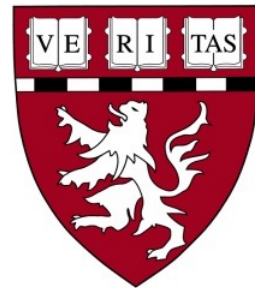


Hypersensitivity Pneumonitis: Pigeons, Farmers and Hot Tubs, Oh My

Rachel S. Knipe, MD

Division of Pulmonary and Critical Care Medicine
Center for Immunology and Inflammatory Diseases

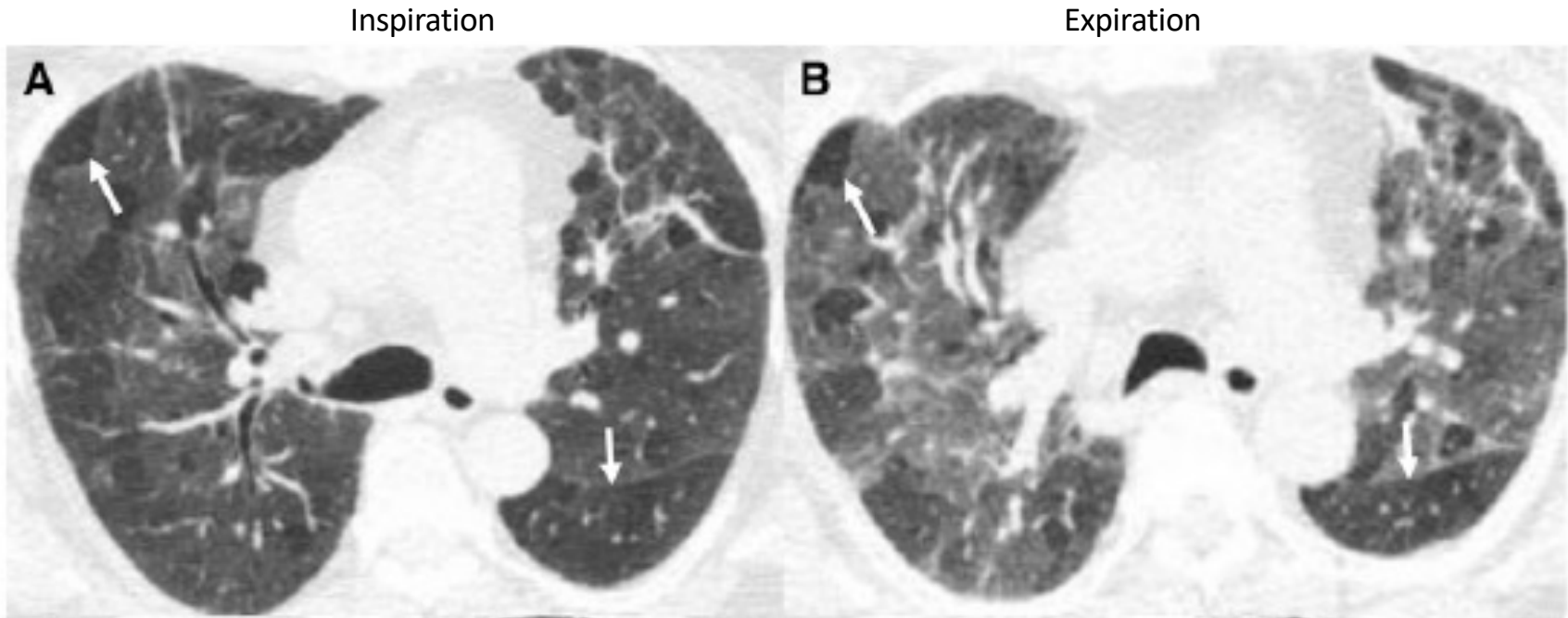
Massachusetts General Hospital
Harvard Medical School



Case Presentation

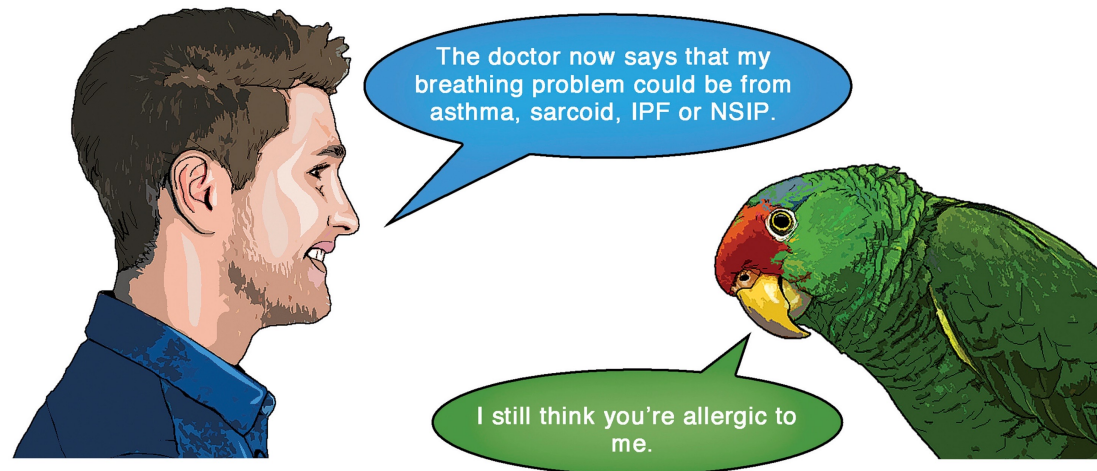
- 50y F never smoker presents to PCP with progressive DOE, nonproductive cough and fatigue over the last 3 months
- History reveals she has been working in her husband's parakeet shop more since he became ill several months ago
- Exam: bilateral diffuse fine crackles
- Labs: normal
- PFTs: FVC 64% predicted, DLCO 65% predicted
- CXR: bilateral interstitial and patchy opacities

Case Presentation



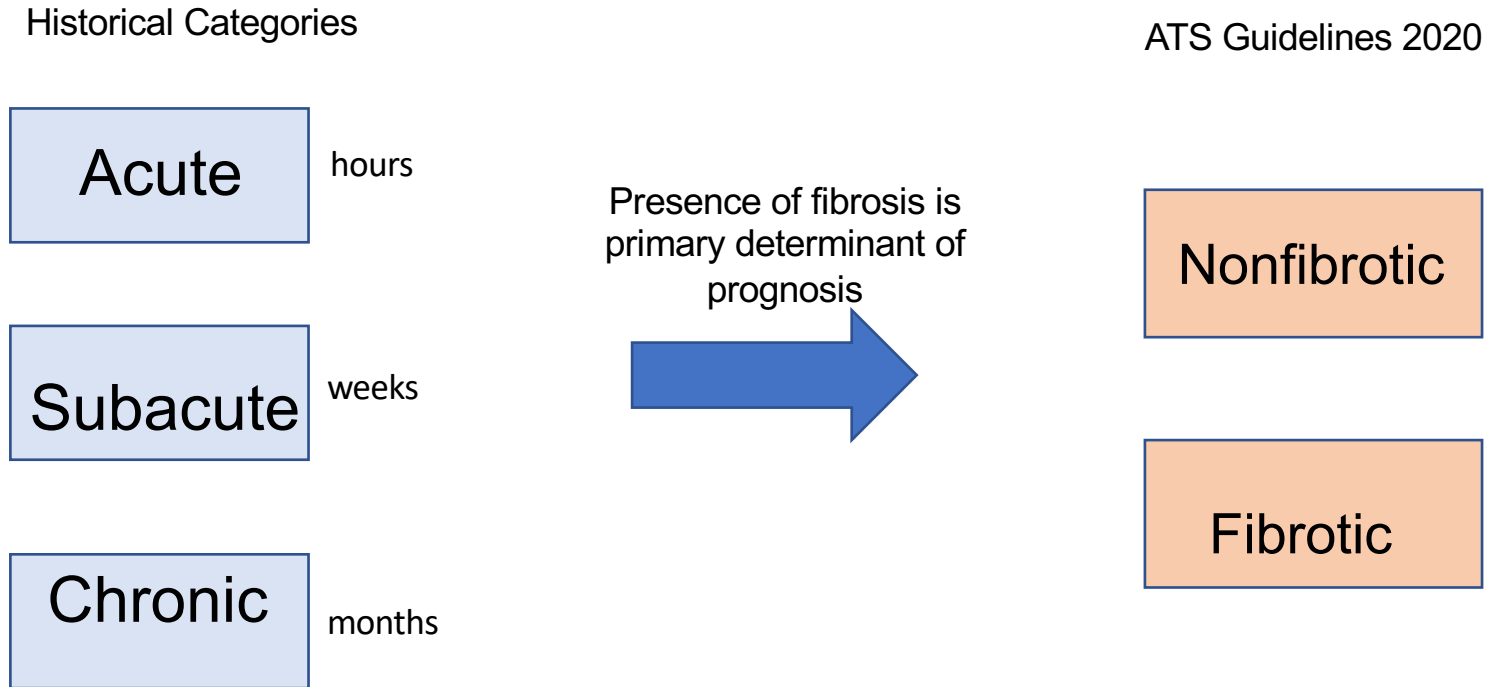
HRCT: patchy GGO, mid lung zone predominance, mosaic attenuation and air trapping

