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

Rachel S. Knipe, MD

May 2024

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

Massachusetts General Hospital
Harvard Medical School

Disclosures

- Discovery ILD Award (PI = Knipe, sponsored by Boehringer Ingelheim)

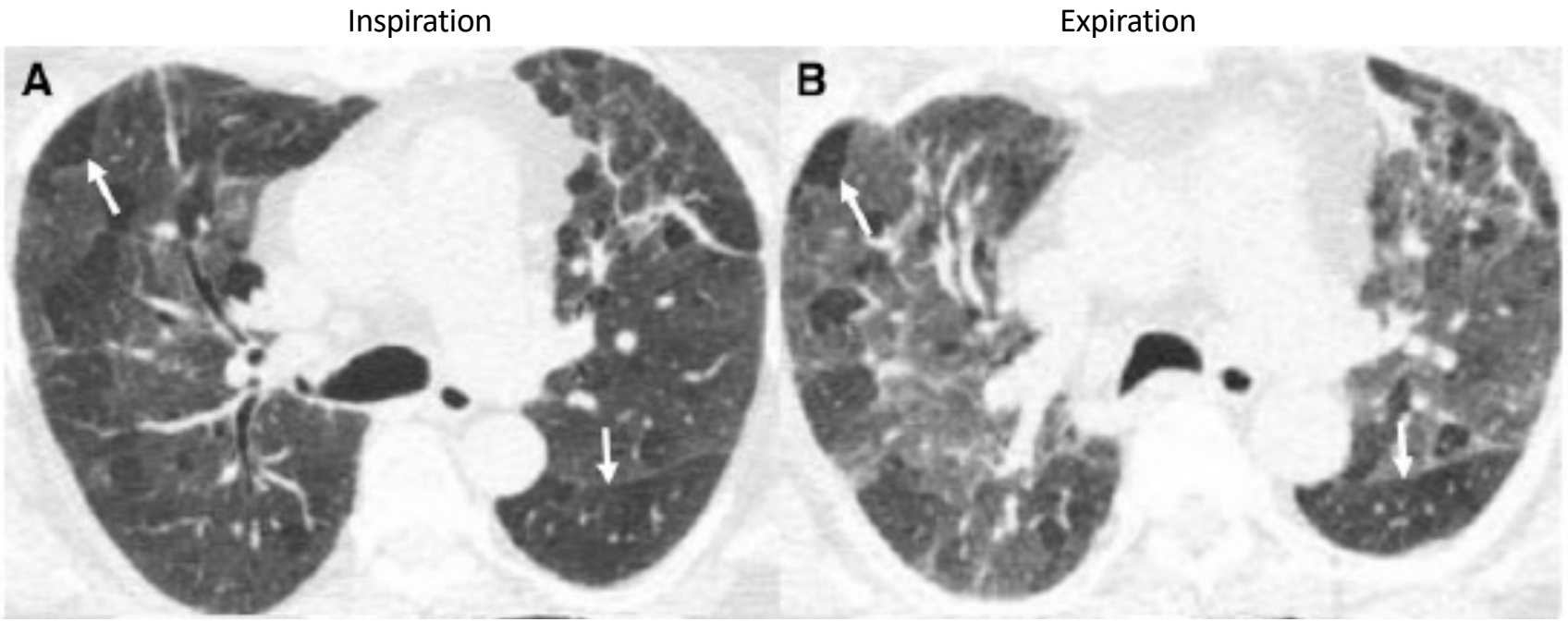
Outline

- Case presentation
- Introduction
- Pathogenesis
- Immunopathology
- Diagnosis
- Treatment

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

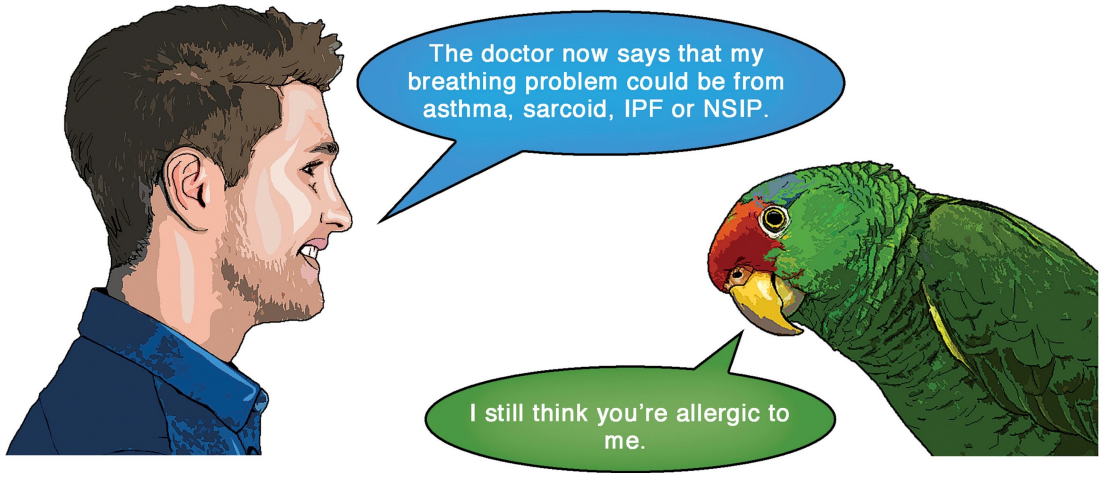
Case Presentation



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

Salisbury et al. AJRCCM 2017

Hypersensitivity Pneumonitis

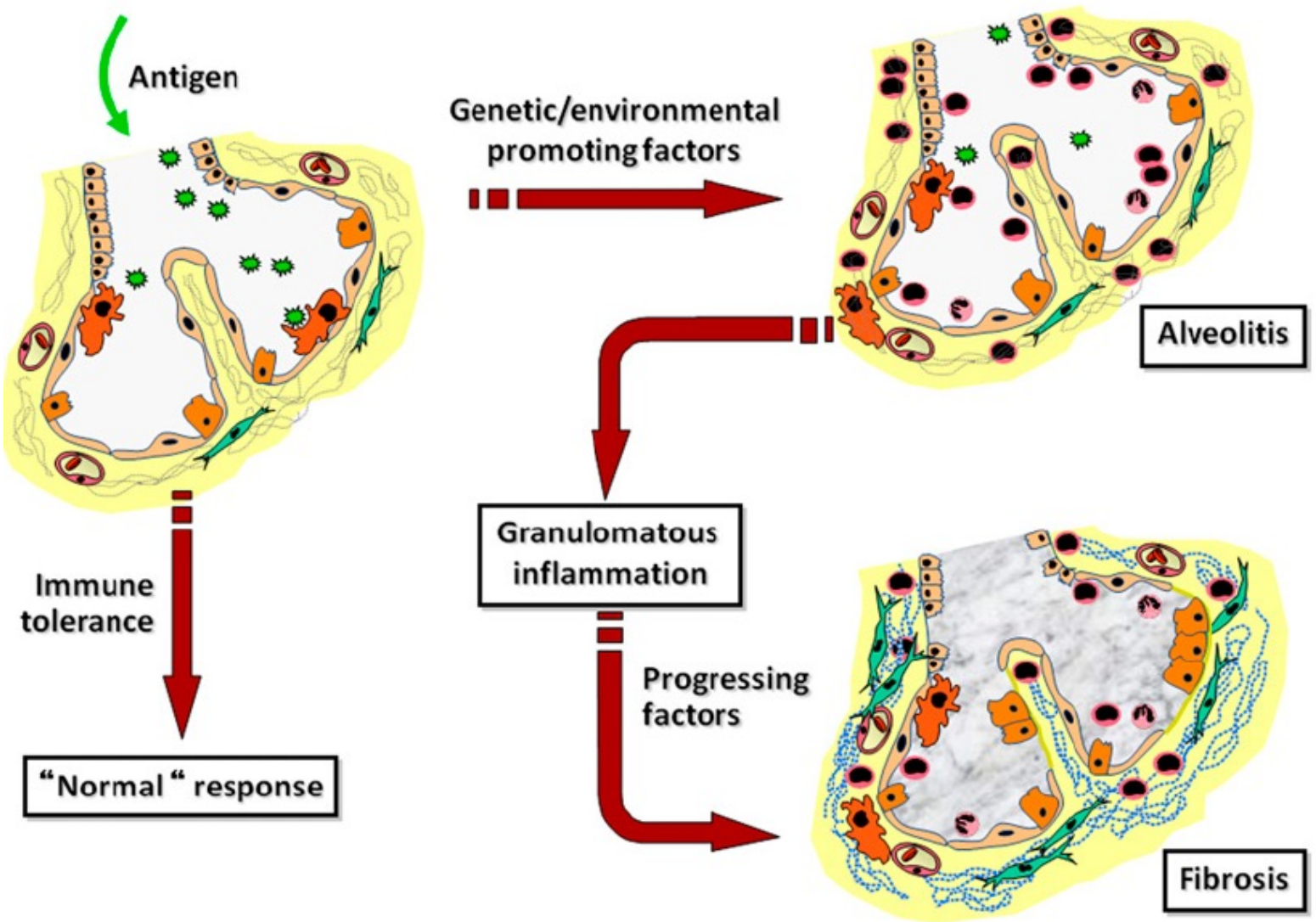


- Extrinsic allergic alveolitis
- Airway centered inflammation induced by an exaggerated immune response to an inhaled foreign substance
- Syndrome results from repeated exposure to variety of organic (mostly) particles
- Up to 30% have no identifiable exposure
- 2 hit hypothesis (antigen exposure +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

