± 16	51 ± 19	48 ± 18	.893

Granulomas	Organizing Pneumonia	Fibrosis	Fibroblast Foci	Microscopic Honeycombing
97 (81.5%)	77 (64.7%)	73 (61.3%)	36 (30.3%)	24 (20.2%)

Wang P *et al*. *Chest*. 2017; 152(3)

Prognosis of HP
- Fibrosis matters (Pathology) -



Wang P *et al*. *Chest*. 2017; 152(3)

Prognosis of HP (Fibrosis vs. No fibrosis)

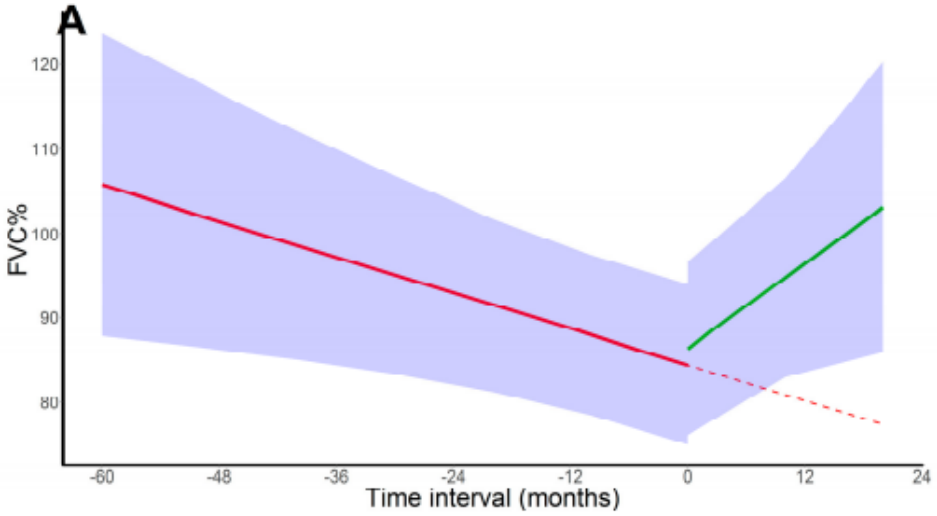
- 202 patients with HP (93 nonfibrotic + 109 fibrotic)
- Retrospective observational study (Univ. of Leuven)
- Fibrosis determined by HRCT (Reticulation, traction BE, HC)

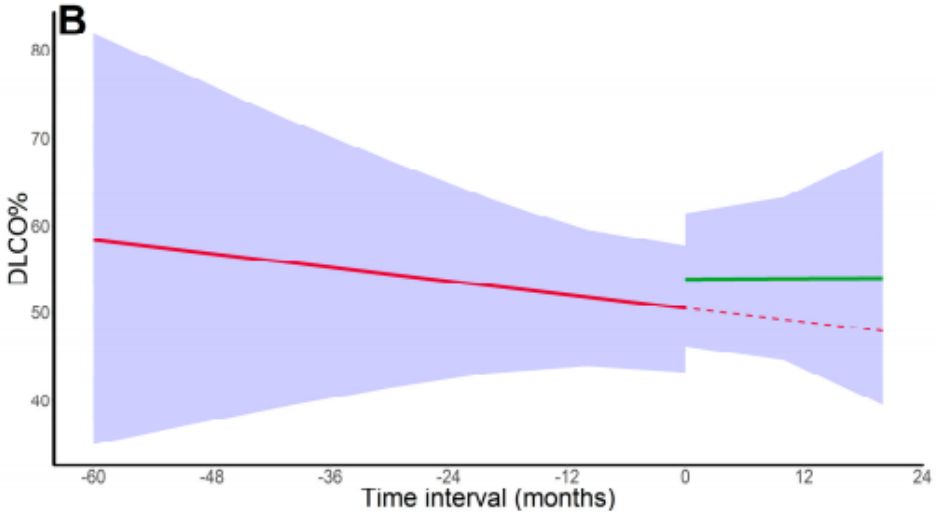
	nfHP (N = 93)	fHP (N = 109)	p Value
Age (year)	55.12 ± 13.19	65.29 ± 11.72	<0.001
Gender (male)	53 (57%)	69 (63.3%)	0.441
Ever smoker	36 (39.6%)	49 (45.8%)	0.46
Active smoker	1 (1.1%)	3 (3%)	0.624
Exposure unknown	10 (10.8%)	31 (28.4%)	0.003
Positive SsIgGs	53 (79.1%)	55 (63.2%)	0.06
BAL lymphocytosis	40.51 ± 25.57	19.64 ± 18.76	<0.001
FVC% baseline	81.61 ± 22.91	72.26 ± 21.89	0.005
DLCO% baseline	57.2 ± 20.7	45.3 ± 17.5	<0.001
Traction bronchiectasis	0 (0%)	87 (79.8%)	<0.001
Honeycombing	0 (0%)	40 (36.7%)	<0.001
Discussed at MDD	34 (39.1%)	61 (58.1%)	0.013
Corticosteroid treatment	67 (78.8%)	82 (80.4%)	0.934
2nd line immunosuppressive treatment *	8 (10%)	24 (24.5%)	0.021

De Sadeleer LJ *et al*. *J Clin Med*. 2019;8

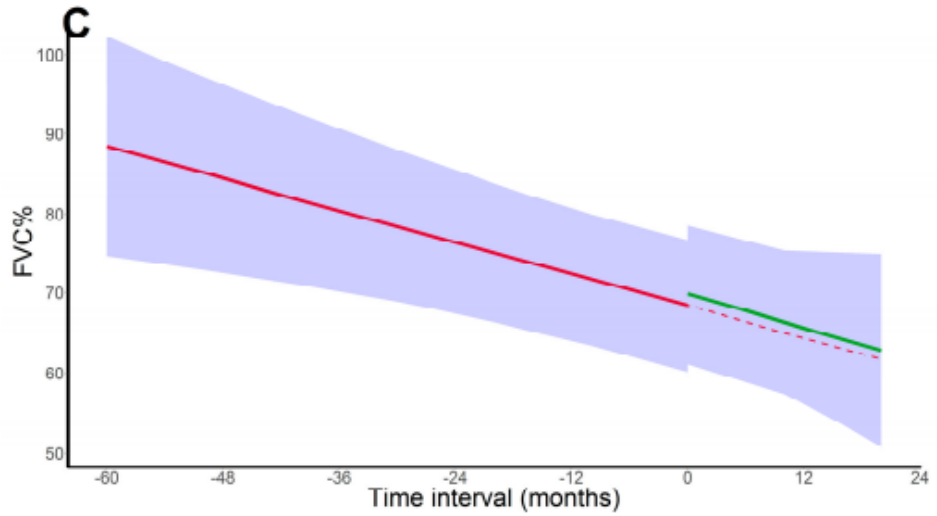
Prognosis of HP (Fibrosis vs. No fibrosis)