Hypersensitivity Pneumonitis

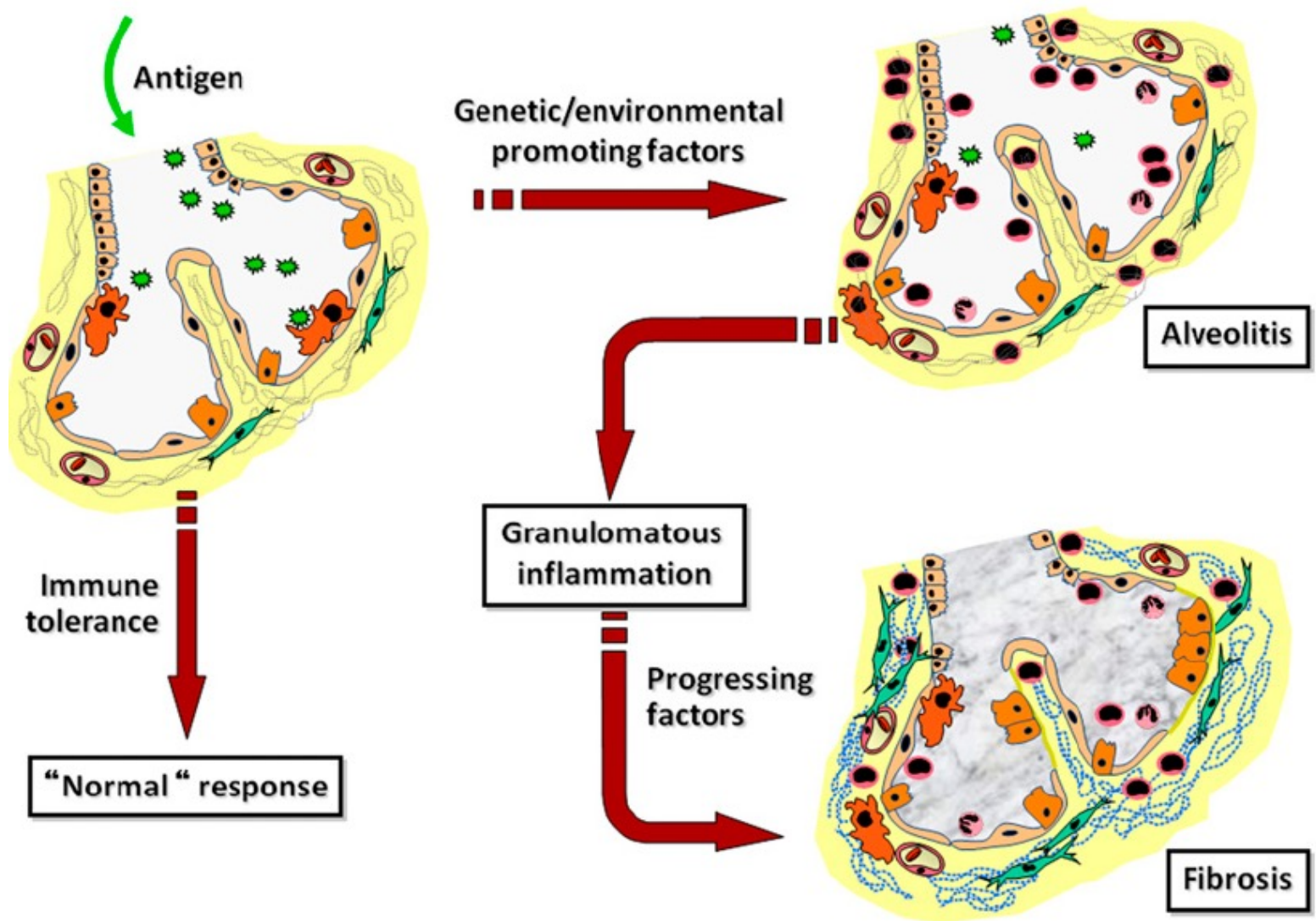


- Airway centered inflammation induced by an exaggerated immune response to an inhaled foreign substance
- Syndrome results from repeated exposure to variety of organic particles
- Up to 30% have no identifiable exposure
- 2 hit hypothesis (antigen exposure + genetic predisposition)

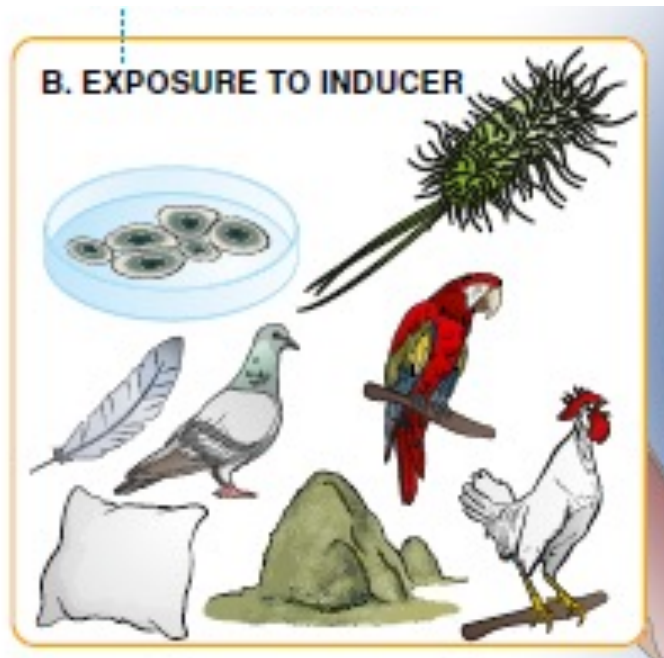
Hypersensitivity Pneumonitis: Categories



HP Pathogenesis



Exposure to Environmental Antigens

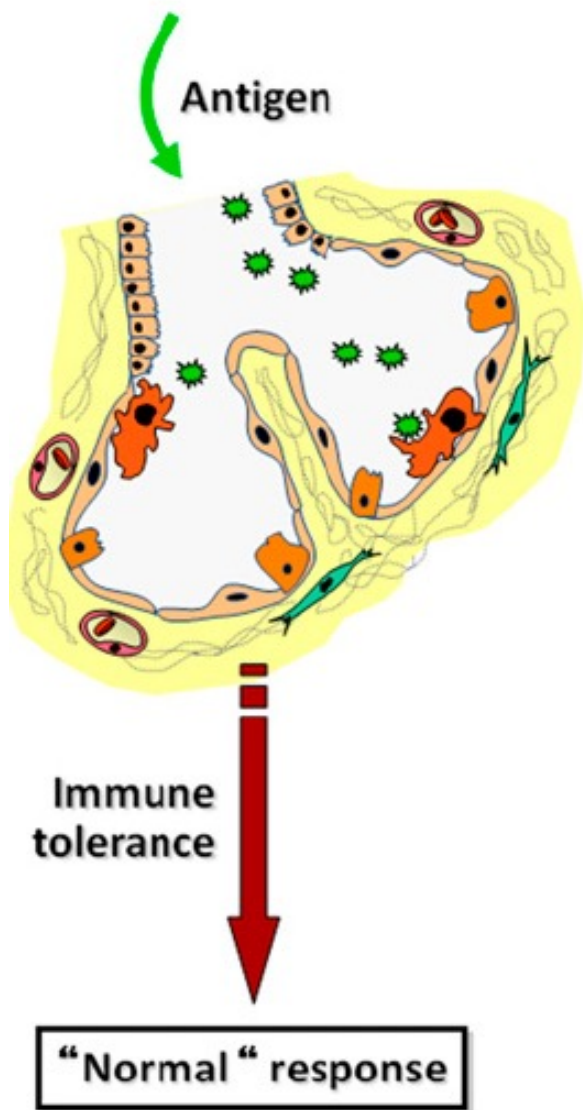


- Immune mediated reaction in susceptible and sensitized people to a large variety of inhaled environmental antigens
- Exposure can occur at work, home, hobbies
- Large list of HP inducers, 3 main groups
 - **Animals** (mostly birds)
 - **Microbes** (fungi, mold, bacteria)
 - **Chemicals** (solvents, drugs)
- Identification of source is crucial for management

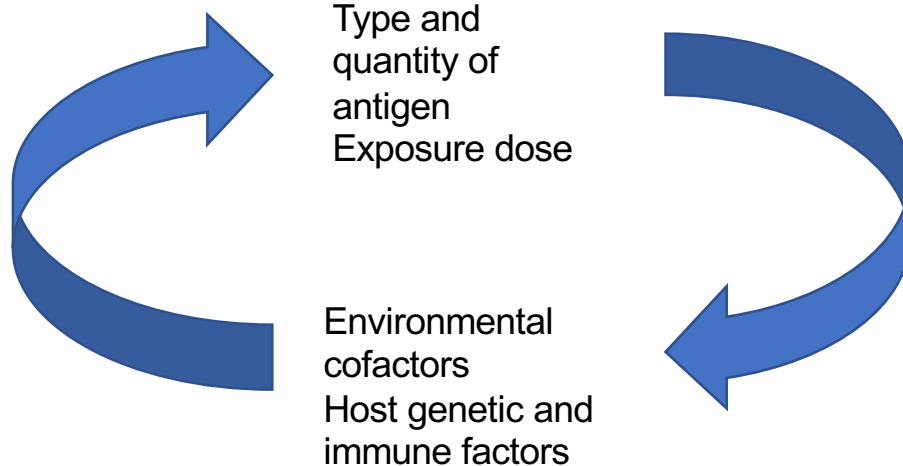
Examples of HP Inducers

Antigen	Antigen source	HP variant
Bacteria		
<i>Thermophilic actinomycetes</i>	Mouldy hay and straw	Farmer's lung
<i>Klebsiella oxytoca</i>	Humidifiers	Humidifier's lung
<i>Thermophilic actinomycetes</i>	Sugar cane dust	Bagassosis
Mycobacteria		
<i>Mycobacterium avium</i> complex	Outdoor hot tubs	Hot-tub lung
<i>Mycobacterium immunogenum</i>	Metal-working fluid	Machine operator's lung
Fungi		
<i>Absidia corymbifera</i>	Mouldy hay and straw	Farmer's lung
<i>Trichosporon cutaneum</i>	Indoor households	Summer-type HP
<i>Penicillium roqueforti</i>	Cheese washing and/or industrial source	Cheese-worker's lung
Animal proteins		
Feathers and excrements	Birds	Bird breeder's or fancier's lung
Serum and urine	Rats	Rat protein alveolitis
Plant proteins		
Nut dust	Processing of tiger nuts	Tiger nut alveolitis
Soy dust	Soy foods	Soy dust alveolitis
Enzymes		
Phytase	Animal feed	Phytase alveolitis
Enzymes from <i>Bacillus subtilis</i>	Detergent industry and/or cleaning products	Detergent worker's lung
Chemicals		
Toluene diisocyanate, methylene diphenyl isocyanate and hexamethylene diisocyanate	Paint and/or varnish	Isocyanate lung
Acid anhydrides	Plastic industry	Acid anhydride alveolitis
Metals		
Zinc vapour	Zinc welding	Zinc vapour alveolitis
Zirconium	Ceramic tile work	Zirconium silicate alveolitis

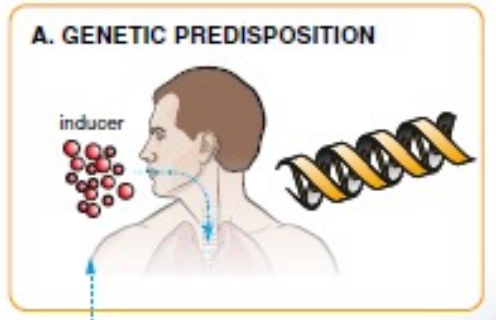
Why do only some people develop HP?