Selman, Pardo, King, AJRCCM 2012

Journal of Allergy and Clinical Immunology 2019 1431295-1301DOI: (10.1016/j.jaci.2018.09.040)

HP Pathogenesis



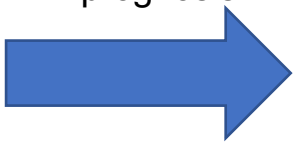
Selman et al. ARJCCM 2012

Hypersensitivity Pneumonitis: Categories

Historical Categories

- Acute — hours
- Subacute — weeks
- Chronic — months

Presence of fibrosis is primary determinant of prognosis



ATS Guidelines 2020

- Nonfibrotic
- Fibrotic

ATS Guidelines, AJRCCM 2020

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

Vasakova et al. AJRCCM 2019

Examples of HP Inducers

Antigen	Antigen source	HP variant
Bacteria		
Thermophilic actinomycetes	Mouldy hay and straw	Farmer's lung
Klebsiella oxytoca	Humidifiers	Humidifier's lung
Thermophilic actinomycetes	Sugar cane dust	Bagassosis
Mycobacteria		
Mycobacterium avium complex	Outdoor hot tubs	Hot-tub lung
Mycobacterium immunogenum	Metal-working fluid	Machine operator's lung
Fungi		
Absidia corymbifera	Mouldy hay and straw	Farmer's lung
Trichosporon cutaneum	Indoor households	Summer-type HP
Penicillium roqueforti	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 *Bacillus subtilis*	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

Costabel et al. Nat Rev 2020

Farming and Cattle Workers

- Farmer's lung one of most common forms of HP
- Main source of antigens is proliferation of thermophilic actinomycetes in hay or dust + humidity and heat
- Round bales of hat tend to have higher humidity and increased microbial growth
- *distinct from febrile, toxic reactions to inhaled mold dust (organic dust toxic syndrome ODTS), non immunologic 30-50x more common than HP

Cano-Jimenez Arch Bronco 2016

Ventilation and water-related

- Antigens from microorganisms that colonize
  - Forced air systems
  - Heated water reservoirs
  - Portable ultrasonic humidifiers
  - Cool-mist vaporizers
  - Swimming pools
  - Hot tubs, whirlpools, spas
  - Water damaged carpeting
  - Musical instruments
- Fungi (Penicillium, Aspergillus) or M. avium complex (hot tub lung)
- Hot tub lung = hypersensitivity to MAC, like HP, but some differences
  - Well formed granulomas

Agarwal et al. Respir Med 2006

Bird and Poultry

- HP can be induced by exposure to excreta and proteinaceous material on dust from pigeons, parakeets, canaries, chickens, turkey, other fowl
- Aerosol spread from dropping by a vent or clothes dryer, heating vents from a garage
- Exposure to feather pillows, down comforters
- Worse prognosis than Farmer's Lung
  - Higher dose and duration of exposure
  - Persistence of antigen

Chan et al. Clin Rev Allergy Immunol 2012
Tsutsui et al. Annals ATS 2015

Veterinary work and animal handling

- Laboratory workers lung (urine, serum)
- Pelts of rats and gerbils
- Furrier’s lung from exposure to animal pelts in the process of sewing furs

Grain and flour processing

- While processing grains, colonization can occur
  - Sporobolomyces
  - Aspergillus
  - Sitophilus granaries
- Antigens are easily aerosolized, and then inhaled

Lumbar milling, construction

- Trees and plants can become colonized with mold during processing
- Antigens become aerosolized, and easily inhaled

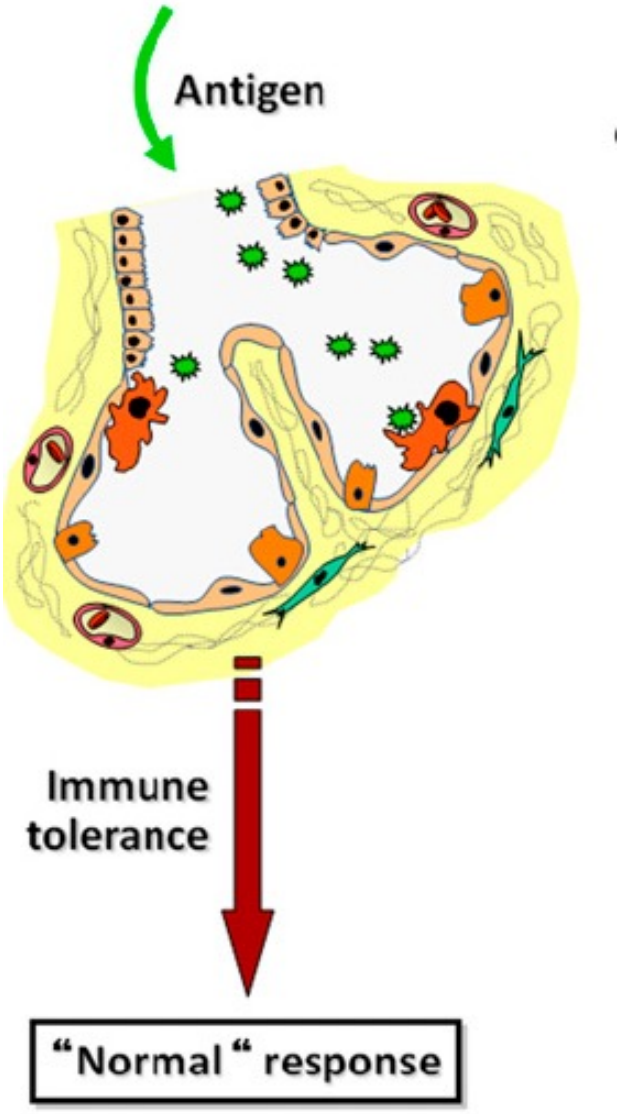
Braun et al. J Occup Med Toxicol 2021

Plastic manufacture, Painting

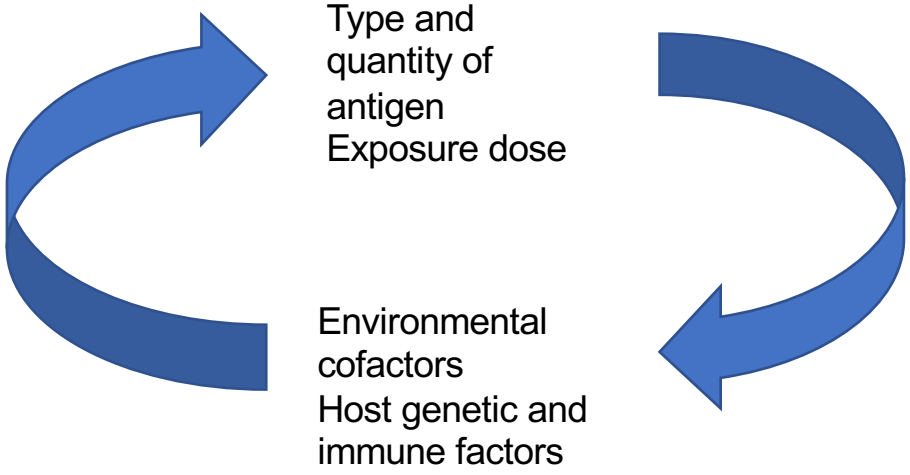
- Some HP inducers are synthetic
- Occupational exposure to aerosolized of gas phase organic chemicals can cause HP
- 12 workers developed HP exposure linked to metal working fluid with likely bacterial contamination (mist) in 2003-2004 in UK

Robertson et al. Thorax 2007

Why do only some people develop HP?

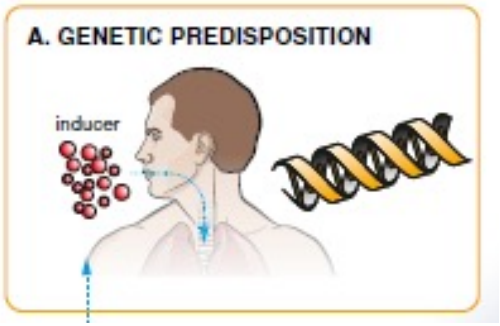


Antigen is not enough!