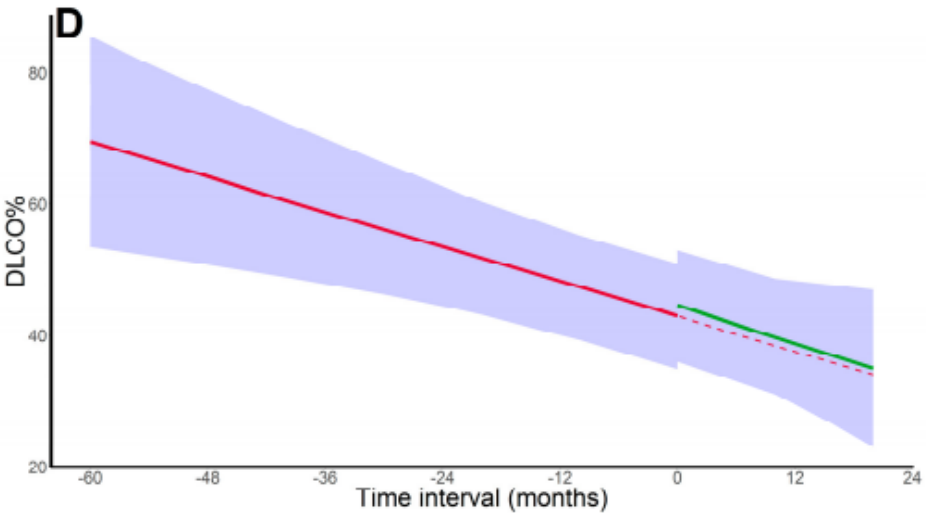
Nonfibrotic HP





Fibrotic HP





De Sadeleer LJ *et al*. *J Clin Med*. 2019;8

Potential Treatment for Fibrotic HP

- **Immunosuppressive agents**
  - ✓ Mycophenolate mofetil
  - ✓ Azathioprine
  - ✓ Rituximab

- **Antifibrotic agents**
  - ✓ Nintedanib
  - ✓ Pifenidone

Morriset J *et al*. *Chest*. 2017; 151(3)
Adegunsoye A *et al*. *ERJ Open*. 2017; 3
Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)
Guenther A *et al*. *ERS Abstract*. 2019

Mycophenolate mofetil and Azathioprine

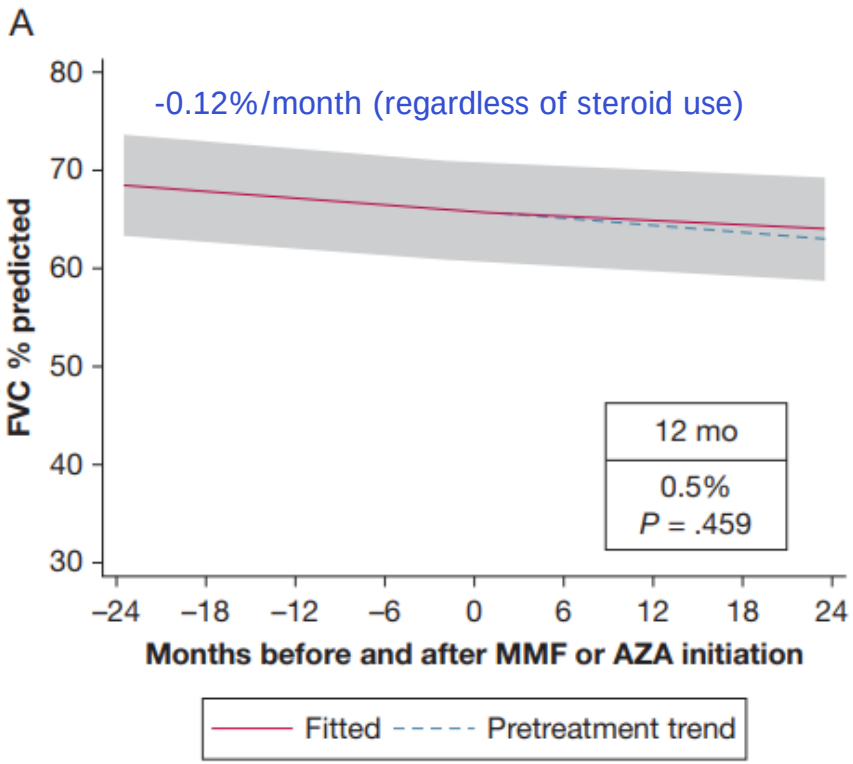
- 70 CHP patients (51 MMF and 19 AZA)
- Retrospective study (4 Cohorts of UCSF, UBC, CHUM, UCalgary)
- Outcome: Changes in lung function (adjusted for age, gender, smoking, corticosteroid use), Tolerability