Antigen is not enough!



Genetic Susceptibility to HP



- Most polymorphisms involved in antigen presentation (MHC)

- Fibrotic HP shares some genetic polymorphisms with other ILDs

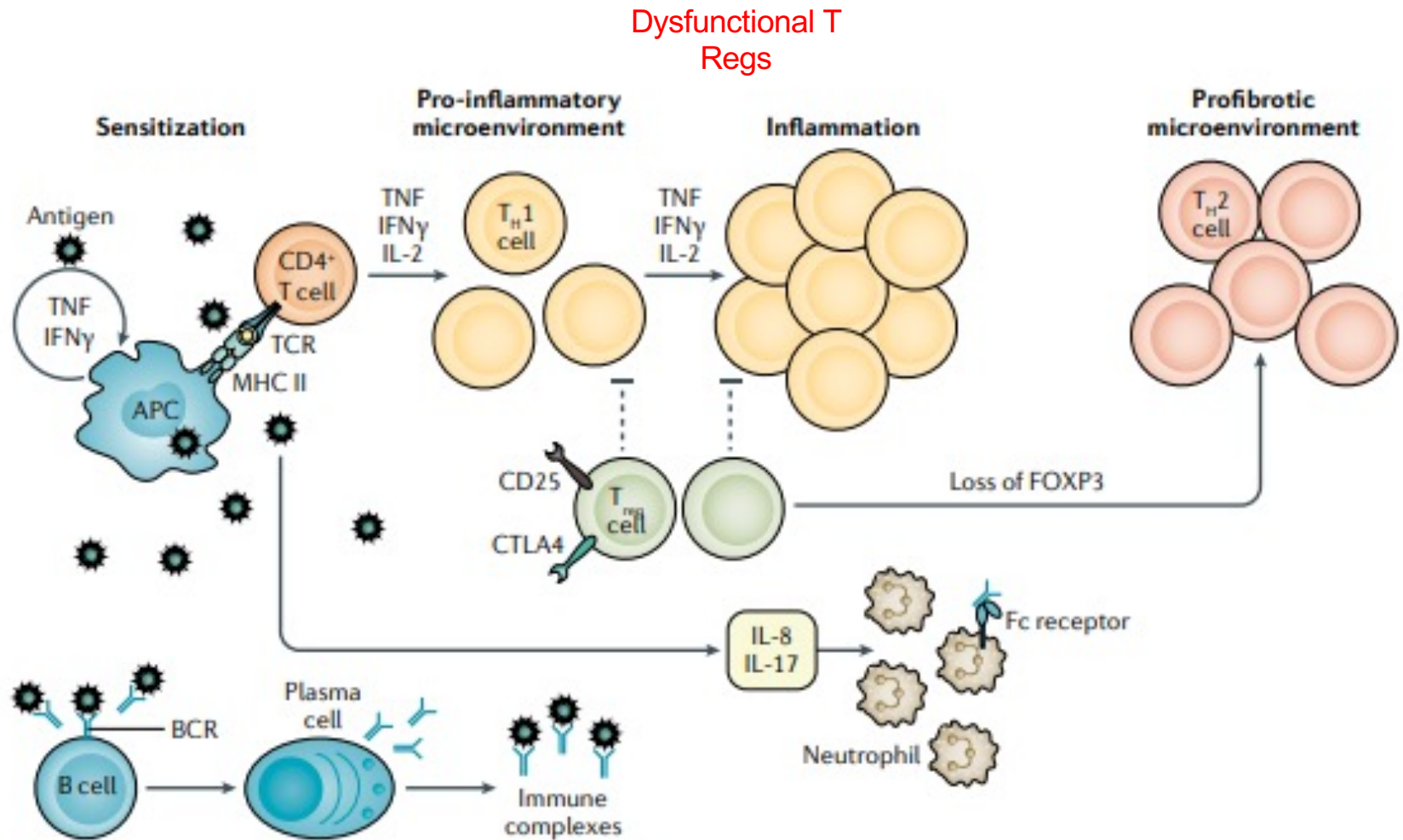
- Telomere length mutations
- MUC5B

Familial clusters reported even when affected family members live far apart

- Okamoto et al. Respiration 2013

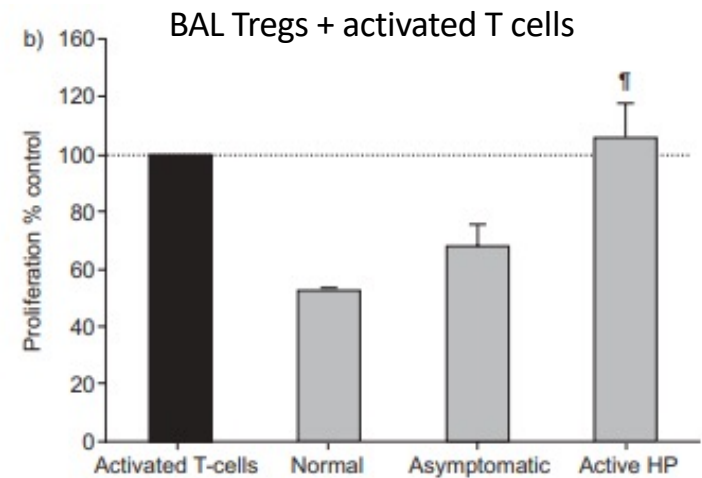
Genes and Genetic Variants	Population Race or Nationality	First Author (Year) (Reference)
MHC II polymorphisms		
HLA-DR3	White	Rittner (1983) (63)
HLA-DR7	Mexican	Selman (1987) (64)
HLA-DQ3	Japanese	Ando (1989) (65)
HLA-DRB1*04	Mexican	Falfán-Valencia (2014) (66)
MHC II haplotypes		
Increased DRB1*1305-DQB1*0301; decreased DRB1*0802-DQB1*0402	Mexican	Camarena (2001) (67)
Proteasome and transporter polymorphisms		
PSMB8 KQ	Mexican	Camarena (2010) (68)
TAP1 637, 661	Mexican	Aquino-Galvez (2008) (69)
Mucin polymorphisms		
MUC5B rs35705950	White	Ley (2017) (70)
Telomere length and mutations		
Telomere length <10th percentile	White	Ley (2017) (70)
Telomere-related gene mutations	White	Newton (2016) (71)
Antiprotease polymorphisms		
TIMP-3-915 TIMP-3-1296 (protective role)	White	Hill (2004) (72)

Immunopathology of HP

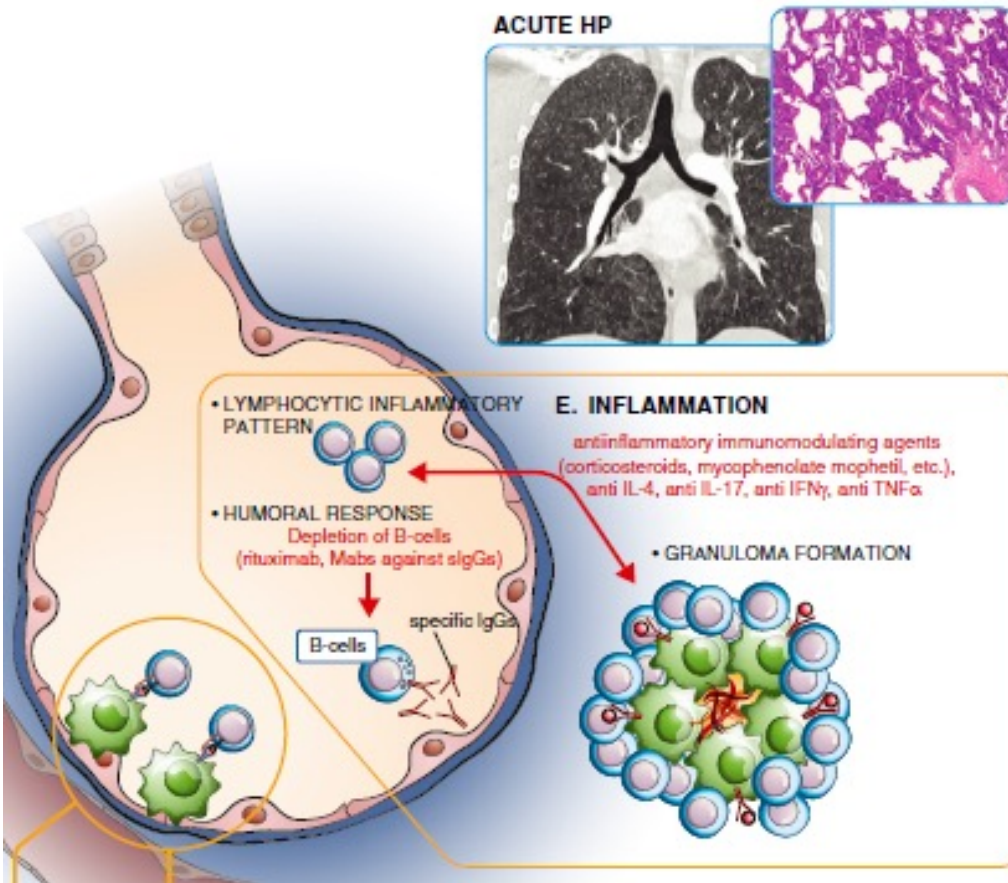


Immunopathology of HP

- T regs from HP patients have no functional suppressive activity
- A second hit may further promote inflammation
 - **Viruses** often found in distal airways
 - Dakhama et al. AJRCCM 1999
 - Animal models of virus + HP antigen enhances inflammatory response
 - Girard et al. ERJ 2009
 - **Pesticides** potential risk factor for development of farmer's lung
 - Hoppin et al. Occup Env Med 2007
 - **Air pollution** associated with increased HP cases in India, may reduce MCC and increase inflammation
 - Singh et al. ERJ 2019