Selman et al. ARJCCM 2012

Genetic Susceptibility to HP

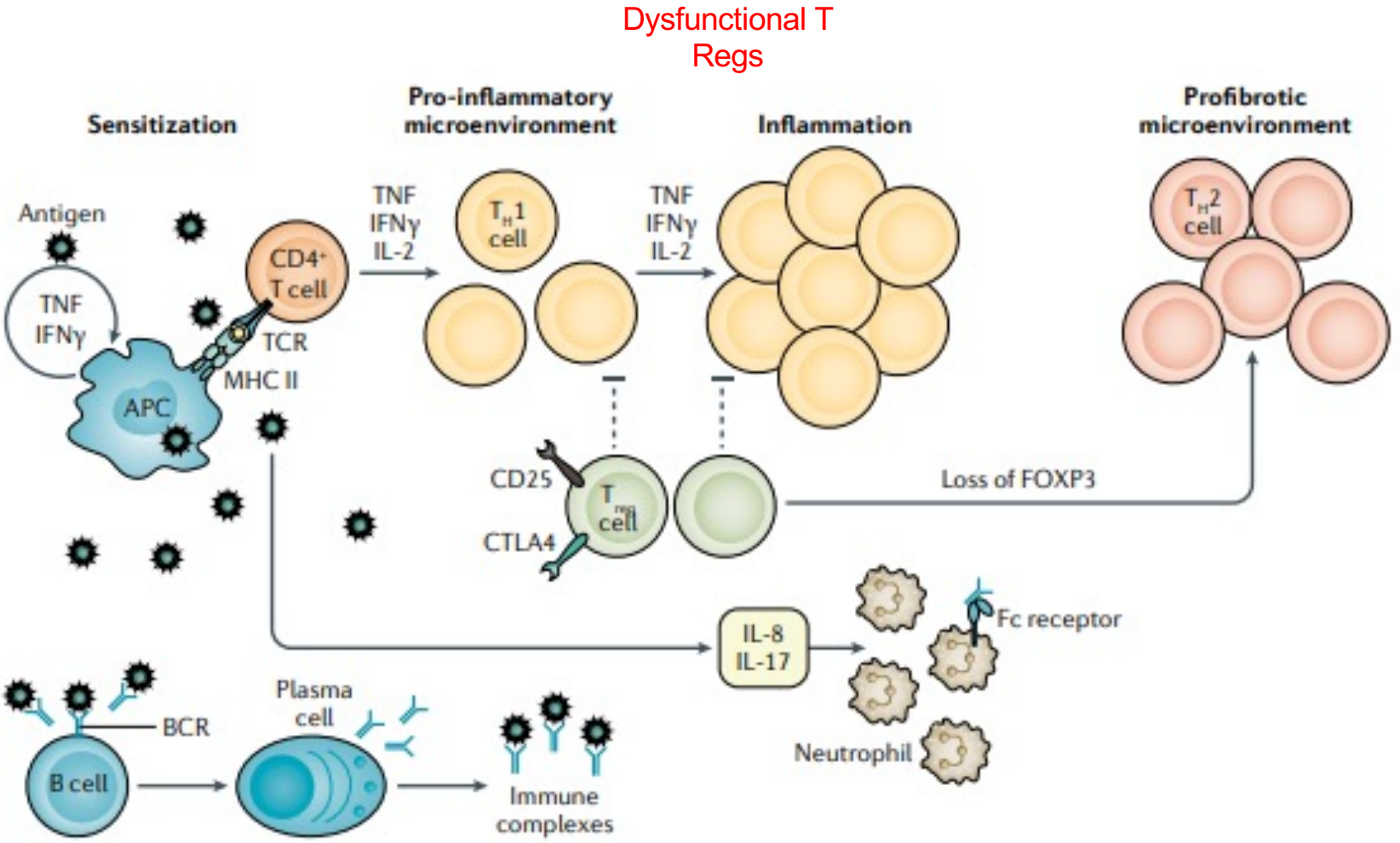


Genes and Genetic Variants	Population Race or Nationality	First Author (Year) (Reference)
MHC II polymorphisms		
HLA-DR3	White	Rittner (1983) (63)
HLA-DR7	Mexican	Selman (1987) (64)
HLA-DQ3	Japanese	Ando (1989) (65)
HLA-DRB1*04	Mexican	Falfán-Valencia (2014) (66)
MHC II haplotypes		
Increased DRB1*1305-DQB1*0301; 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)

- 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

Vasakova et al. AJRCCM 2019

Immunopathology of HP



Costabel et al. Nat Rev 2020

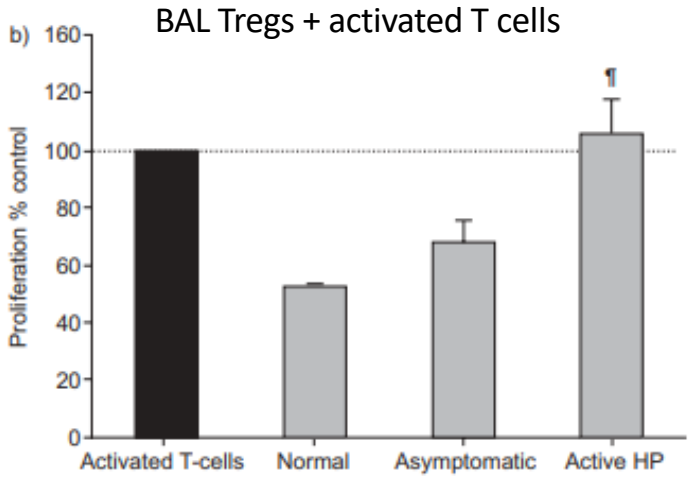
Immunopathology of HP

- 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 enha 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



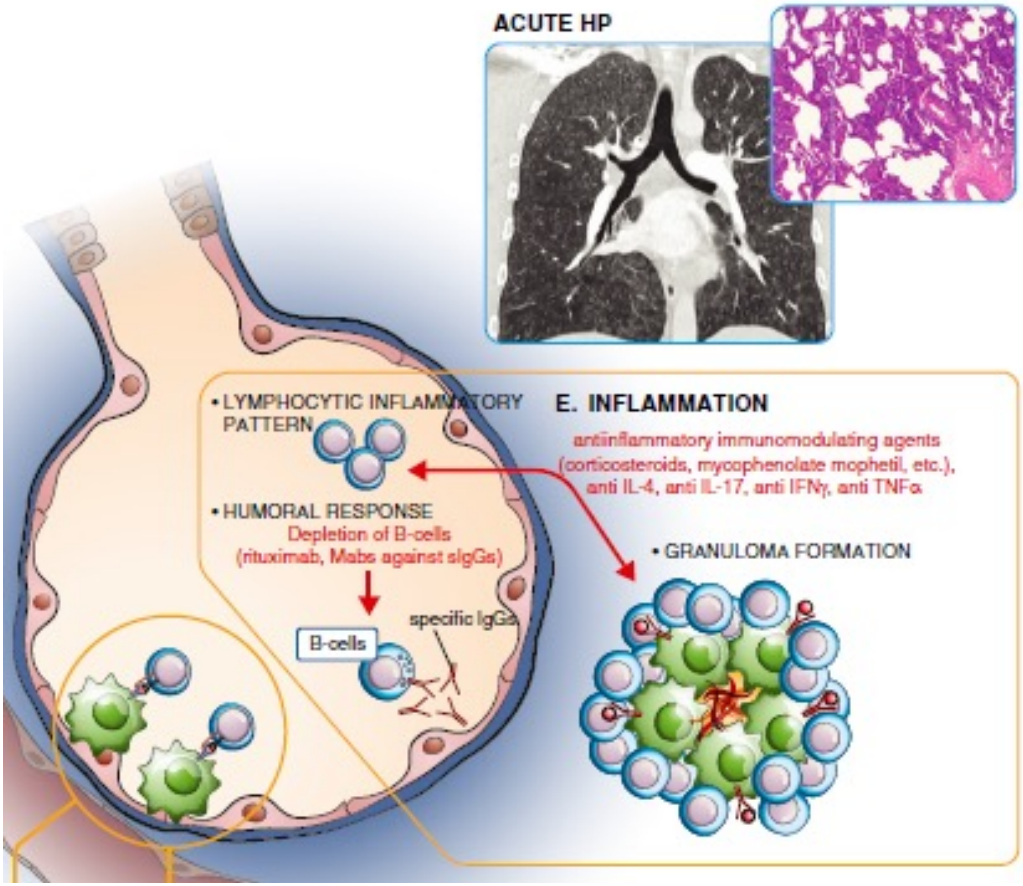
Berrera et al. AJRCCM 2008
Girard et al. ERJ 2011

Associated Exposures

- Cigarette Smoking decreases risk of HP
  - Once disease established, outcomes similar
- May reflect decreased immune response to inhaled antigens
  - Possibly related to nicotine dampening macrophage activation, decreasing lymphocyte proliferation and impairing T cell function
- Association appears to be reversible, no difference in former smokers

McSharry et al. Clin Allergy 1985
Furuiye et al. J Med Dent Sci 2007
Selman et al. AJRCCM 2012