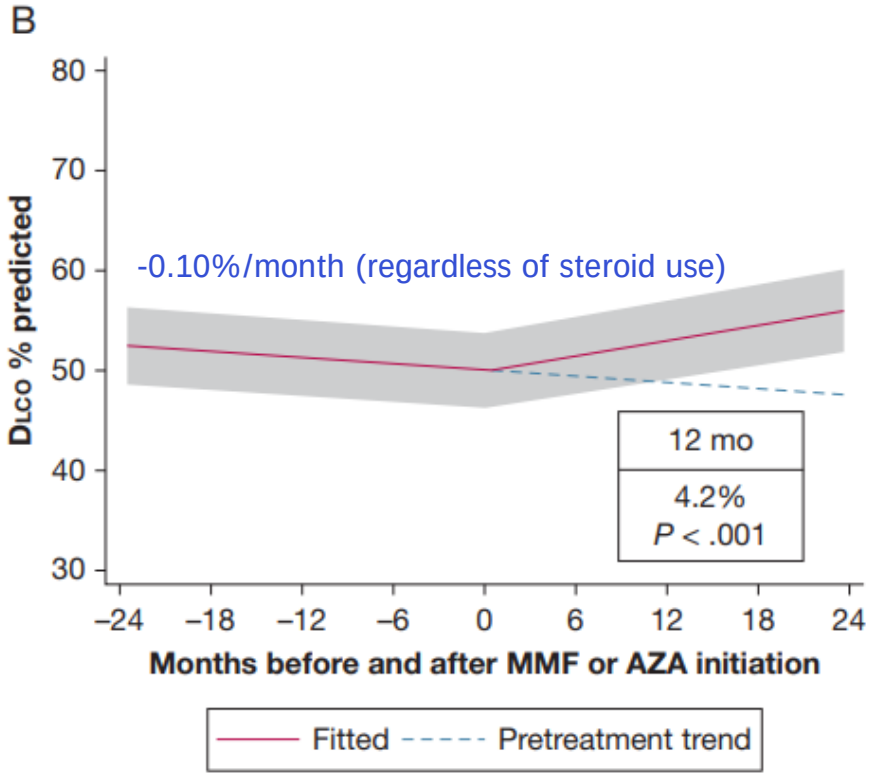
Characteristic	(N = 70)
Mean age (SD), y	60.5 (11.3)
Male, No. (%)	39 (55.7)
Ever smoker, No. (%)	24 (34.3)
Surgical lung biopsy, No. (%)	55 (78.6)
Exposure, No. (%)	
Mold	20 (28.6)
Bird	11 (15.7)
Down feather products	6 (8.6)
Other[a]	4 (5.7)
Unknown	29 (41.4)
Pulmonary function at MMF or AZA initiation	
Mean FVC % predicted (SD)	65.2 (18.0)
Mean D_{LCO} % predicted (SD)	49.8 (15.2)

Characteristic	(N = 70)
MMF, No. (%)	51 (72.9)
Daily dose, range, mg	1,000-3,000
AZA, No. (%)	19 (27.1)
Daily dose, range, mg	100-150
Mean dose (SD), mg	114.9 (23.1)
Prednisone, No. (%)	59 (84.3)
Dose, range, mg	10-30
Patients treated with prednisone prior to MMF or AZA initiation, No. (%)	14 (23.0)
Prednisone dose at MMF or AZA initiation, mg	12.33 (13.99)
Prednisone dose at 6 mo after MMF or AZA initiation, mg	3.75 (5.25)

Morriset J *et al*. *Chest*. 2017; 151(3)