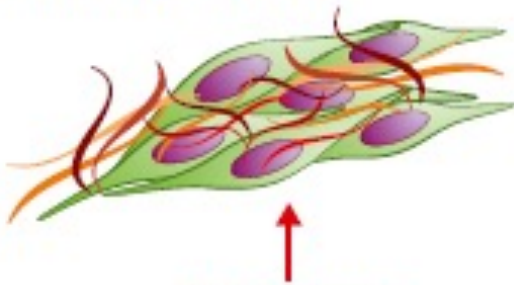
Inflammation Abundant in Nonfibrotic HP



- Lymphocytic alveolitis: expansion of T and B lymphocytes in lung tissue
- Formation of granulomas
- Activation of both humoral (Ig) and cellular (T cell) immune responses

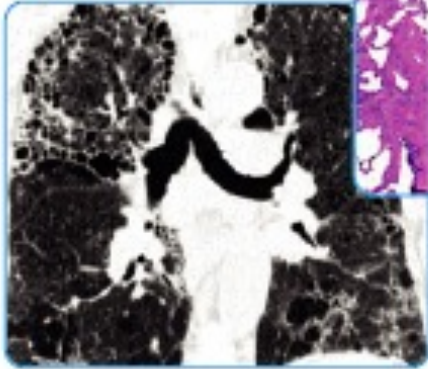
Some Patients Develop Fibrotic HP

F. FIBROPROLIFERATION



Antifibrotic treatment

CHRONIC HP



- Progressive pulmonary fibrosis can occur, which can appear similar to IPF
 - Include HP on differential for new ILD!
- Potential Mechanisms include:
 - Premature senescence
 - Transition from Th1 to Th2 immune response
 - Shortened telomeres / Aging

Diagnosis of HP

- In the context of respiratory sx's, diagnosis based on combination of history, imaging and BAL/tissue data
1. Evidence of **exposure** to antigen (history, serum IgG antibodies)
 2. **Radiologic** patterns consistent with HP
 3. **Lymphocytosis** in BAL (>30%)
 4. **Histopathologic** patterns consistent with HP

Likelihood	Criteria	Next Step in Diagnosis
Confident	1,2,3 or 1,2	Lung biopsy not needed in most cases
Probable	1,3 but CT more c/w other ILD	Lung biopsy needed
Possible	1 but CT more c/w other ILD	Lung biopsy needed
Unlikely	none	Lung biopsy may be appropriate

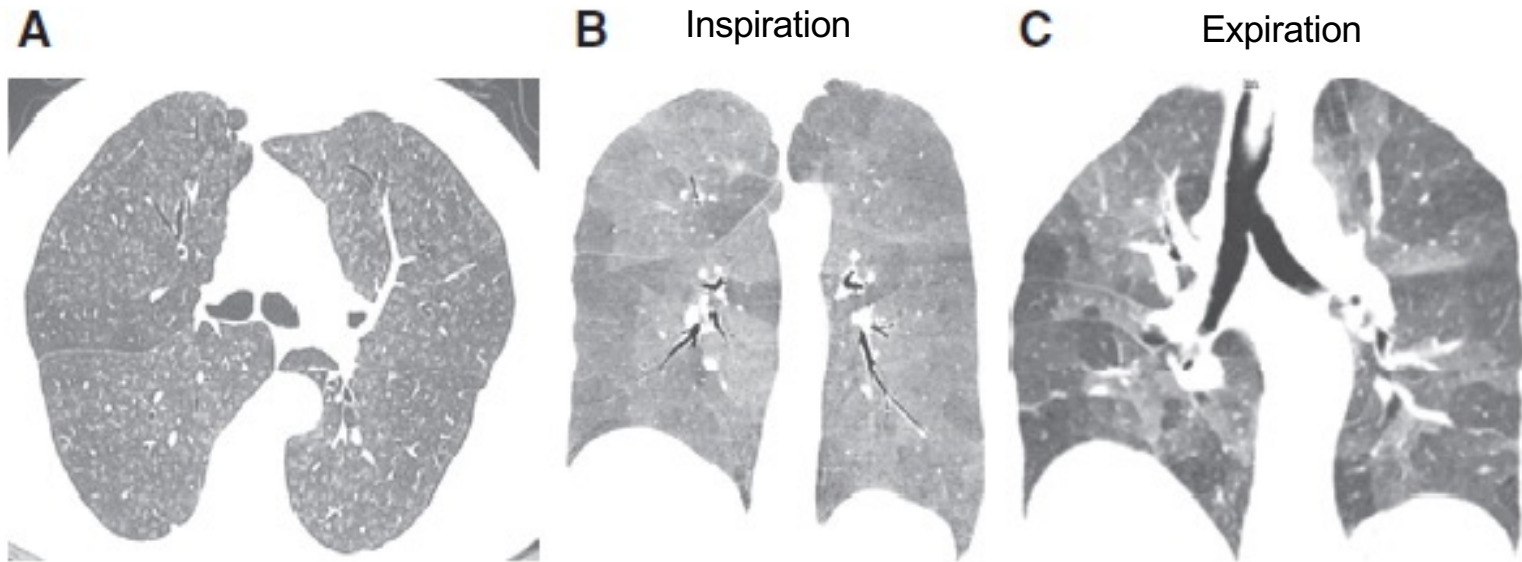
Diagnosis: Evidence of Exposure

- Obtain detailed exposure history
 - Standardized questionnaire may be helpful, though none currently validated
 - Pets (especially birds)
 - Use of feather pillow, duvet, sleeping bag, jacket
 - Wind instrument player
 - History of water damage to home or office, carpet (even if cleaned)
 - Use of hot tub, jacuzzi, sauna, swimming pool
 - Use of air conditioning units, humidifier, air cooler
 - Workplace exposures (lab animals, vet work, barn, horse stable, farming, hay handling, mushroom growing, brewery, winery, metalwork, plastics or epoxy manufacturing, spray painting)

Diagnosis: Evidence of Exposure

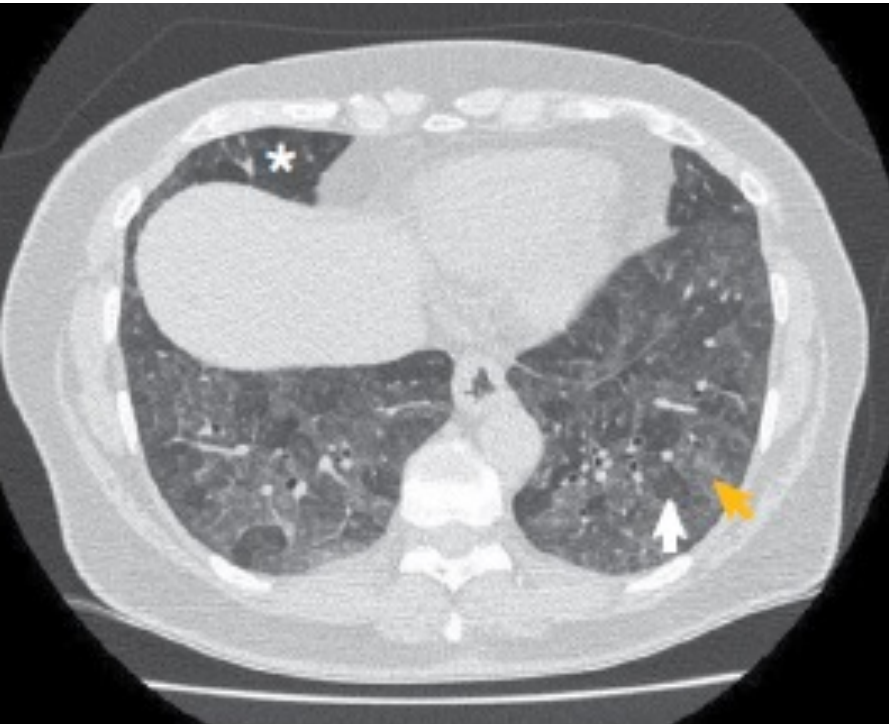
- Antigen specific serum IgG antibodies
 - Only markers of sensitization and not disease
 - Can support diagnosis of HP in the right clinical setting
 - Can facilitate identification of responsible antigen
 - Many different commercial tests exist with limited antigens and different sensitivities and specificities

Radiology of Nonfibrotic HP



Confidence	Criteria
Typical of HP	Requires diffuse evidence of : 1 pattern of infiltration (GGO, mosaic attenuation) and 1 pattern of small airway disease (centrilobular nodules, air trapping)
Compatible with HP	Nonspecific patterns that have been described in HP
Indeterminate for HP	N/A

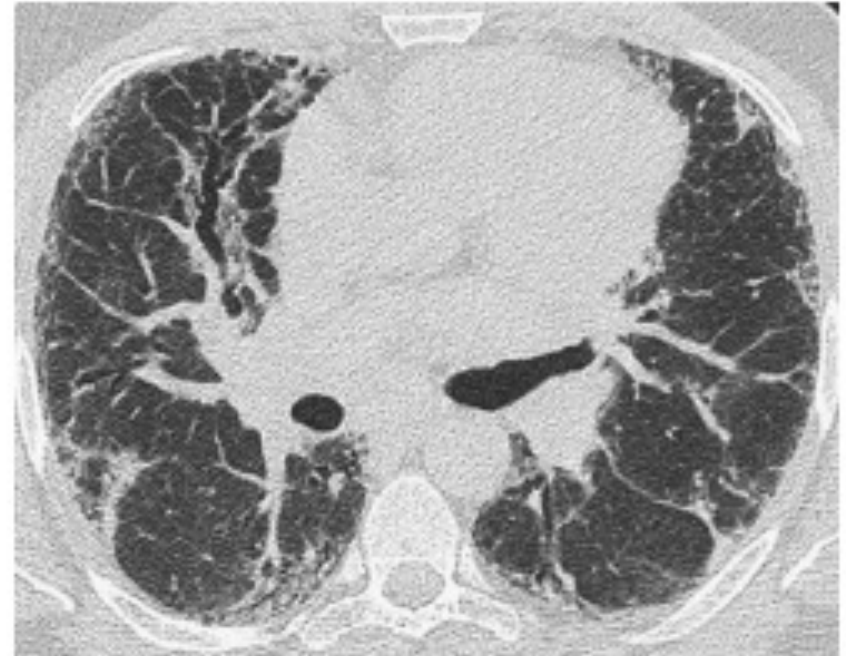
Radiology of HP



3 density pattern “headcheese sign”

1. GGO (increased attenuation, inflammation/infiltration) yellow arrow
 2. Lobules of decreased attenuation (small airways obstruction) white arrow
 3. Normal appearing lung asterisk
- Highly specific pattern for HP