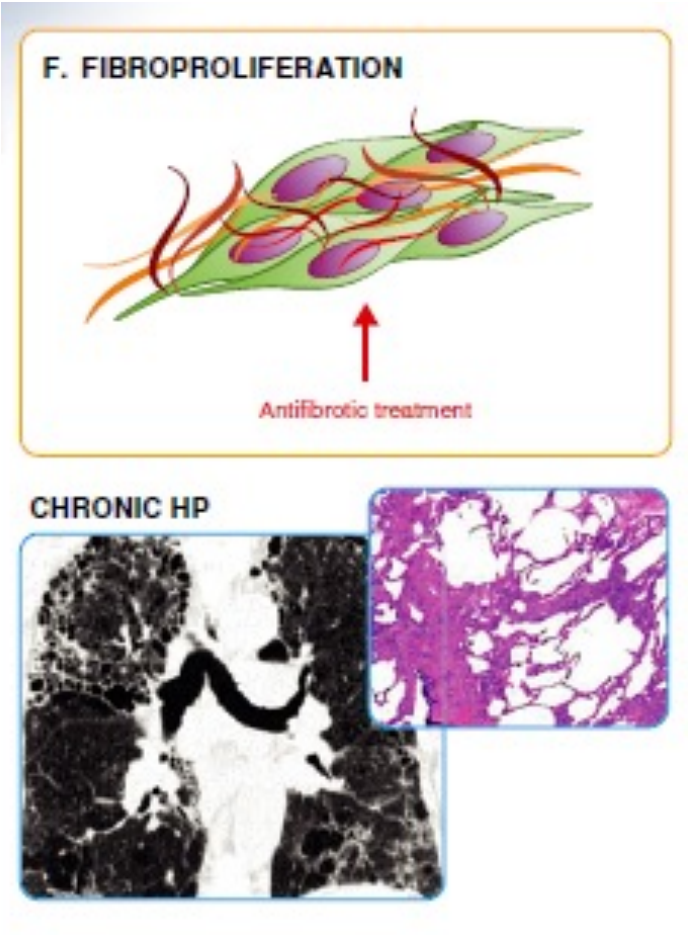
Inflammation Abundant in Nonfibrotic HP



- 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

Vasakova et al. AJRCCM 2019

Some Patients Develop Fibrotic 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

Vasakova et al. AJRCCM 2019

Diagnosis of HP

- In the context of respiratory sxs (dyspnea, cough), 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

Vasakova et al. AJRCCM 2017

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)

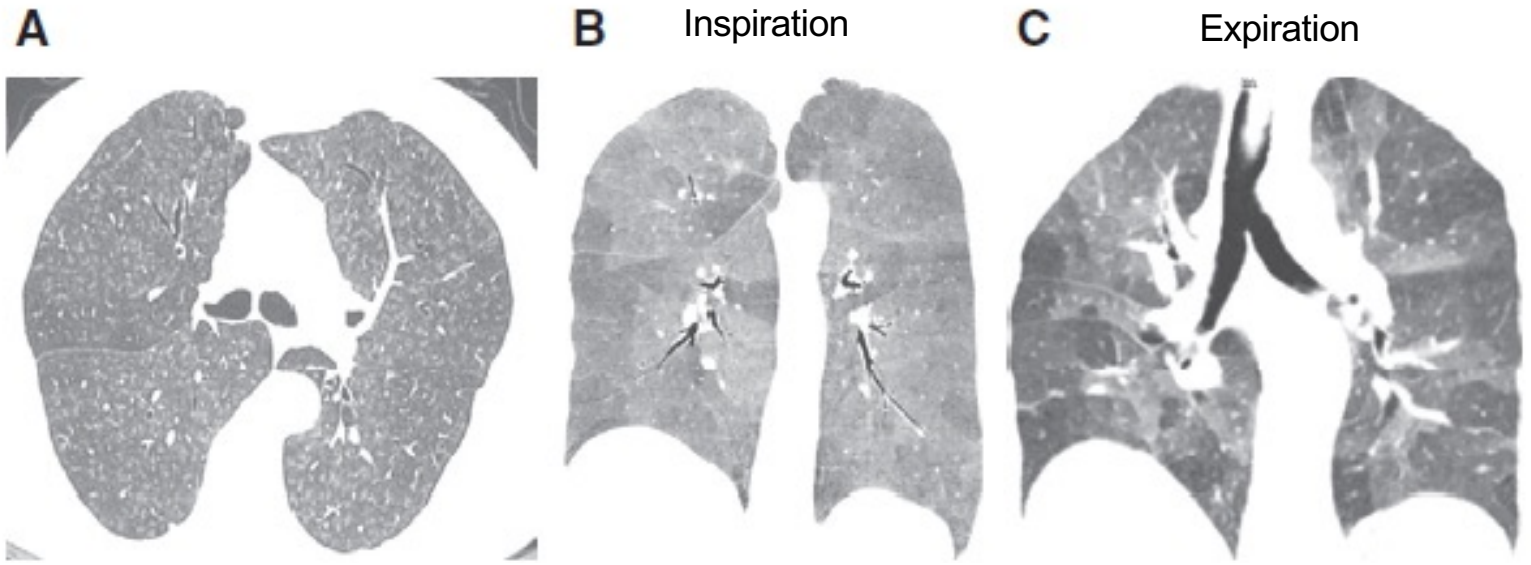
Vasakova et al. AJRCCM 2017

Diagnosis: Evidence of Exposure

- Antigen specific serum IgG antibodies
  - Only markers of exposure 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
- Skin testing not helpful (IgE rather than IgG)

Lacasse et al. AJRCCM 2003

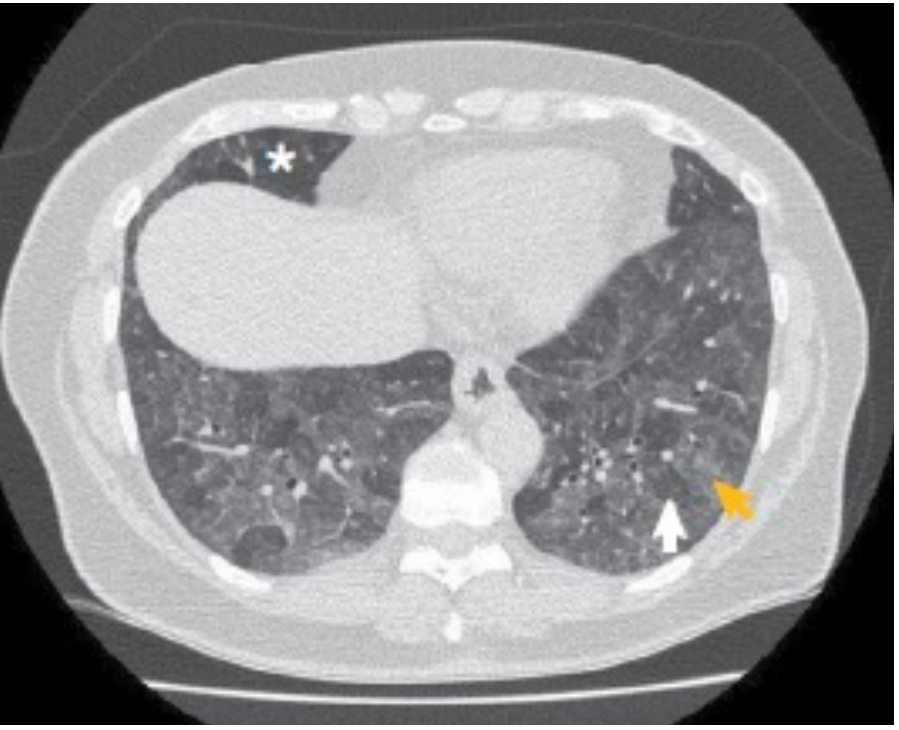
Radiology of Nonfibrotic HP



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

ATS Guidelines, AJRCCM 2020

Radiology of HP



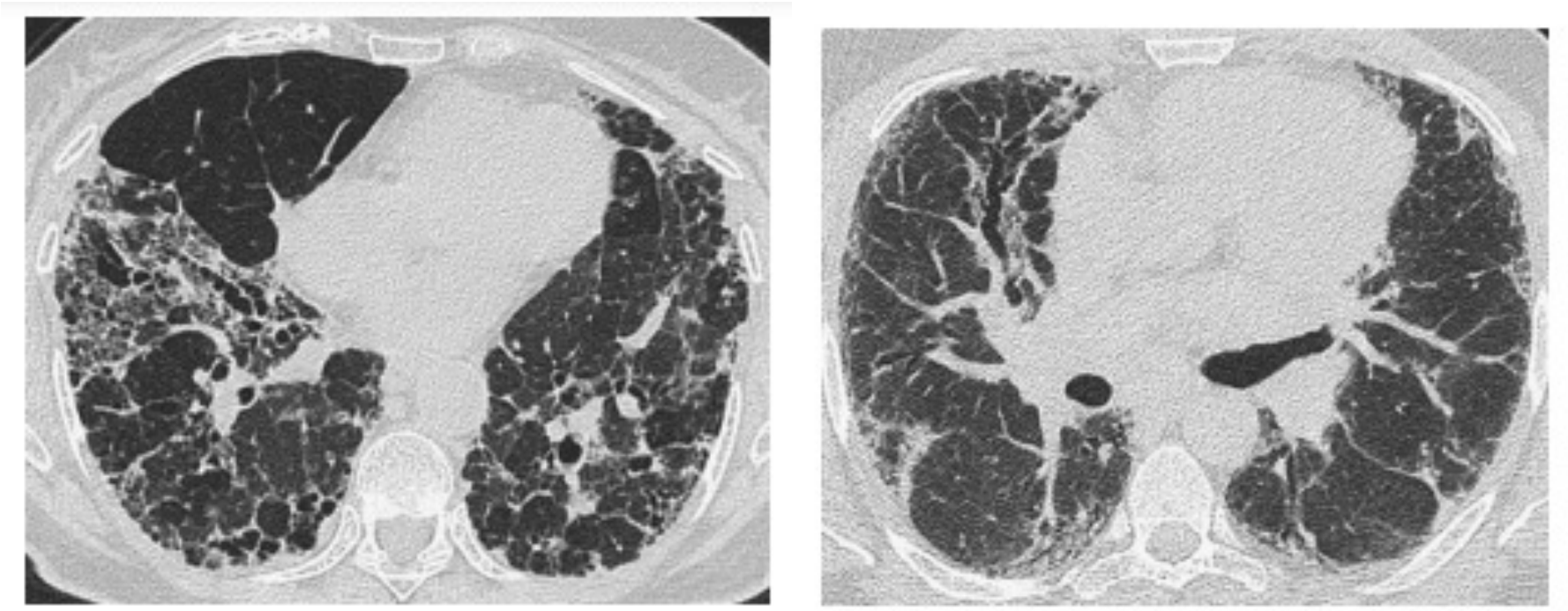
3 density pattern “headcheese sign”