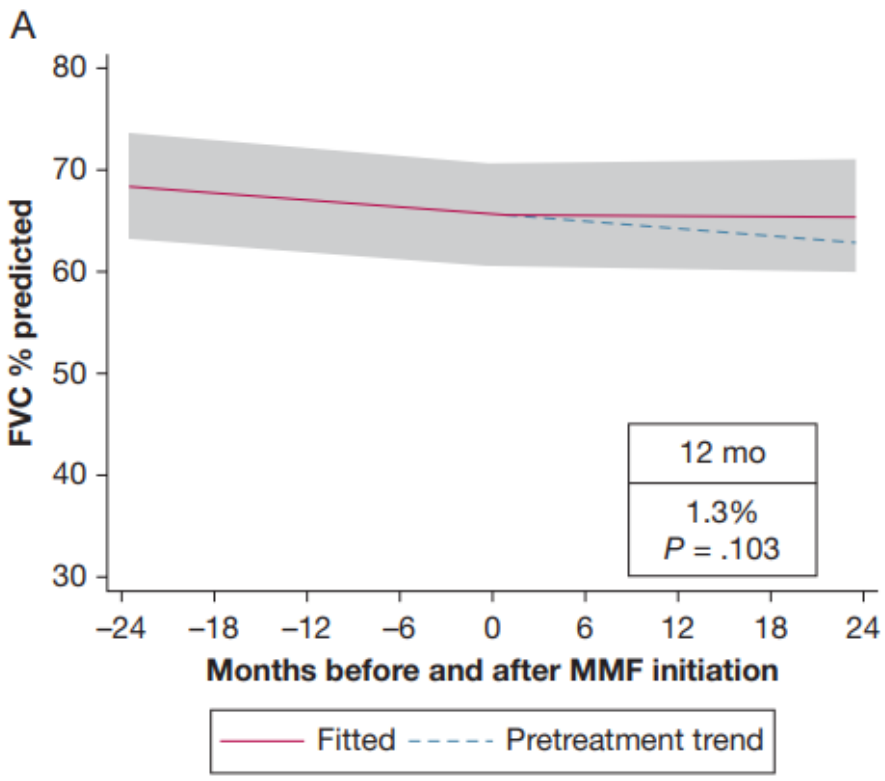
Mycophenolate mofetil and Azathioprine

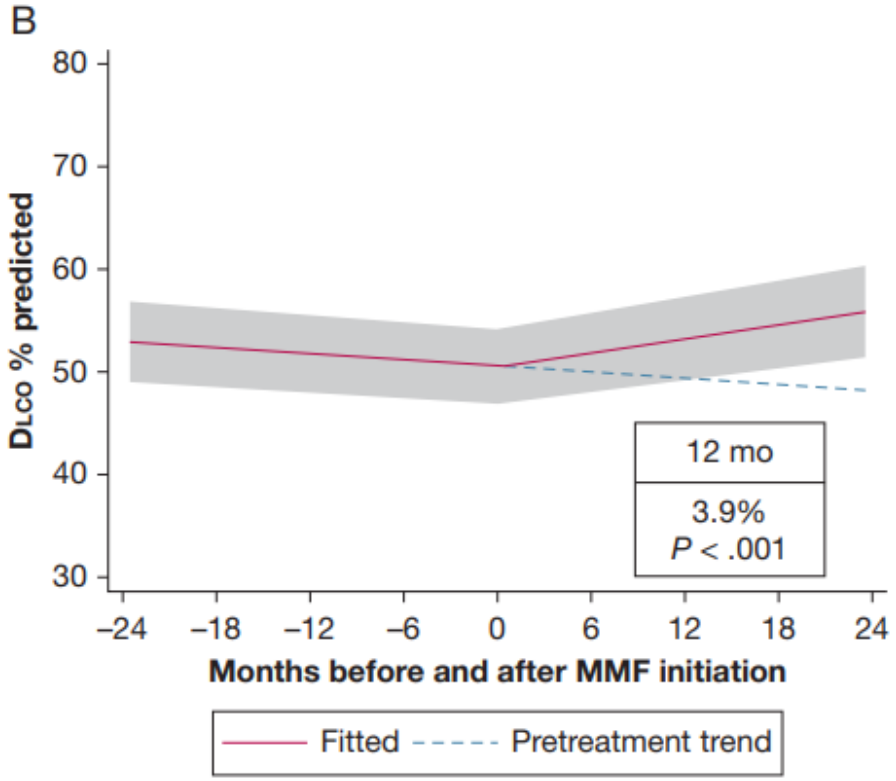




Morriset J *et al*. *Chest*. 2017; 151(3)

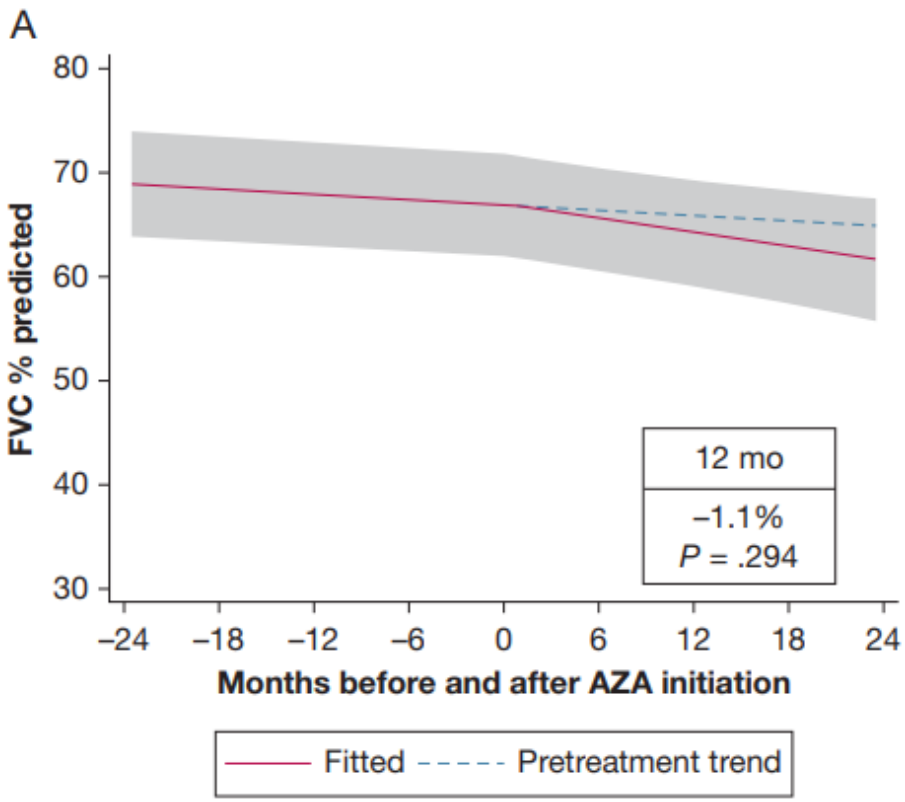
Mycophenolate mofetil in CHP

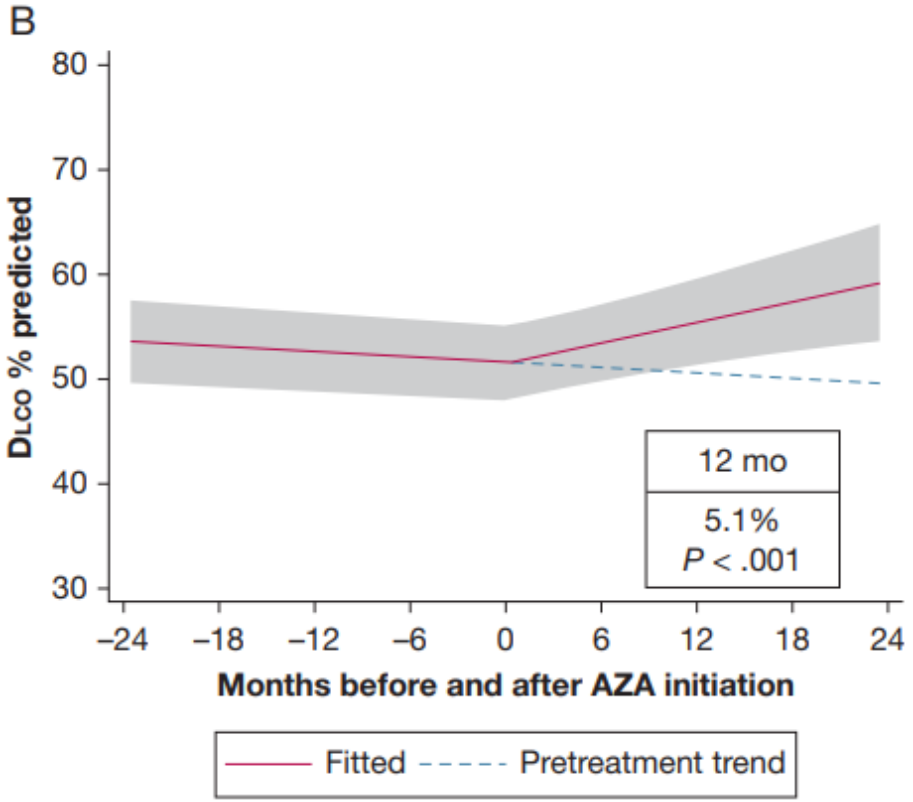




Morriset J *et al*. *Chest*. 2017; 151(3)

Azathioprine in CHP





Morriset J *et al*. *Chest*. 2017; 151(3)