Radiology of Fibrotic HP



- Diffuse reticulation, traction bronchiectasis, mid and lower lobe distribution, relative basal sparing, centrilobular nodules, mosaic attenuation
- UIP pattern in up to 1/3 of fibrotic HP patients; air trapping and diffuse distribution can be key discriminatory features

Diagnosis: HRCT

Acute HP and chronic non-fibrotic HP	Chronic fibrotic HP
Features	
Ground-glass opacities	Reticular opacities, traction bronchiectasis and honeycombing
Centrilobular nodules of ground-glass attenuation that are small and poorly defined	Superimposed with findings of acute HP (for example, combination of ground-glass opacities, centrilobular nodules and mosaic pattern)
Areas of decreased attenuation represent a mosaic pattern secondary to air-trapping ^a , corresponding to areas of bronchiolitis	Emphysema, alone or in combination with other features of chronic HP possible ^b
Head-cheese sign (a combination of ground-glass opacities, mosaic pattern and normal lung tissue) ^c	Thin-walled pulmonary cysts, few and not dominant (may also occur in patients with chronic non-fibrotic HP)
Distribution	
Mostly diffuse, usually bilateral, sometimes patchy and predominantly in the lower lung areas	Mostly lower lung zone predominance, sometimes diffuse or in mid-to-upper lung zones, with a subpleural and peribronchovascular distribution; usually bilateral, with relative sparing of the lower lung zones

Diagnosis: BAL Analysis

- BAL lymphocytosis is characteristic but not specific to HP
 - >20-50% depending on the study, ATS Guidelines recommend >30%
- Not sensitive
 - May be affected by concurrent infections, steroids, etc.
- Not specific
 - Can be seen in sensitized individuals who do not have disease
- Low CD4:CD8 ratio (in comparison to sarcoidosis)
- Large systematic review recently found % BAL lymphocytes higher in fibrotic and nonfibrotic HP compared to IPF and sarcoidosis
 - >20% BAL lymphocytes distinguished:
 - Fibrotic HP from IPF (sens 69%, spec 61%)
 - Nonfibrotic HP from IPF (sens 95%, spec 61%)
 - Fibrotic HP from sarcoidosis (sens 69%, spec 26%)
 - Nonfibrotic HP from sarcoidosis (sens 95%, spec 26%)

Diagnosis: Tissue Sampling

- **Transbronchial Biopsy**

- ATS Guidelines recommend TBBx for diagnosing nonfibrotic HP > fibrotic HP based on higher yield with more diffuse disease
 - May be due to higher yield of granulomas in nonfibrotic HP
- Diagnostic yield only ~50% but those pts were spared lung biopsy

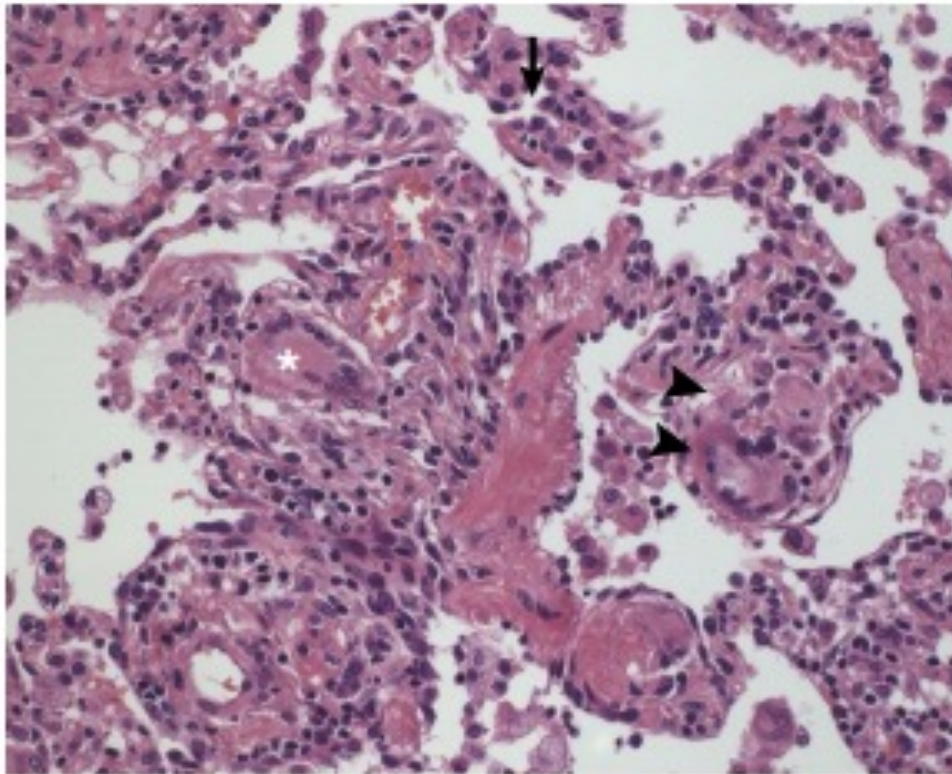
- **Transbronchial Cryobiopsy**

- Systematic review showed higher diagnostic yield as compared to TBBx
- 11% bleeding, 11% PTX
 - Chami et al. Annals ATS 2021
- ATS Guidelines recommend consideration in experienced centers

- **Surgical Lung Biopsy**

- Higher morbidity and mortality but also higher diagnostic yield
- Reasonable to consider once other diagnostic tests fail to make diagnosis

Pathology of Nonfibrotic HP



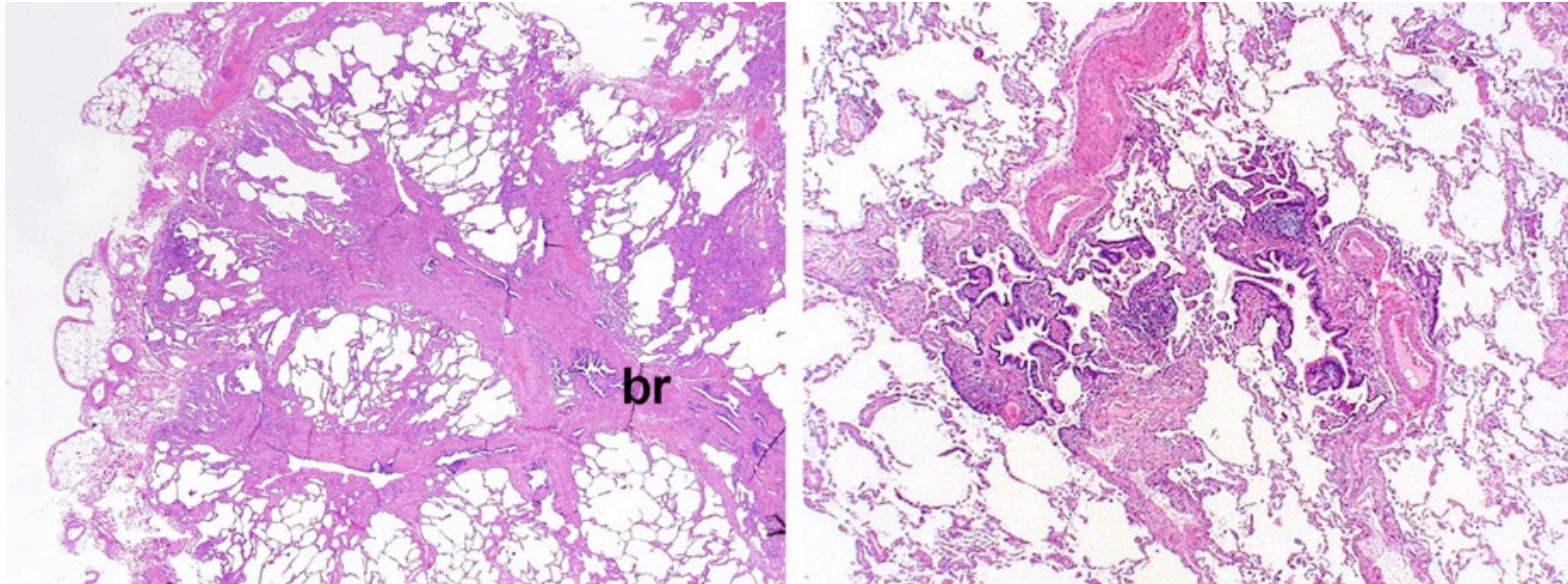
H&E, 100x

Typical histopathological features of HP:

1. Bronchiolocentric pattern
2. Cellular interstitial infiltrate (arrow)
3. Granulomatous inflammation:
 - Loosely formed granulomas (arrowhead)
 - Multinucleated giant cells (asterisk)