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

Costabel et al. Nat Rev 2020

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

Walsh et al. Eur Radiol 2012

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 peribroncho-vascular distribution; usually bilateral, with relative sparing of the lower lung zones

Costabel et al. Nat Rev 2020

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 exposed 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%)

Patolia et al. Annals ATS 2020
Costabel et al. Nat Rev 2020

Diagnosis: Tissue Sampling

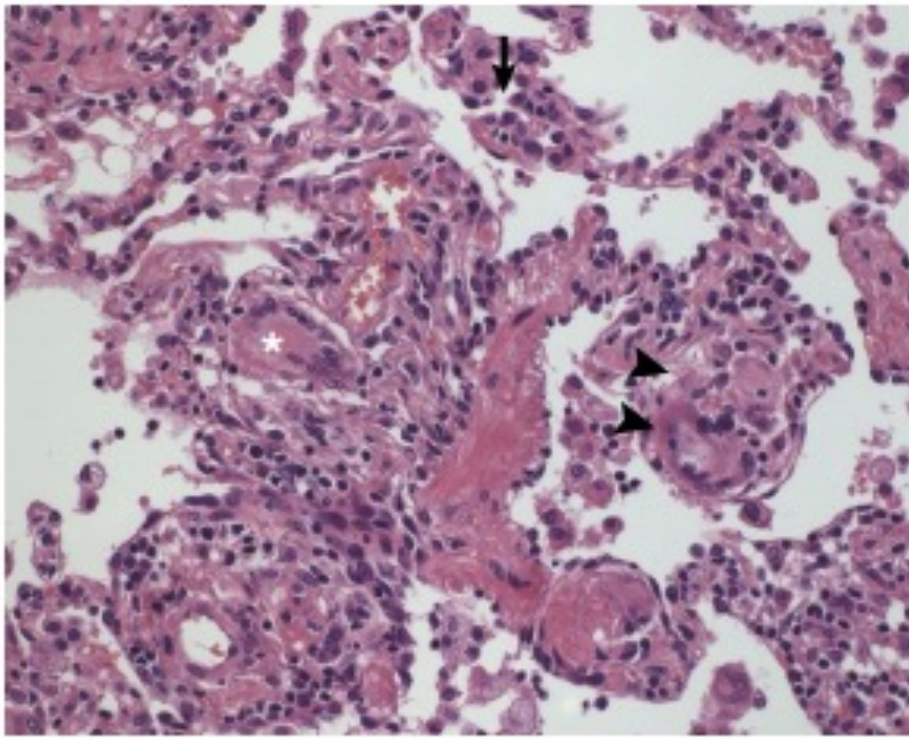
- **Transbronchial Biopsy**
  - ATS Guidelines recommend TBBx for diagnosing nonfibrotic HP > fibrotic HP based on higher yield with more diffuse disease
    - May be due to higher yield of granulomas in nonfibrotic HP
  - Diagnostic yield only ~50% but those pts were spared lung biopsy

- **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
  - Most helpful when other ILDs are on the differential (IPF)

ATS Guidelines, AJRCCM 2020

Pathology of Nonfibrotic HP



H&E, 100x

Typical histopathogical features of HP:

1. Bronchiolitis (lymphocyte predominate)

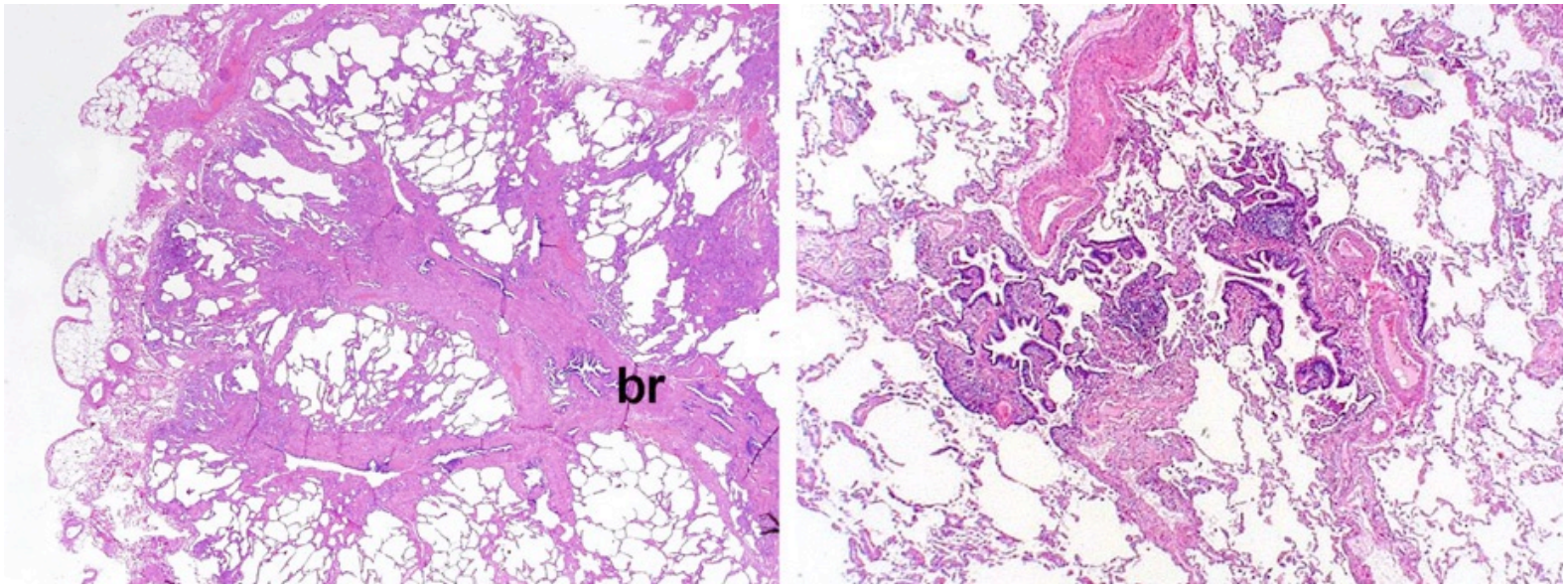
2. Pneumonitis (cellular interstitial infiltrate) (arrow)