Tolerability of MMF and AZA

	All (N=70)	MMF (n=51)	AZA (n=19)
Side effect	10 (14.3)	7 (13.7)	3 (15.8)
Nausea	3 (4.3)	3 (5.8)	0
Diarrhea	2 (2.9)	1 (1.9)	1 (5.3)
Transaminitis	2 (2.9)	1 (1.9)	1 (5.3)
GI upset	1 (1.4)	1 (1.9)	0
Bloating	1 (1.4)	1 (1.9)	0
Fatigue	1 (1.4)	0	1 (5.3)
Management of Side Effect			
Dose reduction	3 (4.3)	3 (5.8)	0
Discontinuation	2 (2.9)	2 (5.8)	2 (10.5)

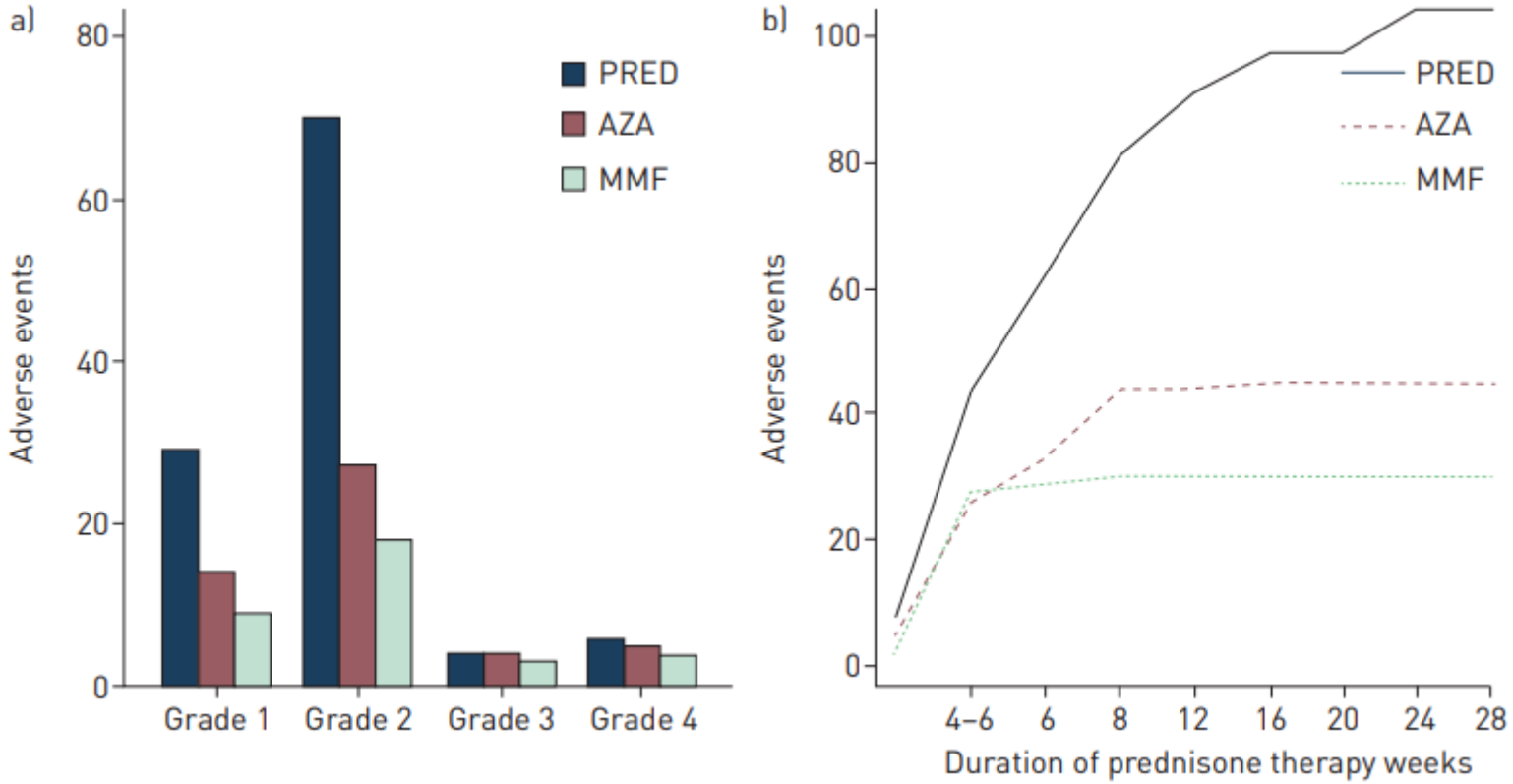
Morriset J *et al*. *Chest*. 2017; 151(3)

Mycophenolate mofetil and Azathioprine

- 131 CHP patients [93 (71%) receiving immunosuppressant; 41 PD alone, 24 PD + AZA, 28 PD + MMF]
- Retrospective study (University of Chicago ILD Registry)
- Outcome: Treatment-emergent adverse event, Changes in lung function
- External validation (National Jewish Hospital, U Kanasas MC, Columbia UH, UC Davis)