Confidence	Criteria
Typical HP	1,2,3
Probable HP	1+2
Indeterminate HP	1 or 2

Pathology of Fibrotic HP

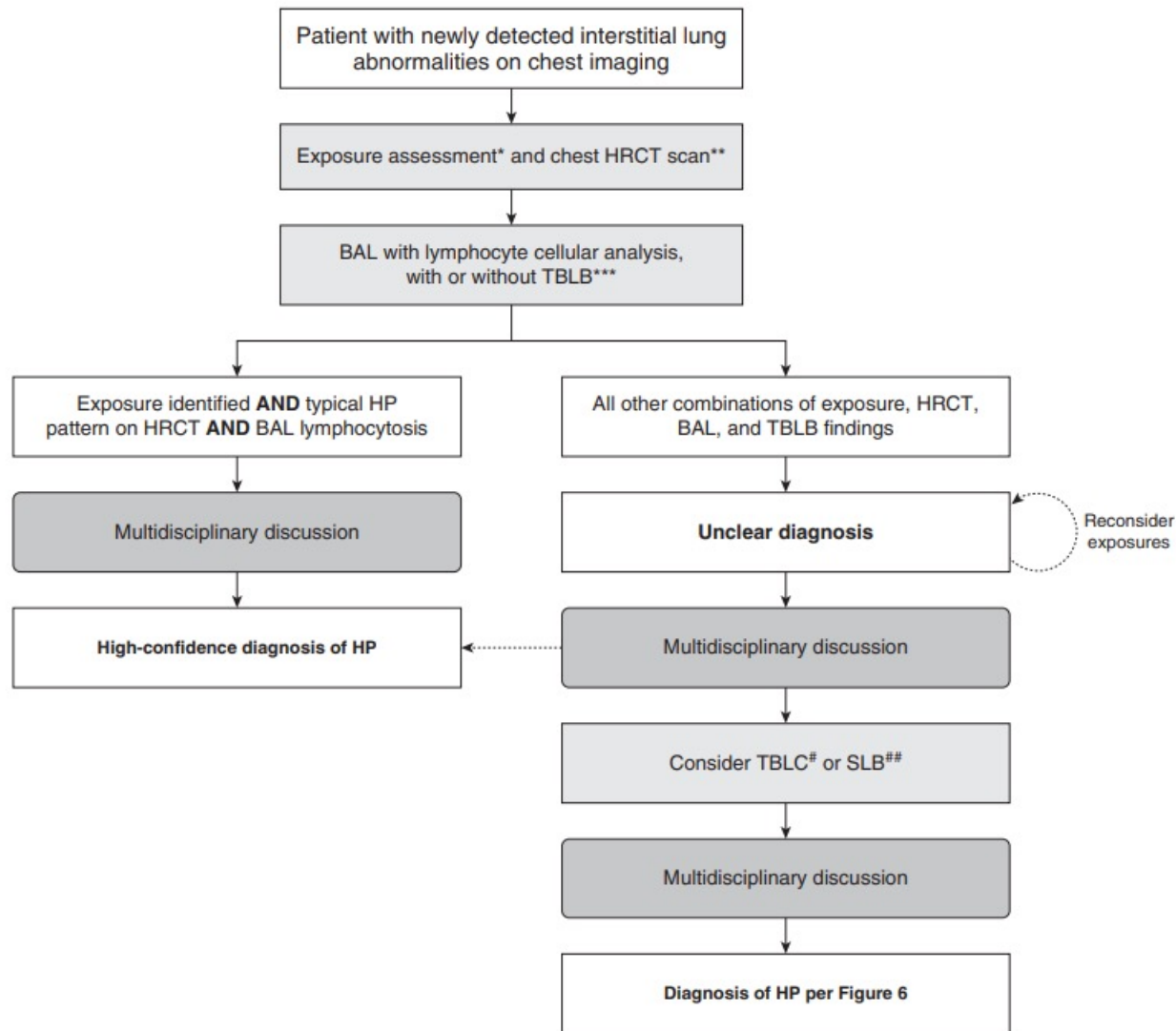


H&E, 20x

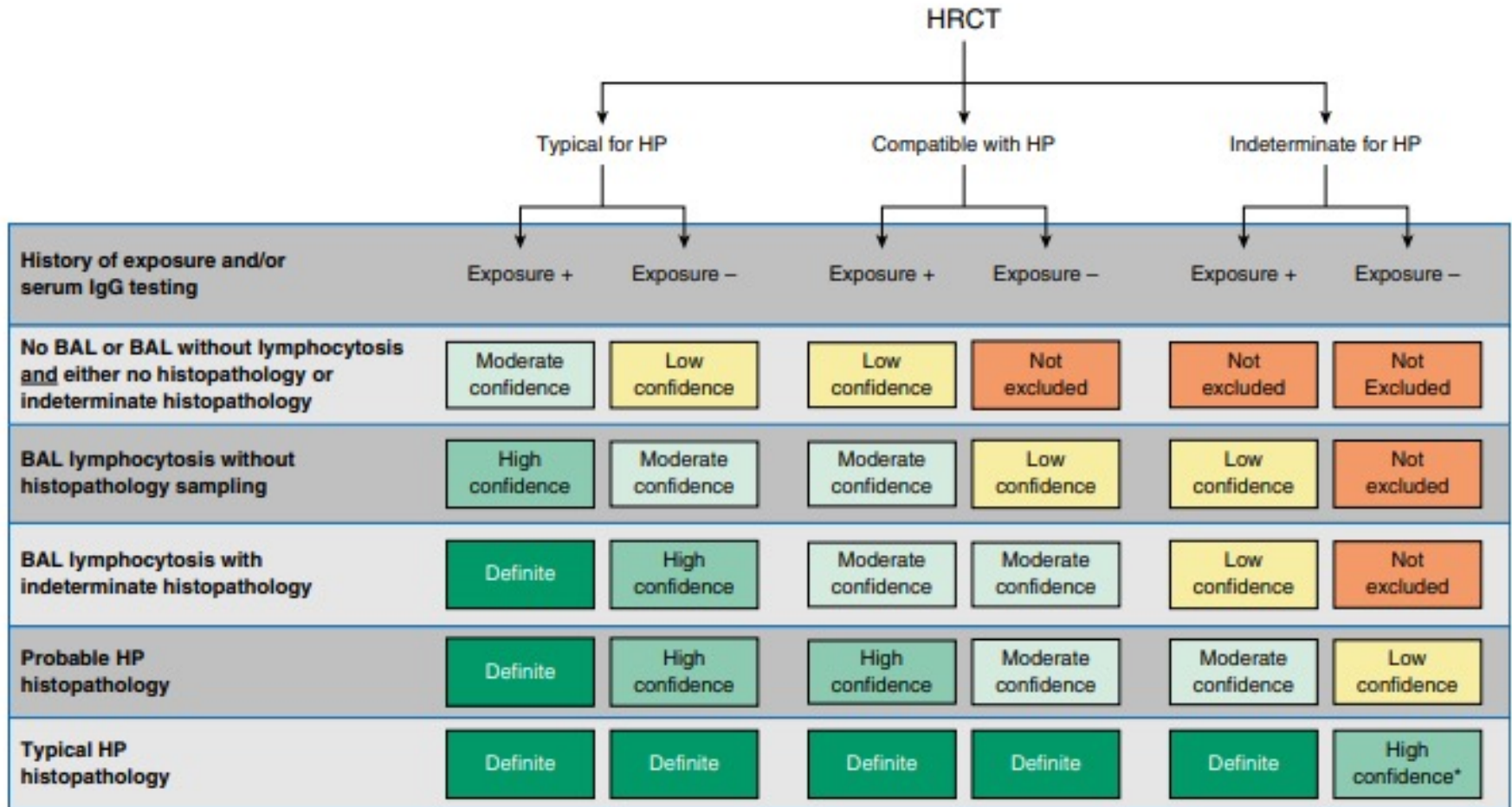
Typical histopathological features of HP:

- Bronchiolocentric fibrosis with dense fibrosis adjacent to bronchiole (br = bronchovascular bundle)
- Alveolar septal thickening

ATS Diagnostic Algorithm



ATS Diagnostic Algorithm



Treatment for Nonfibrotic HP

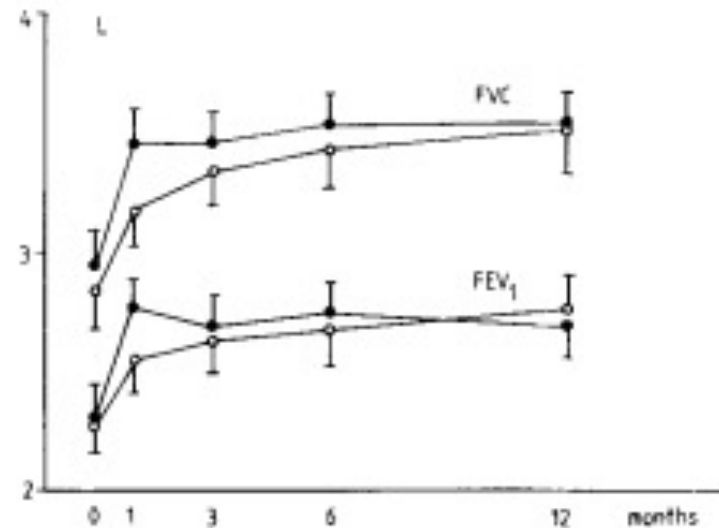
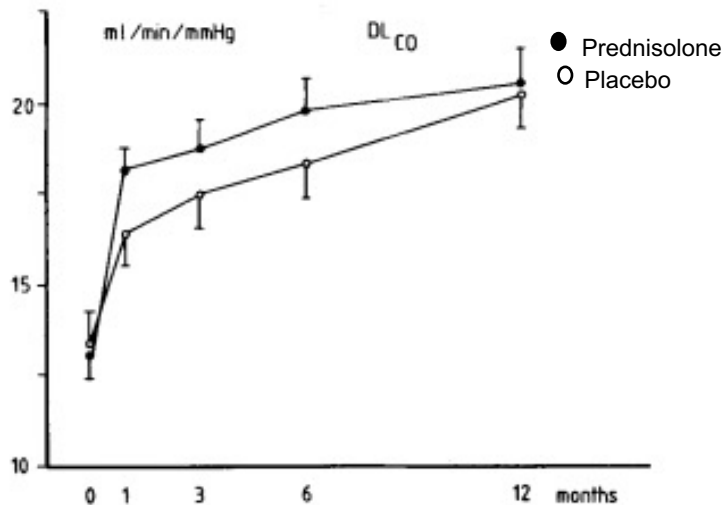
- **Elimination** of exposure most important intervention
 - Remove birds or feather bedding from house (antigens may persist despite cleaning)
 - Avoid hot tubs
 - Sterilize humidifiers and vaporizers
 - May require relocation to new job or home
- For acute HP with minimal or transient symptoms, complete antigen avoidance can be sufficient treatment
- Not always possible, in up to 60% cases inducer is never found

Treatment for Nonfibrotic HP: Corticosteroids

- If avoidance alone is insufficient, consider **steroid** course
 - Persistent symptoms (dyspnea, cough, fatigue, weight loss)
 - Abnormal lung function tests
 - Hypoxemia
 - Radiologic evidence of extensive lung involvement
- Prednisone 0.5mg/kg per day
 - Initial dose for 1-2 weeks, then taper over 4-8 weeks
 - Dose and duration not formally studied
- Can accelerate initial recovery, but long-term outcome appears unchanged