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

Costabel et al. Nat Rev 2020

Pathology of Fibrotic HP



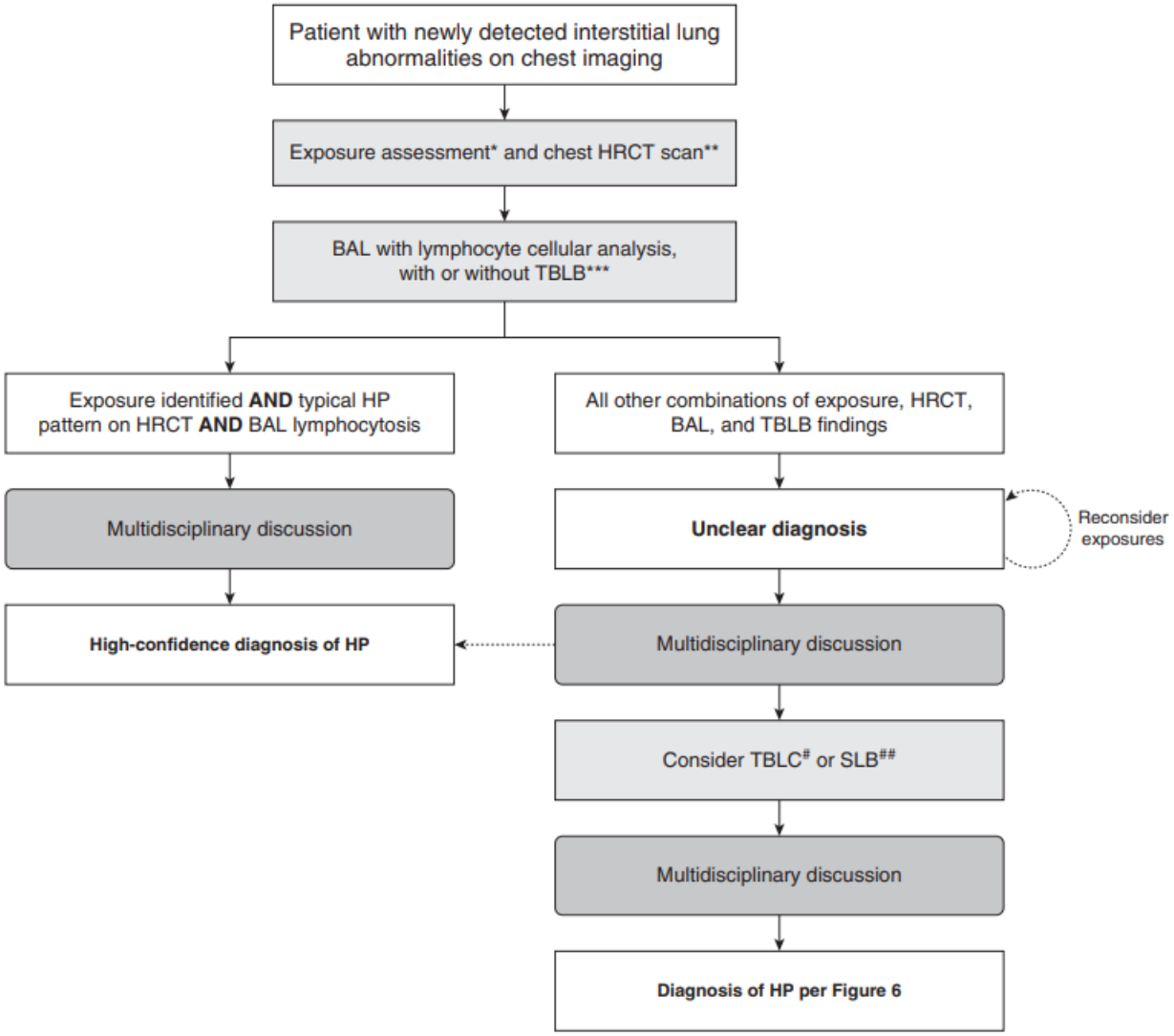
H&E, 20x

Typical histopathogical features of HP:

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

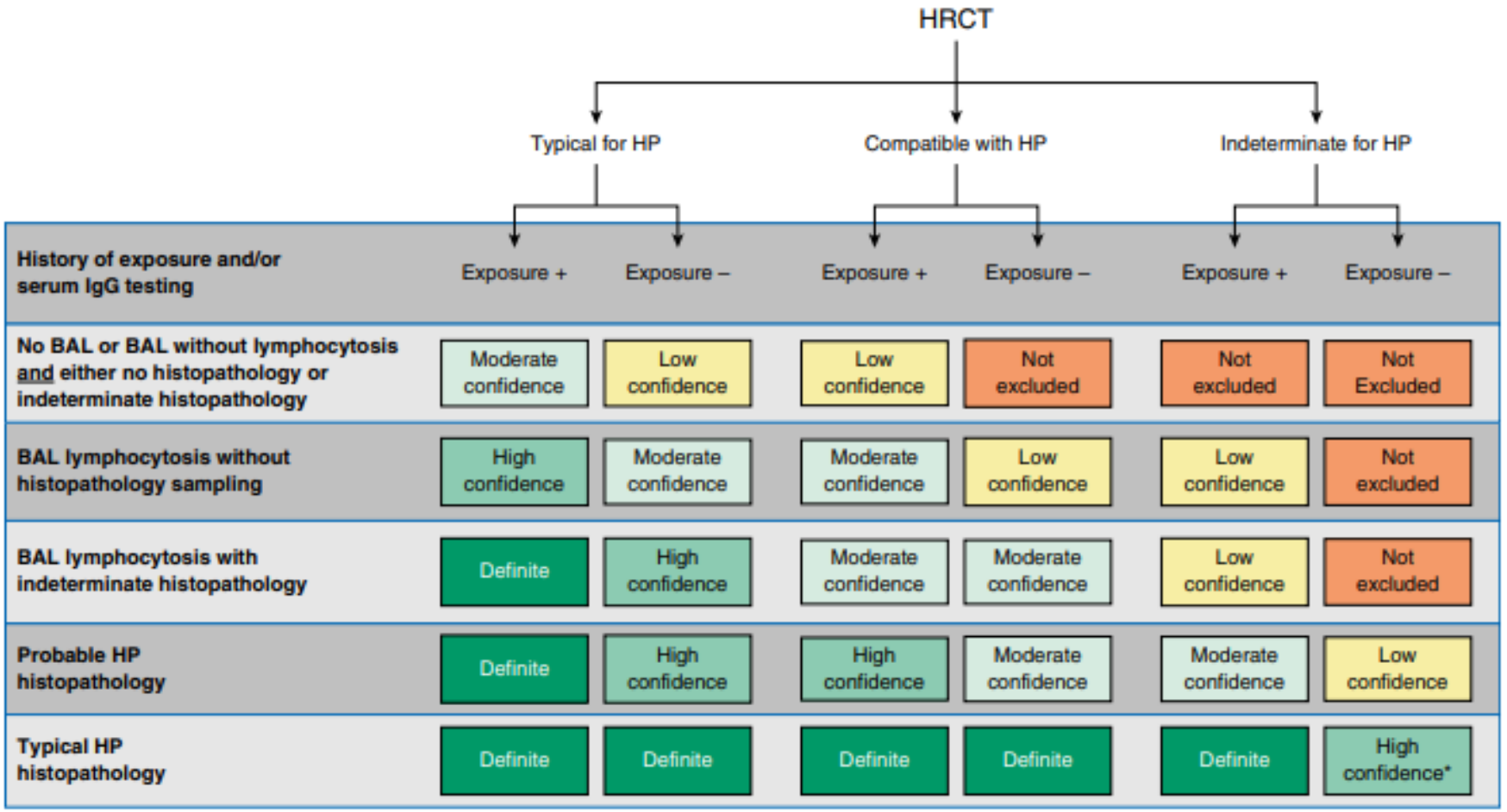
Vasakova et al. AJRCCM 2017

ATS Diagnostic Algorithm



ATS Guidelines, AJRCCM 2020

ATS Diagnostic Algorithm



ATS Guidelines, AJRCCM 2020

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 30% cases inducer is never found

Fernandez Perez Chest 2013
Craig Ann Allergy 1992

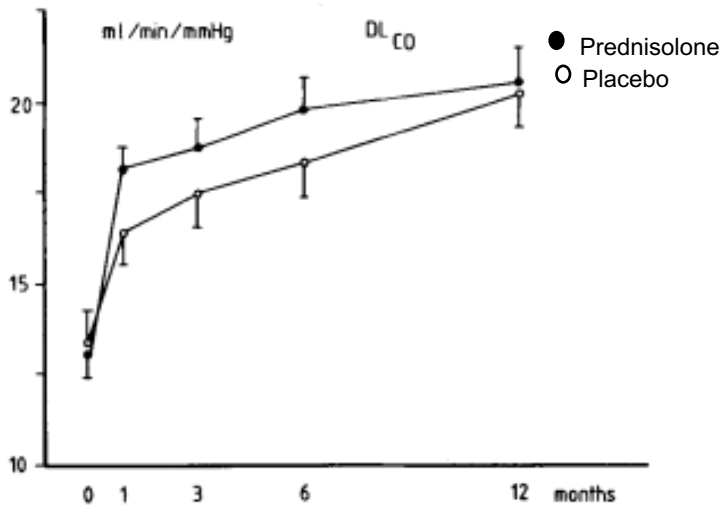
Treatment for Nonfibrotic HP: Corticosteroids

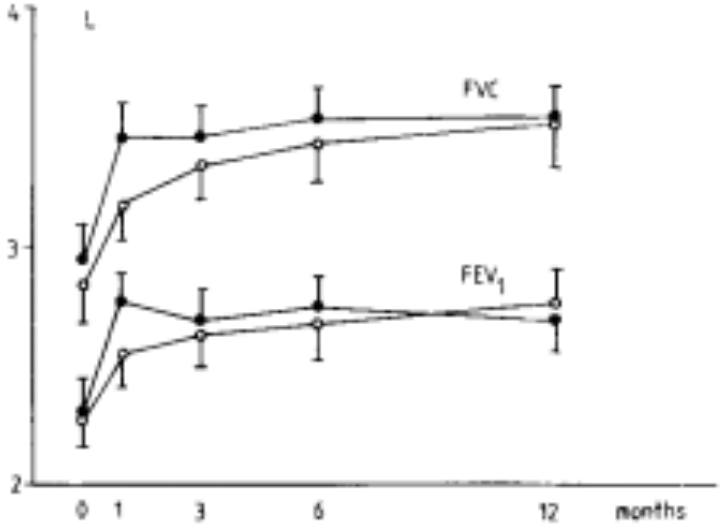
- If avoidance alone is insufficient, consider steroid course
  - Persistent symptoms (dyspnea, cough, fatigue, weight loss)
  - Abnormal lung function tests
  - Hypoxemia
  - Radiologic evidence of extensive lung involvement
- Prednisone 0.5mg/kg per day
  - Initial dose for 1-2 weeks, then taper over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