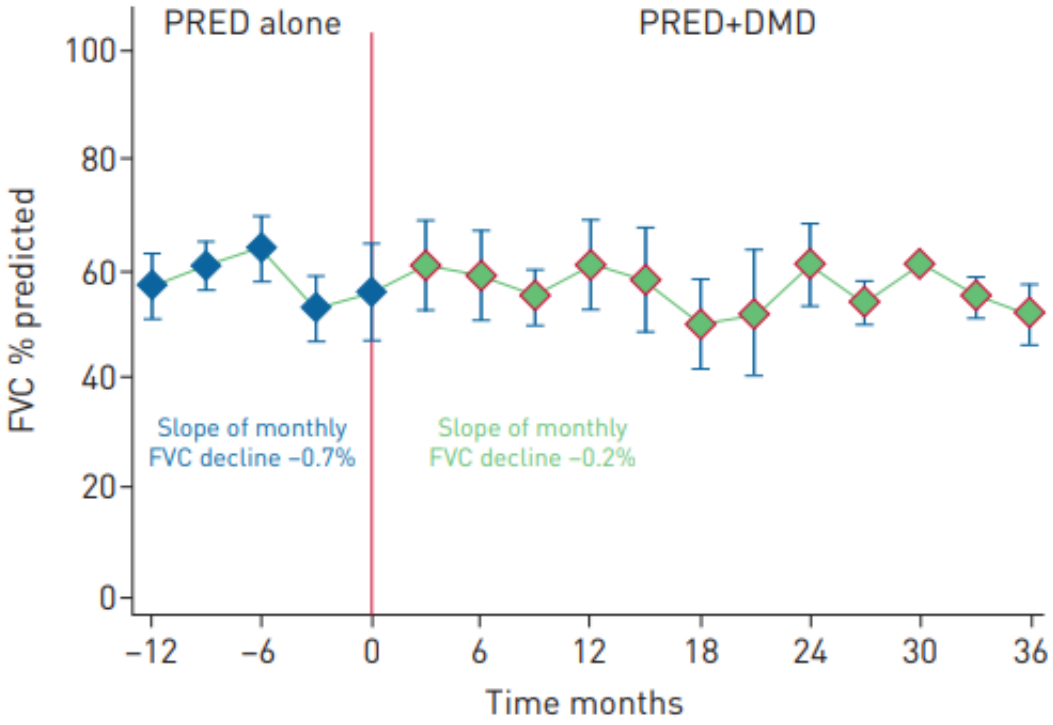
Adegunsoye A *et al*. *ERJ Open*. 2017; 3

Adverse Event of MMF and AZA



Adegunsoye A *et al*. *ERJ Open*. 2017; 3

Mycophenolate mofetil and Azathioprine



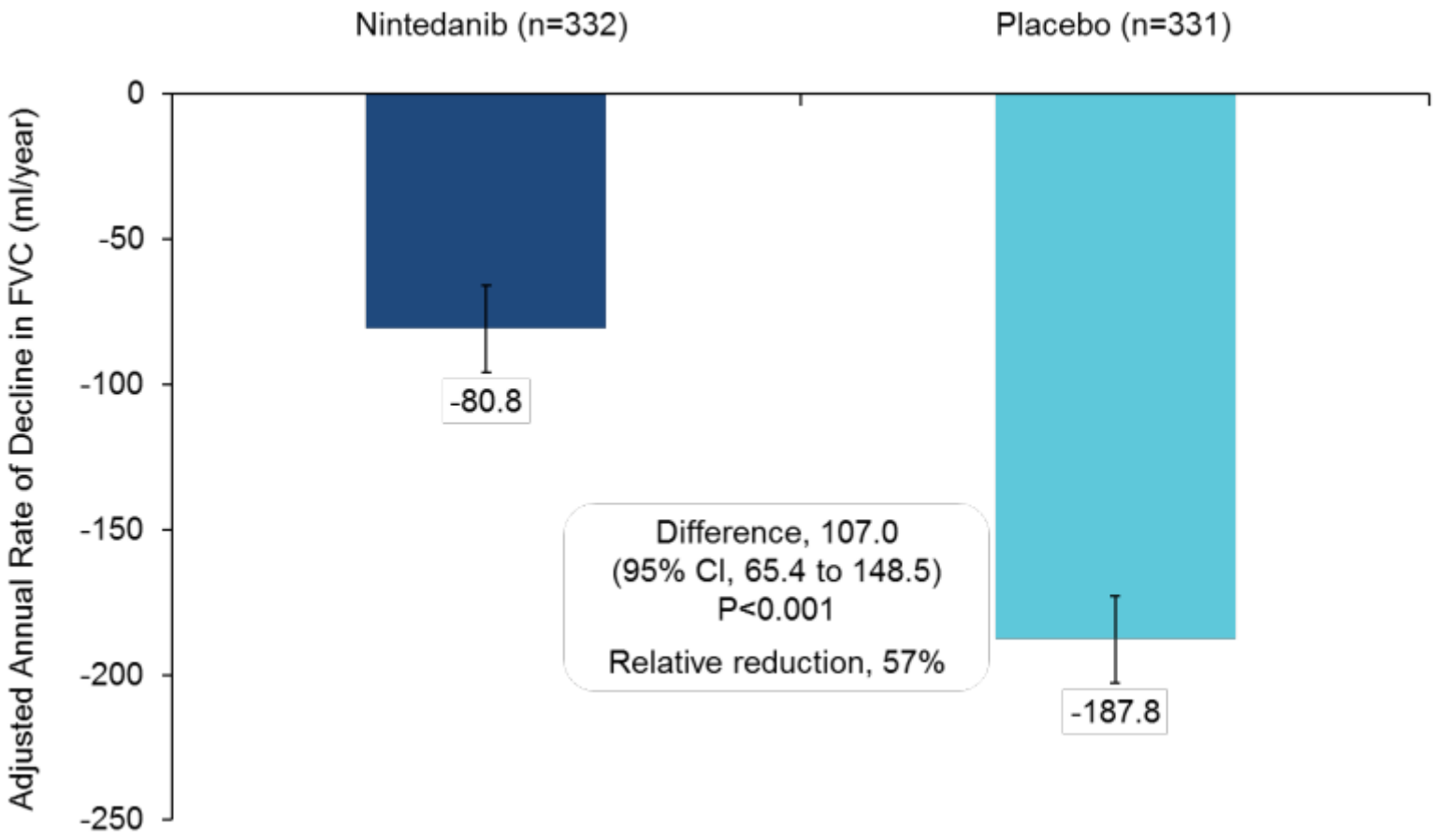
Adegunsoye A *et al*. *ERJ Open*. 2017; 3

Nintedanib for PF-ILD

- Double-blind placebo controlled phase 3 trial (15 countries)
- 663 Progressive fibrosing ILD [173 CHP (84 Nintedanib vs. 89 Placebo)]
- PF-ILD (Progression within 24 months despite standard treatment)
  - ✓ FVC decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT
- Exclusion
  - ✓ AZA, CYC, MMF, Tacrolimus, Rituximab, Cytoxan, Steroid (>20mg) within 6 mo
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + Increased fibrosis on CT
- Protocol
  - ✓ Nintedanib 150mg bid vs. Placebo for 52 weeks
- Outcome
  - ✓ Annual rate of FCV decline
  - ✓ Change of K-BILD, time till 1st AE, and time till death

Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Nintedanib for PF-ILD



Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Nintedanib for PF-ILD

Event	Nintedanib (N=332)	Placebo (N=331)
	no. of patients (%)	
Adverse event		
Any	317 (95.5)	296 (89.4)
Any except for progression of interstitial lung disease†	317 (95.5)	295 (89.1)
Most frequent adverse events‡		
Diarrhea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of interstitial lung disease†	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)

Event	Nintedanib (N=332)	Placebo (N=331)
	no. of patients (%)	
Severe adverse event§	60 (18.1)	73 (22.1)
Serious adverse event¶	107 (32.2)	110 (33.2)
Fatal adverse event		
Any	11 (3.3)	17 (5.1)
Any except for progression of interstitial lung disease†	10 (3.0)	14 (4.2)
Adverse event leading to treatment discontinuation	65 (19.6)	34 (10.3)
Adverse event leading to permanent dose reduction	110 (33.1)	14 (4.2)

Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Pirfenidone for CHP

- Open-label randomized controlled trial (Single center in Mexico)
- 22 CHP patients [9 patients (PD+AZA) vs. 13 patients (PD+AZA+PFD)]
- Outcome
  - ✓ Change of FVC at 12 mo
  - ✓ Change of DLco at 12 mo, 6MWT SaO_2 and distance, SGRQ, ATA-IPF score, VAS

Variable	Group 1 $n=9$	Group 2 $n=13$	p
Age, years (±SD)	57 ± 9	55 ± 7	0.56
Female (%)	5 (56)	11 (85)	0.17
Time of respiratory symptoms, years (IQR)	3 (2–5)	2 (1–3)	0.55
Identified source of antigen (%)	8 (89)	12 (92)	1.00
Birds (%)	7 (78)	11 (85)	1.00
Corn chaff (%)	0	5 (39)	0.05
Bagasse (%)	0	1 (8)	1.00
Home humidity (%)	1 (11)	1 (8)	1.00
Former smoker (%)	6 (67)	3 (23)	0.07
Systemic hypertension (%)	4 (44)	3 (23)	0.37
Diabetes mellitus (%)	1 (11)	1 (8)	1.00
Hypothyroidism (%)	1 (11)	0	0.40
Dyslipidemia (%)	1 (11)	2 (15)	1.00
% of Lymphocytes in BAL (±SD)	$n=8$ 33 ± 22	$n=10$ 42 ± 20	0.35
FVC % predicted (±SD)	62 ± 20	59 ± 15	0.71
FVC (L) (±SD)	1.76 ± 0.49	1.58 ± 0.42	0.55
D_{LCO} % predicted (±SD)	59 ± 14	47 ± 23	0.17
Total SGRQ score (±SD)	6.56 ± 4.82	7 ± 2.51	0.78
ATAQ-IPF score (IQR)	$n=8$ 71 (64–94)	$n=13$ 79 (70–85)	0.75
VAS score (IQR)	$n=9$ 80 (65–90)	$n=12$ 75 (60–83)	0.60
HRCT Total extension % (IQR)	84 (64–88)	80 (66–90)	0.84
HRCT Ground glass % (IQR)	75 (61–81)	64 (59–70)	0.08
HRCT fibrosis % (IQR)	8 (7–9)	18 (7–18)	0.11

Mateos-Toledo H *et al*. *Arch Bronchoneumol*. 2019; 381(18)

Pirfenidone for CHP

- Open-label randomized controlled trial
- 22 CHP patients [9 patients (PD+AZA) vs. 13 patients (PD+AZA+PFD)]
- Outcome
  - ✓ Change of FVC at 12 mo
  - ✓ Change of DLco at 12 mo, 6MWT SaO_2 and distance, SGRQ, ATA-IPF score, VAS score, HRCT extension score, HRCT GGO score, HRCT fibrosis

Variable	Group 1	Group 2	*p*
Pulmonary function tests (Δ ± SD; baseline to 12 months)			
FVC (% predicted)	35 ± 152	79 ± 328	0.7
FVC (ml)	1.25 ± 5	3.91 ± 14	0.6
D_{LCO} (% predicted)	−1.63 ± 10.1	10.8 ± 15.1	0.06
Quality of life questionnaires (Δ ± SD or IQR; baseline to 12 months)			
Total SGRQ score	1.50 ± 4.5	−2.36 ± 2.29	0.02
ATAQ-IPF score	3 (−9 to 23)	−7 (−17 to −2)	0.1
VAS score	−10 (−18 to 10)	5 (0–18)	0.07
HRCT score (Δ, IQR; baseline to 12 months)			
Total extension	−9 (−11 to −4)	−4 (−18 to −2)	0.8
Ground Glass	−8.8 (−13 to −6)	−10.1 (−18 to −2)	1.0
Fibrosis	0.45 (−0.7 to 2)	−1.8 (−4.2 to 3.5)	0.4

Mateos-Toledo H *et al*. *Arch Bronchoneumol*. 2019; 381(18)

Pirfenidone for CHP

Variable	Group 1 $n=9$	Group 2 $n=11$	p
Nausea (%)	0 (0)	3 (27)	0.21
Headache (%)	1 (11)	1 (9)	1.00
Diarrhea (%)	1 (11)	3 (27)	0.59
Upper respiratory tract infection (%)	3 (33)	3 (27)	1.00
Fatigue (%)	1 (11)	0 (0)	0.45
Rash – (%)	0 (0)	1 (9)	1.00
Dyspepsia (%)	6 (67)	11 (100)	0.07
Dizziness (%)	0 (0)	1 (9)	1.00
Bronchitis (%)	1 (11)	2 (18)	1.00
Constipation (%)	1 (11)	1 (9)	1.00
Nasopharyngitis (%)	1 (11)	2 (18)	1.00
Anorexia (%)	1 (11)	1 (9)	1.00
Threw up (%)	0 (0)	2 (18)	0.47
GERD (%)	2 (22)	4 (36)	0.64
Insomnia (%)	0 (0)	1 (9)	1.00
Urinary tract infection (%)	2 (22)	2 (18)	1.00
Acute exacerbation (%)	1 (11)	0 (0)	0.45
Oropharyngeal candidiasis (%)	1 (11)	0 (0)	0.45
White cell, 12 month – (IQR)	7725 (530–10,800)	7900 (4400–12,700)	0.87
SGOT, 12 month – (IQR)	19 (13–24)	21 (19–24)	0.35
SGPT, 12 month – (IQR)	16 (10–24)	15 (10–22)	0.83