Treatment for Nonfibrotic HP: Corticosteroids

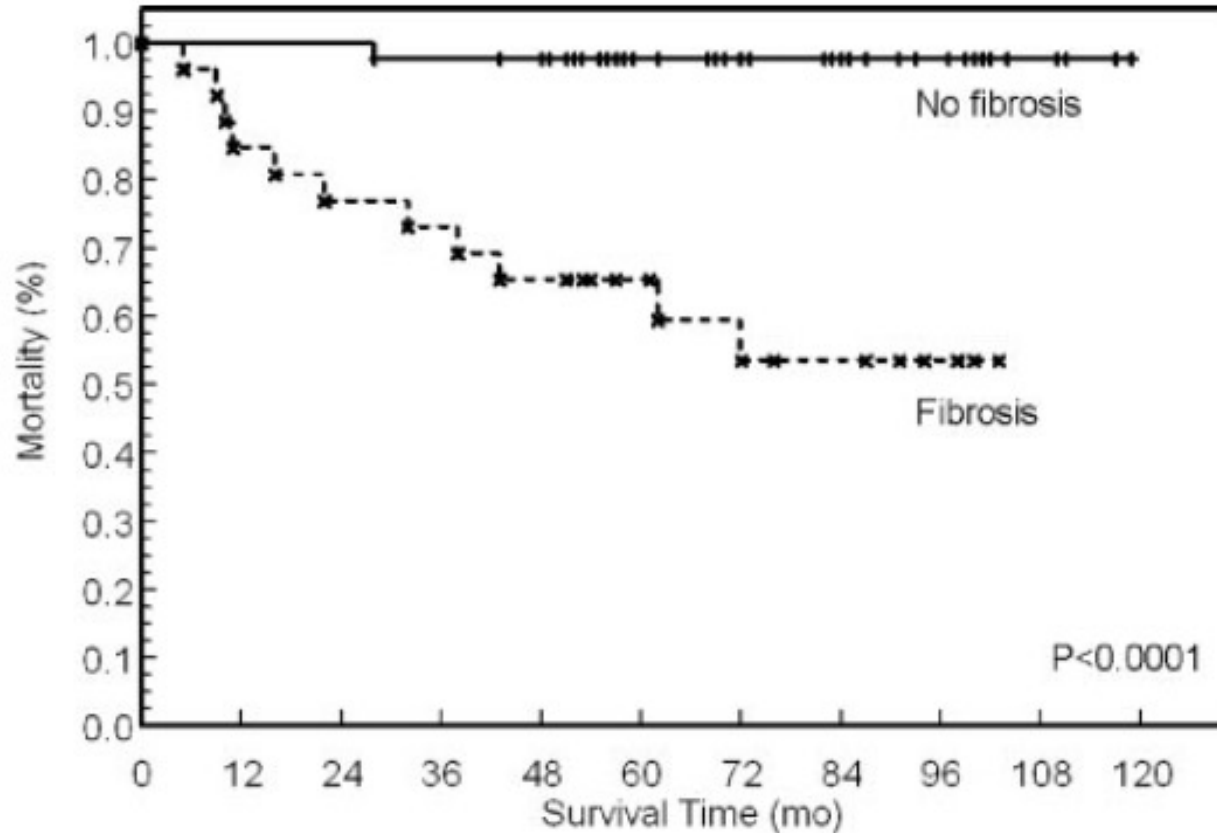
- 36 patients with acute farmer's lung randomly assigned to 8 weeks prednisolone vs. placebo
- Improvement at one month in DLCO but no significant differences in FVC, FEV₁ or DLCO found after that until study terminated at 5 years



Associated Exposures

- HP less frequent in smokers or ex-smokers
- Mechanisms unclear, may be related to nicotine dampening macrophage activation, decreasing lymphocyte proliferation and impairing T cell function
- Short term reduces inflammation, long term increases inflammation and fibrosis

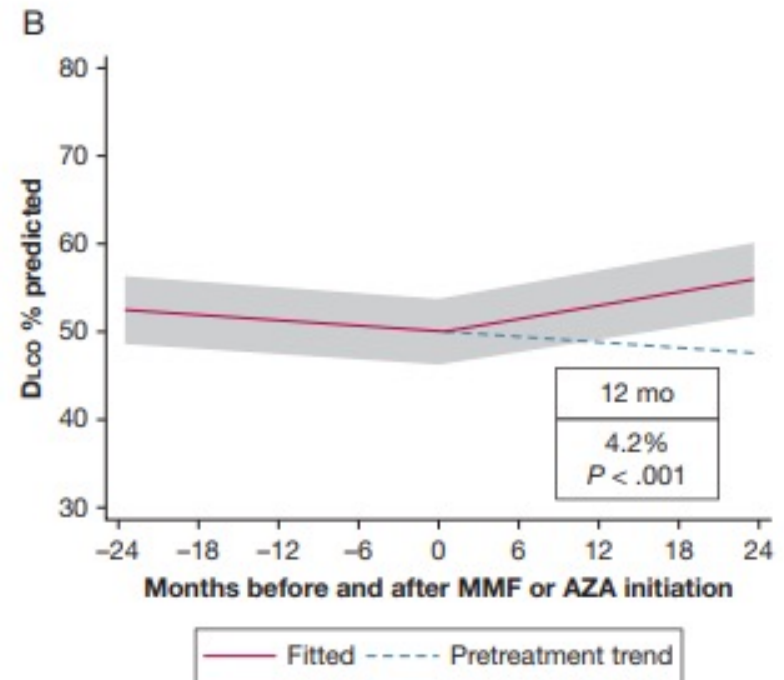
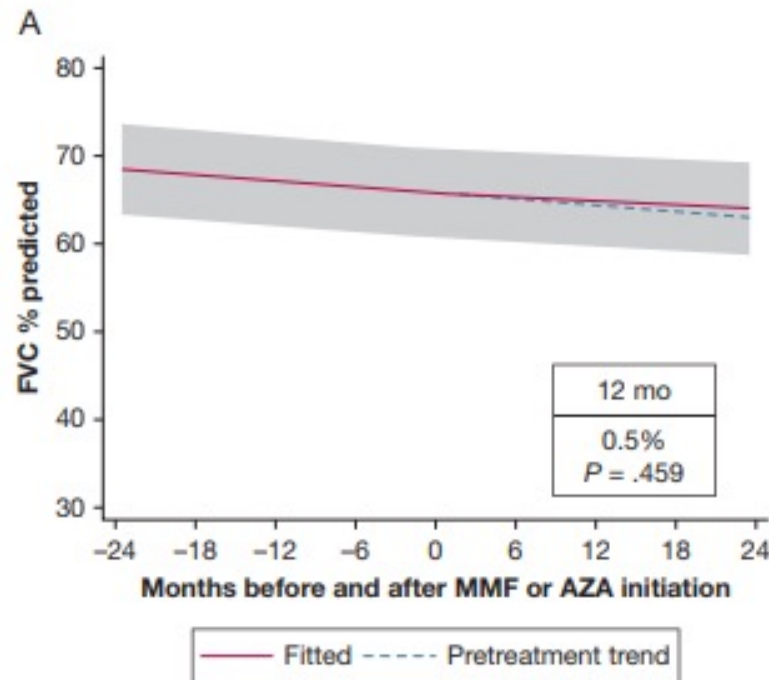
Fibrotic HP Associated with Worse Prognosis



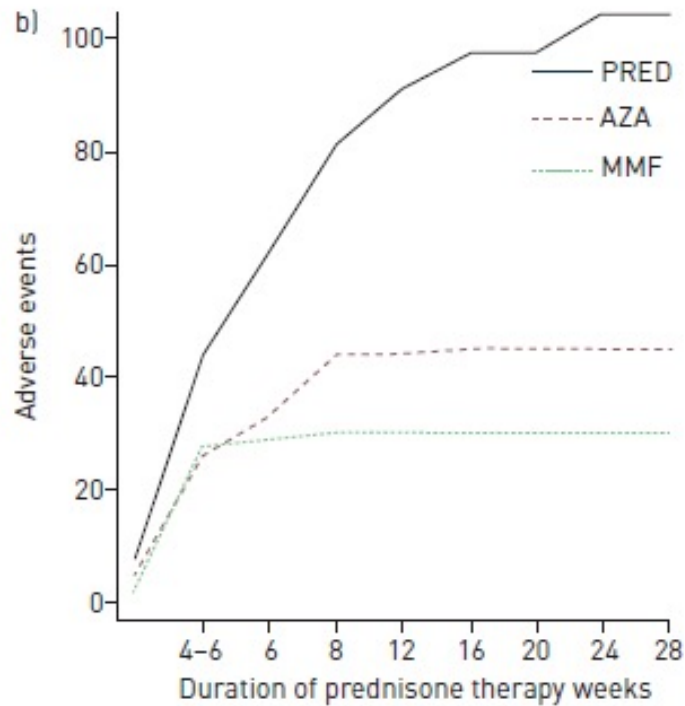
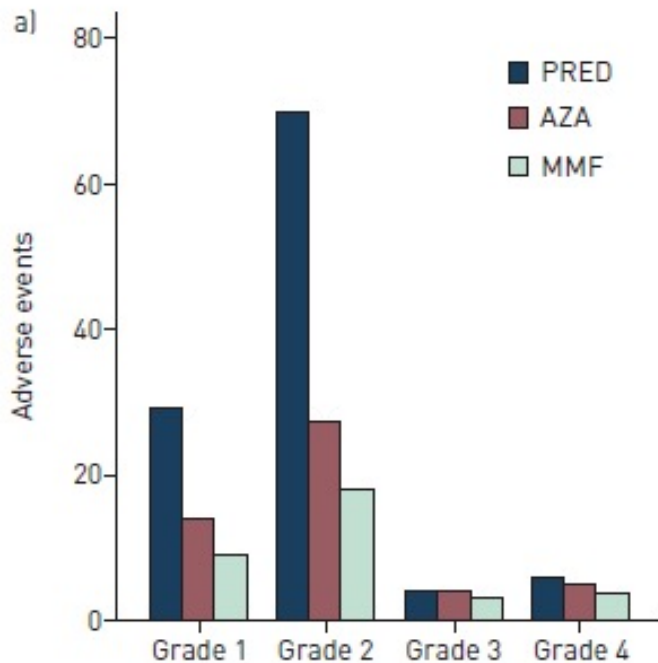
Presence and extent of fibrosis associated with worse survival

Treatment for Fibrotic HP: Immunosuppression

- No prospective studies of corticosteroids, but Prednisone 0.5mg daily x 4-8 weeks, tapering to 10mg by 3 months recommended
- MMP and AZA associated with improved lung function and reduction in prednisone dose in multicenter retrospective study