Vasakova et al. AJRCCM 2017
Salisbury et al. AJRCCM 2017

Treatment for Nonfibrotic HP: Corticosteroids

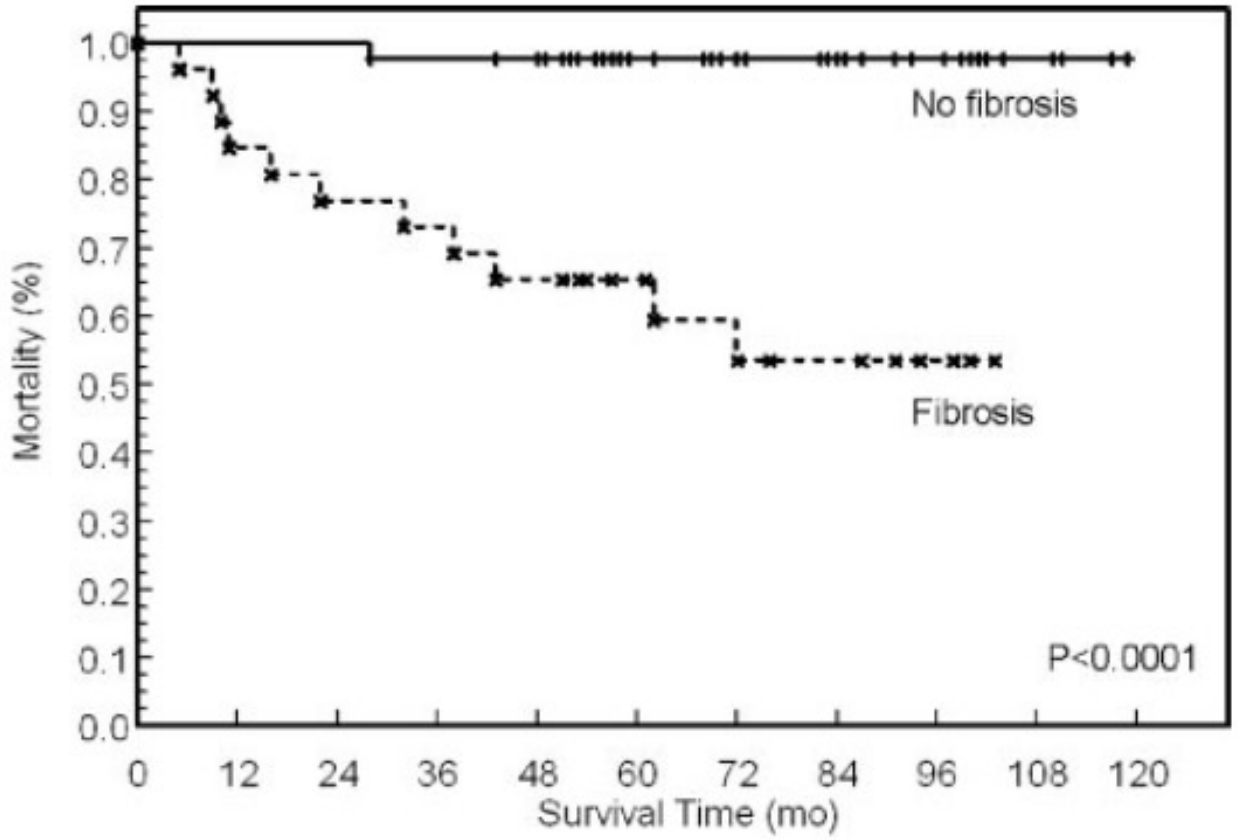
- 36 patients with acute farmer's lung randomly assigned to 8 weeks prednisolone vs. placebo
- Improvement at one month in DLCO but no significant differences in FVC, FEV1 or DLCO found after that until study terminated at 5 years





Kokkarinen et al. Am Rev Respir Dis 1992

Fibrotic HP Associated with Worse Prognosis



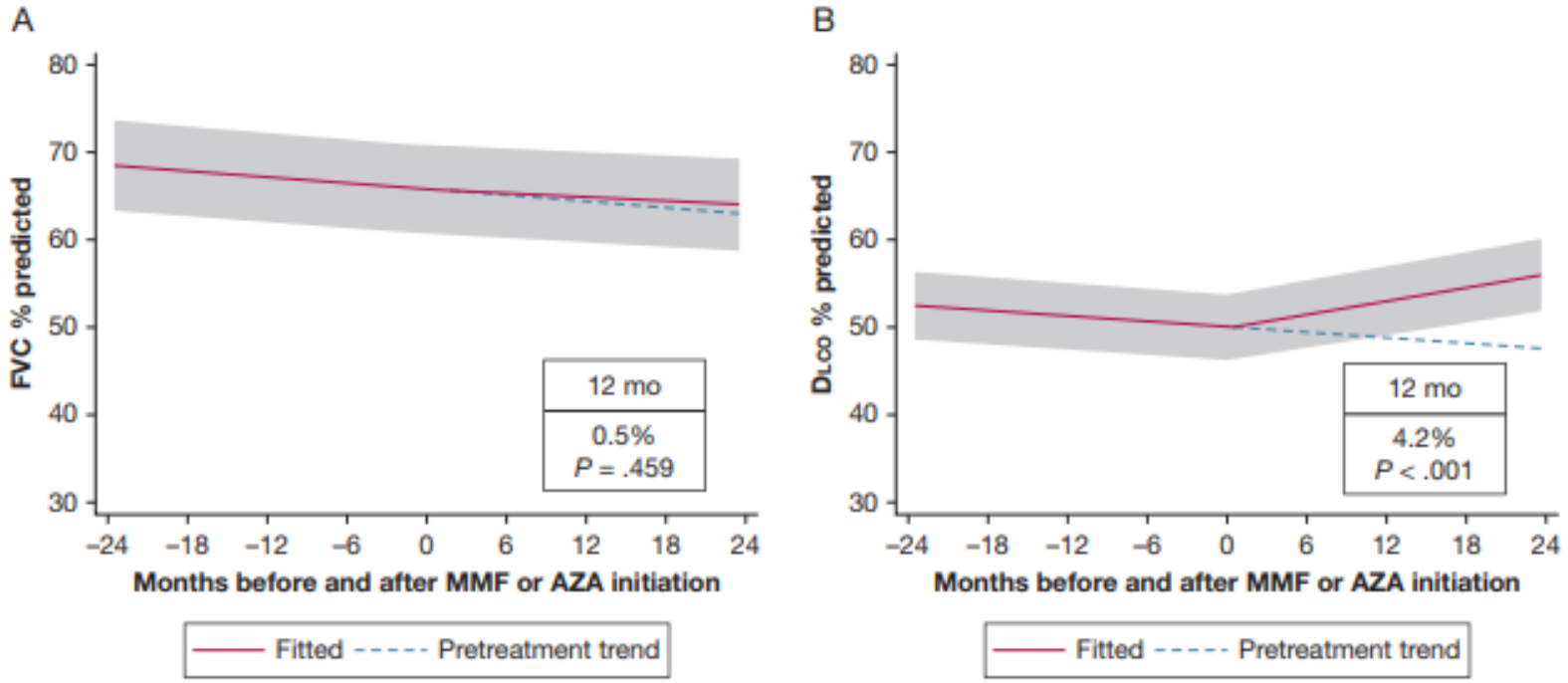
Presence and extent of fibrosis associated with worse survival

Hanak et al. *Chest. 2008*.

Treatment for Fibrotic HP: Immunosuppression

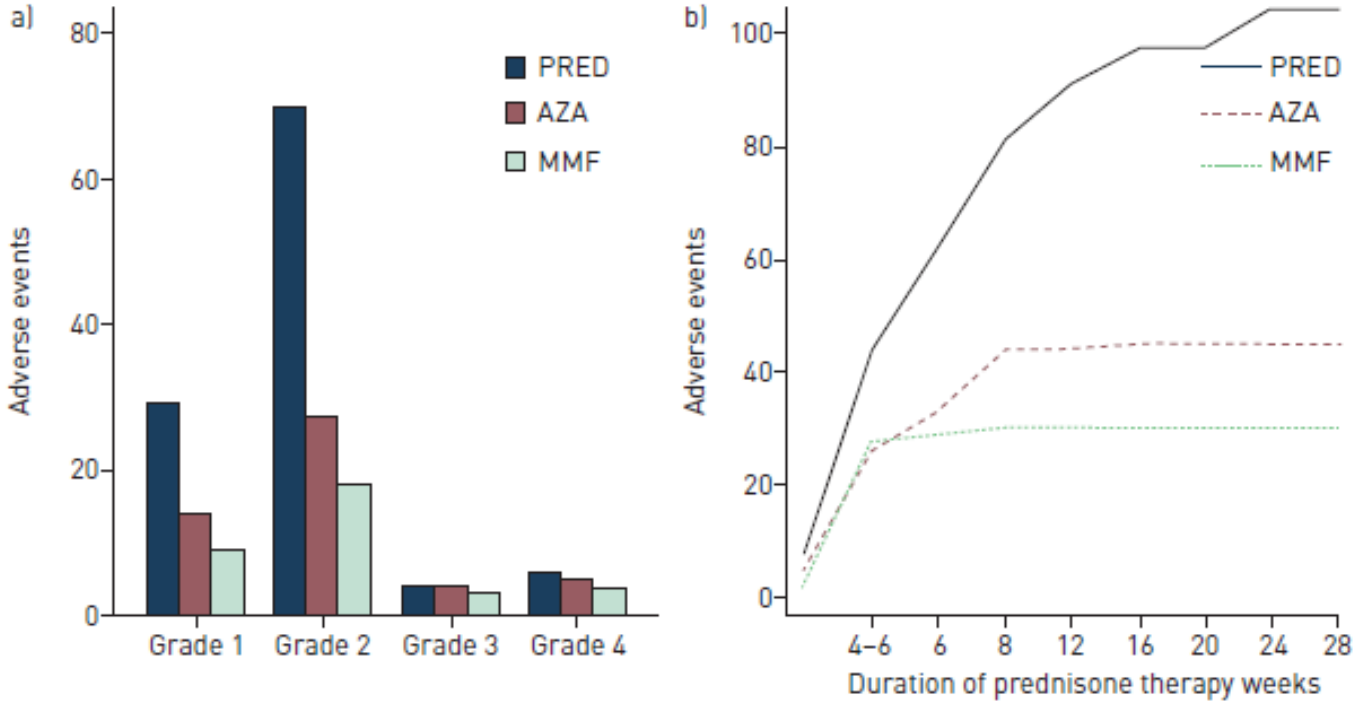
- No prospective studies of corticosteroids, but Prednisone 0.5mg daily x 4-8 weeks, tapering to 10mg by 3 months recommended