Mateos-Toledo H *et al*. *Arch Bronchoneumol*. 2019; 381(18)

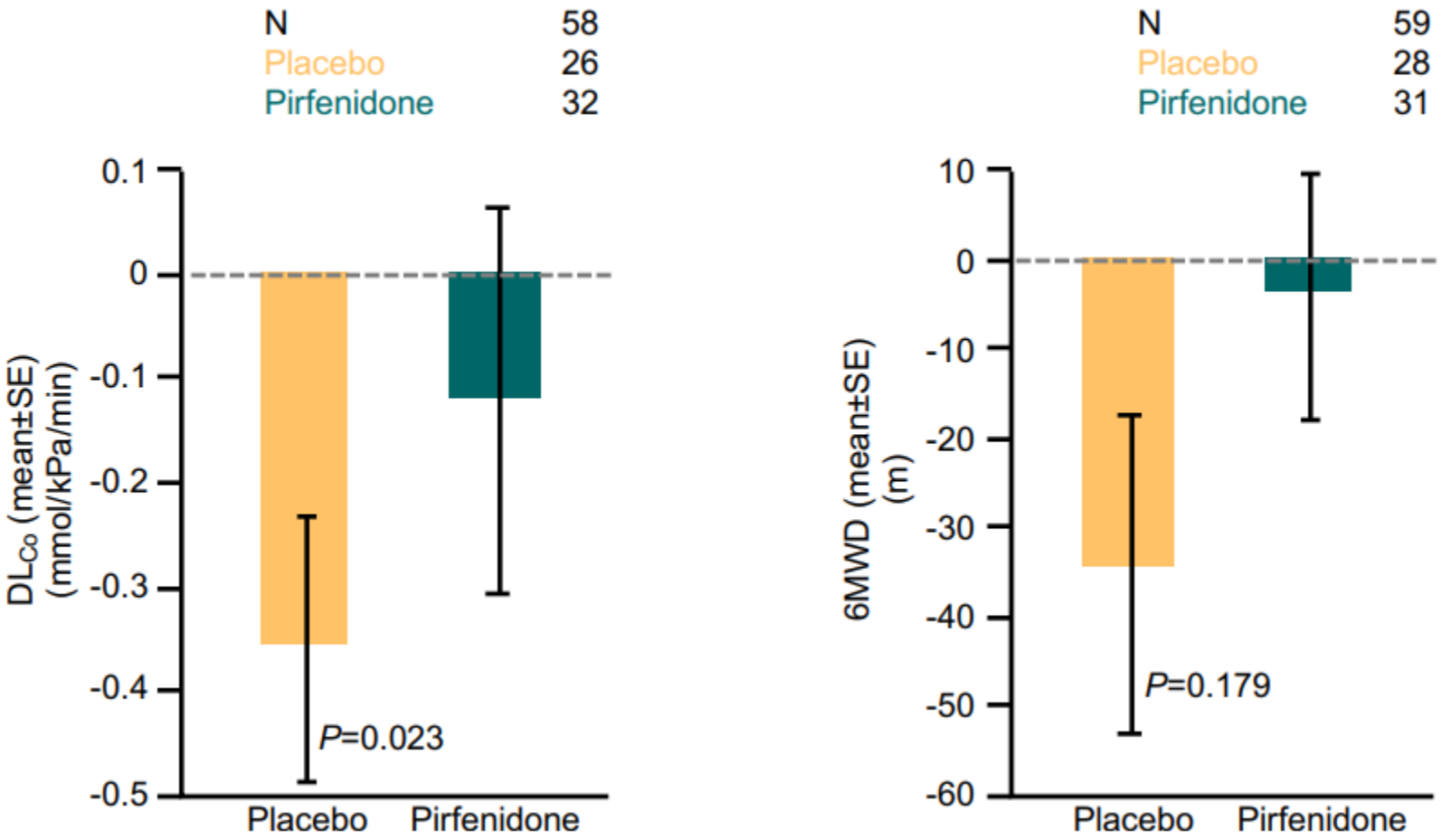
Pirfenidone for non-IPF Lung Fibrosis

- Double-blind placebo controlled phase 2 trial (RELIEF trial)
- 127 non-IPF lung fibrosis (57 CHP)
- Patients
  - ✓ CVD-LF, Fibrotic NSIP, Chronic HP, Asbestos-induced lung fibrosis
  - ✓ Annual absolute FVC decline ≥ 5%
- Protocol
  - ✓ PFD 800 mg tid vs. Placebo for 24 weeks
- Outcome
  - ✓ FVC decline rate (48 weeks)
  - ✓ Change in FVC, DLco, 6MWTD, SGRQ, Adverse event

Guenther A *et al*. *ERS Abstract*. 2019

Pirfenidone for PF-ILD

Figure 1. Relative change in DL_{CO} in patients treated with pirfenidone vs placebo*



Guenther A *et al*. *ERS Abstract*. 2019

Summary (I)

Classification

- Nonfibrotic vs. Fibrotic (Based on radiologic and/or pathologic features)

Diagnosis

- Thorough and detailed history taking including antigen exposure (consider Questionnaire or Serum IgG tests)
- HRCT pattern of HP (Nonfibrotic vs. Fibrotic)
- Bronchoalveolar lavage (esp. consider in Nonfibrotic HP)
- Histopatholgic pattern of HP (Nonfibrotic vs. Fibrotic)
  - ✓ TBLB (Nonfibrotic HP), TBLC (Fibrotic HP), SLB

→ Multidisciplinary discussion

Summary (II)

Treatment

- Antigen avoidance: First step
- Corticosteroid
- Fibrosis is associated with poor prognosis (radiologic or pathologic)
- For fibrotic HP, drugs under investigations are
  - ✓ Immunosuppressant combination (MMF, AZA etc.)
  - ✓ Antifibrotic agents (Pirfenidone or nintedanib)