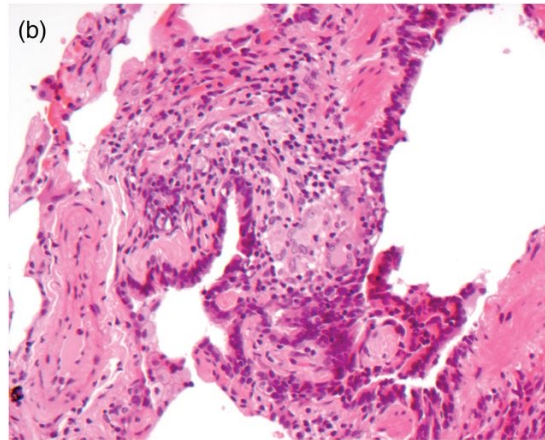
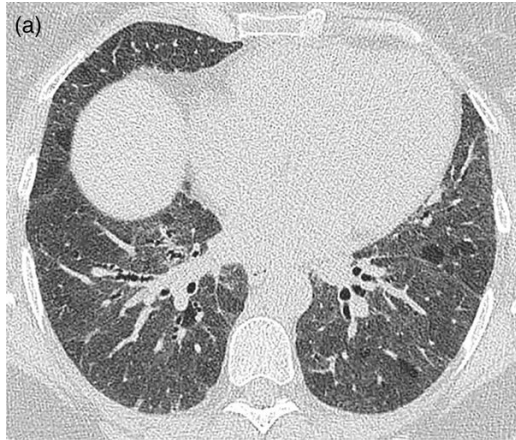


Immunosuppression for Fibrotic HP

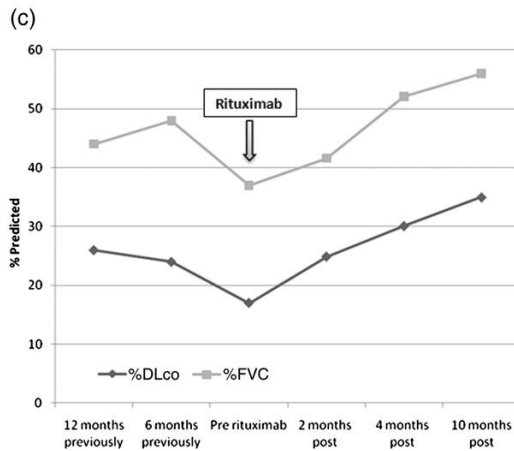


- Pts who required immunosuppression had increased mortality
- MMF or AZA associated with less treatment-emergent adverse events
- No difference in lung function decline or survival compared to prednisone alone

Treatment for Fibrotic HP: Rituxan

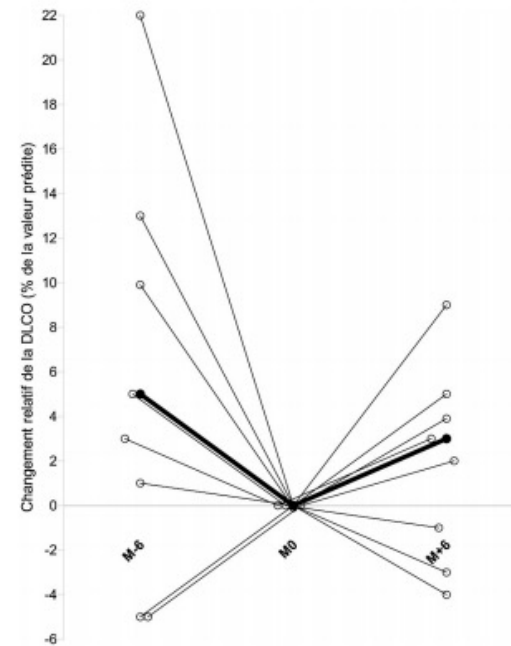
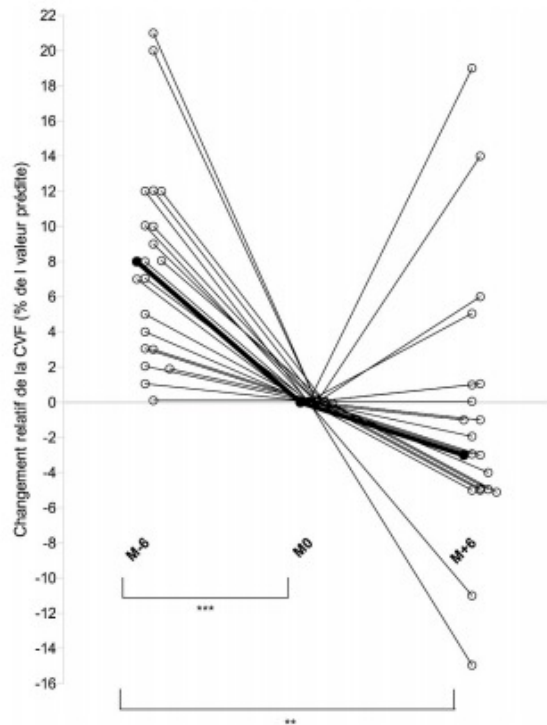


- Case report of cHP responsive to RTX
- IHC showed scattered CD20 follicular aggregates on background of CD3+ T cells
- No causative agent identified
- Failed steroids and Cytoxan
- Improved lung function after RTX



Treatment for Fibrotic HP: Rituxan

- Rituxan appears safe though response is variable
- 7/23 (30%) had stable/improved FVC 6 months af



ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi,
M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock,
M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown,
for the INBUILD Trial Investigators*

-
- Eligible with progression of ILD within prior 24 months despite treatment (FVC down 10%)
 - Excluded pts on AZA, cyclosporine, MMF, tacrolimus, RTX, cyclophosphamide, or steroids >20mg
 - At 6 months these meds could be added if clinical deterioration of ILD or CTD
 - HRCT eligibility = fibrosing lung disease >10% lung involvement

The following co-existing features were accepted:

- ground glass opacity
- upper lung or peribronchovascular predominance
- mosaic attenuation/air trapping
- centrilobular nodules

Nintedanib for Progressive Fibrosing ILD

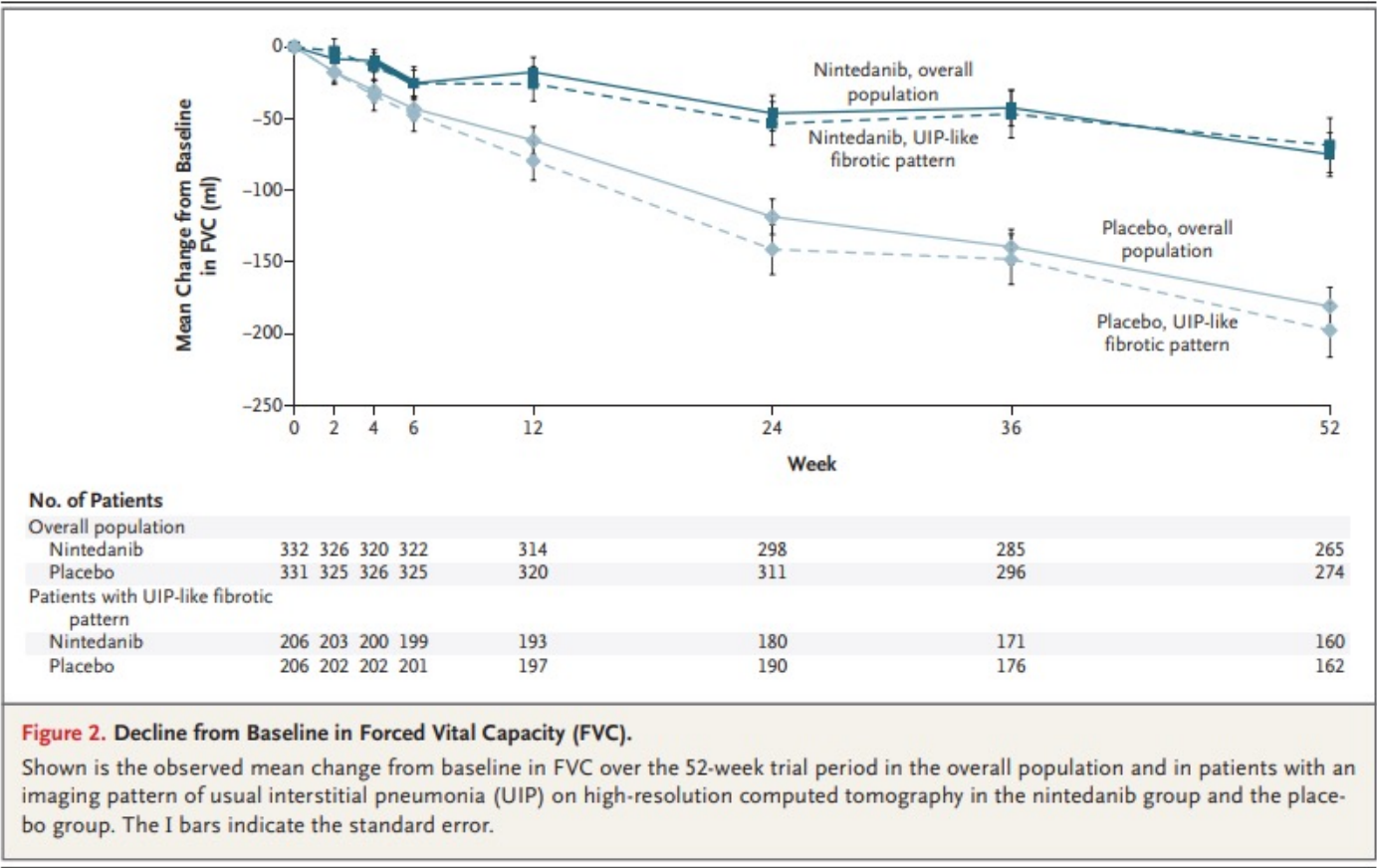


Figure 2. Decline from Baseline in Forced Vital Capacity (FVC). Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

Chronic HP Represented in Nintedanib Study

Section H: Clinical ILD diagnoses

Table S2: Clinical ILD diagnoses (grouped) in the overall population

	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

Take Home Points About HP

- Immune mediated lung disease triggered by variety of inhaled antigens in susceptible individuals
- Search for the offending inducer and eliminate it
- Immunosuppression may help non-fibrotic HP
- Some people develop progressive fibrosis, and anti-fibrotics may help in fibrotic HP
- Include fibrotic HP in the differential for a new ILD

Take Home Points About HP



FIND THE
BIRD!

*Goal to recognize HP in timely manner to potentially change disease course