- MMP and AZA associated with improved lung function and reduction in prednisone dose in multicenter retrospective study



Morisset et al. Chest 2017

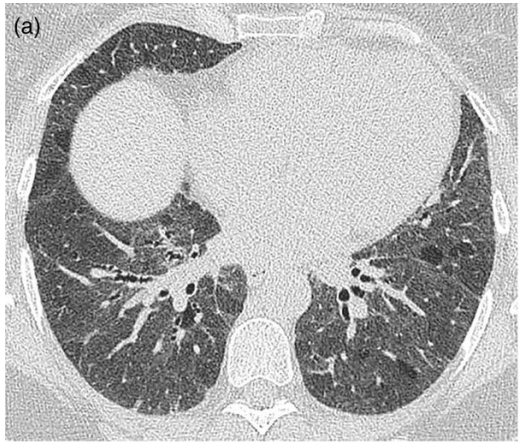
Immunosuppression for Fibrotic HP

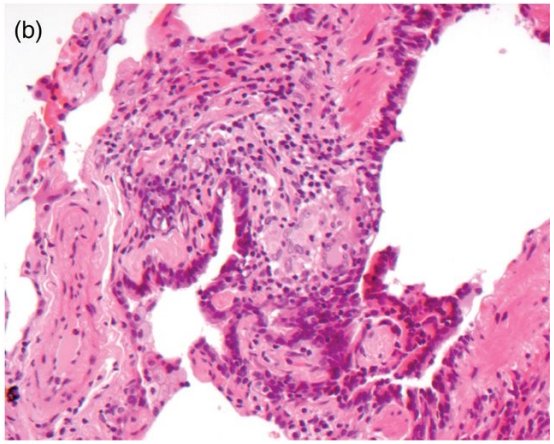


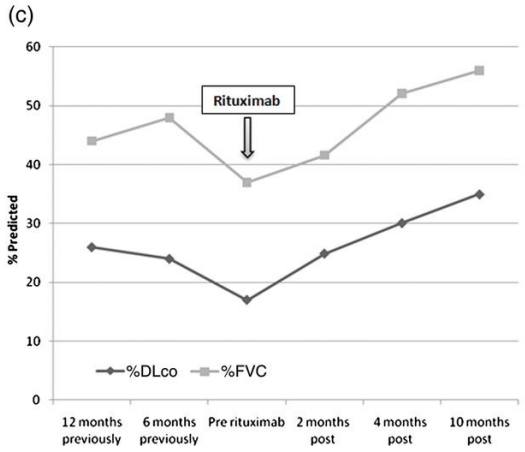
- Pts who required immunosuppression had increased mortality
- MMF or AZA associated with less treatment-emergent adverse events
- No difference in lung function decline or survival compared to prednisone alone

Adegunsoye et al. ERJ 2017

Treatment for Fibrotic HP: Rituxan





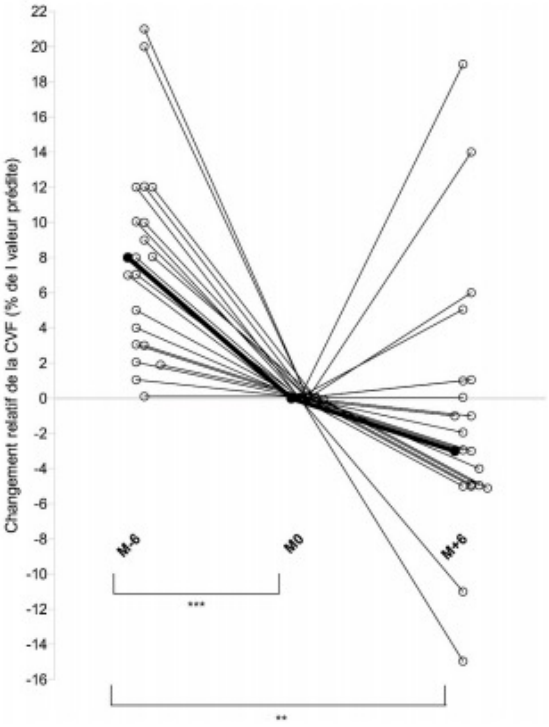


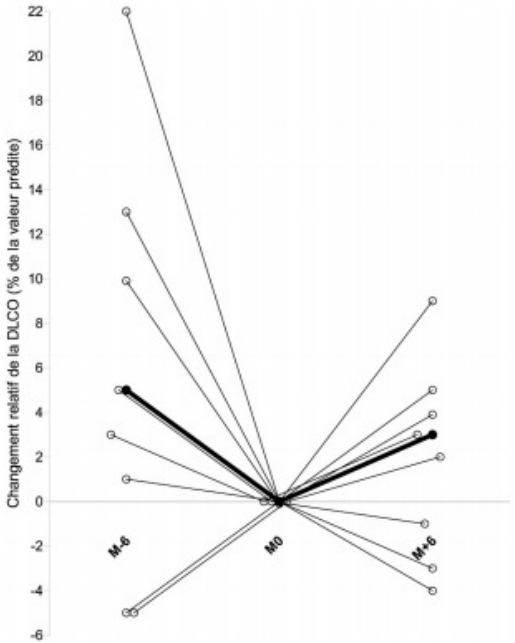
- Case report of cHP responsive to RTX
- IHC showed scattered CD20 follicular aggregates on background of CD3+ T cells
- No causative agent identified
- Failed steroids and Cytoxan
- Improved lung function after RTX

Lota et al. Thorax 2013

Treatment for Fibrotic HP: Rituxan

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





Ferreira et al. Respiratory Medicine 2020

The NEW ENGLAND JOURNAL of MEDICINE September 29, 2019

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

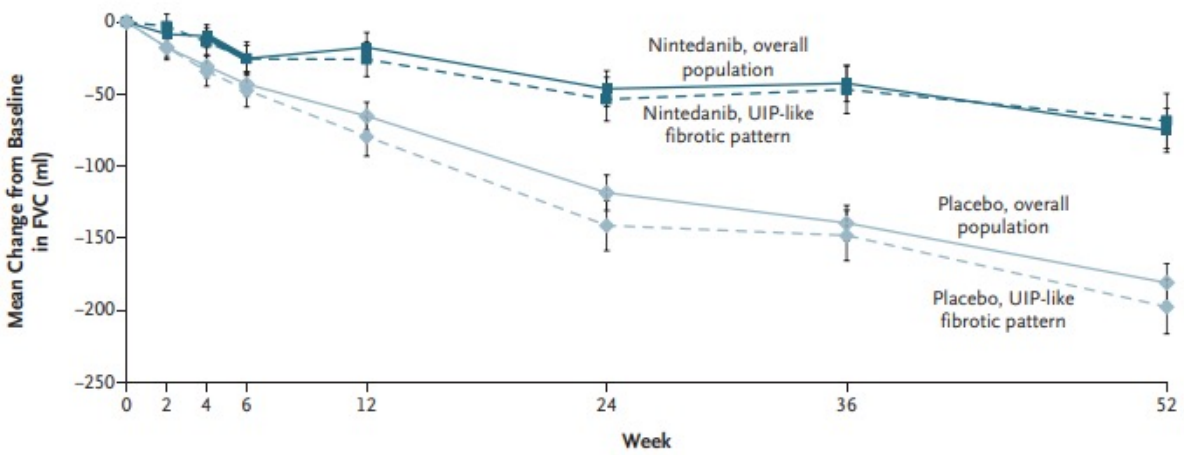
K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

- 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

Flaherty et al. INBUILD, NEJM 2019

Nintedinab for Progressive Fibrosing ILD



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

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.

Flaherty et al. INBUILD, NEJM 2019

Chronic HP Represented in Nintedinab 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".

Flaherty et al. INBUILD, NEJM 2019

Lung Transplantation

- Same indications as other lung diseases
- Good medium-term survival after transplant
- Disease recurrence can occur, but rates appear to be low

Kern et al. Chest 2015

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