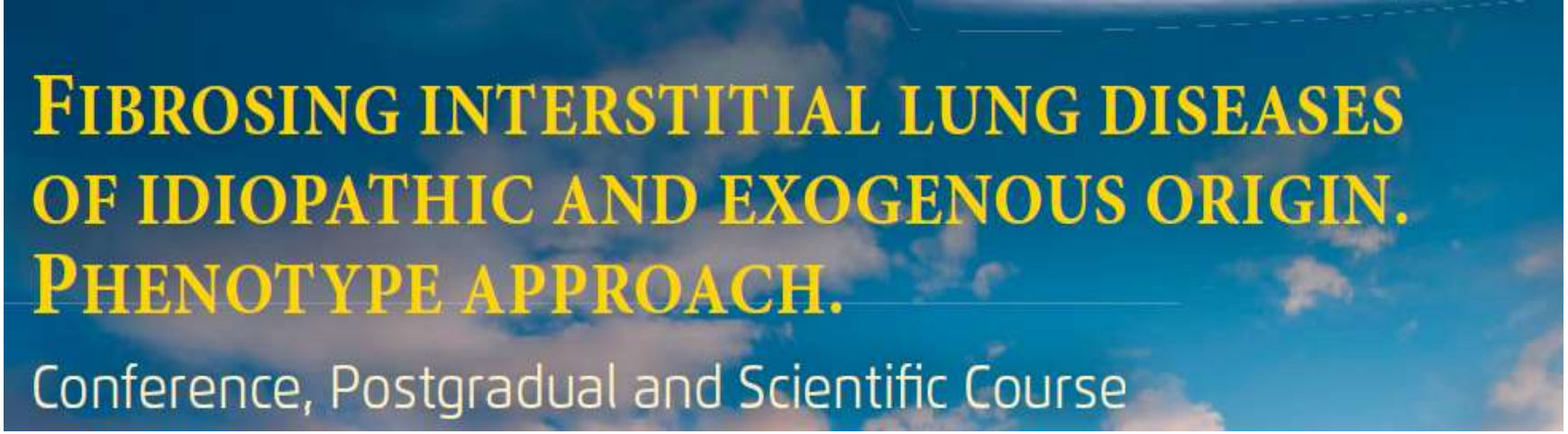


Hypersensitivity pneumonitis:

Causes, clinical course, diagnosis and differential diagnosis, treatment

Katerina M. Antoniou, MD, PhD

As. Professor in Thoracic Medicine

ERS ILD Group Secretary

Medical School, University of Crete

Prague, June 2014

DEFINITION of HP

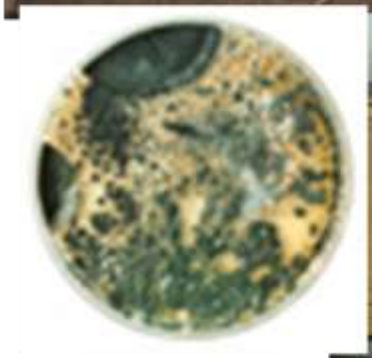
- **Hypersensitivity pneumonitis (HP), also called extrinsic allergic alveolitis, is a complex syndrome of varying intensity, clinical presentation, and natural history, caused by an *exaggerated immune response* to the inhalation of a large variety of organic particles.**
- ***It can progress to disabling,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

Major Antigens causing HP

Table 1—*Major Antigens Causing HP*

Type of Antigen	Examples of Sources
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Bird proteins	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

HP = hypersensitivity pneumonitis.

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COMPANY
Goose Feather
& Down Duvet


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Clinical Presentation

Table 2—*Presenting Features and Causes of HP in Two Large Cohorts of Consecutive Patients*

Characteristics	HP Study[4] (N = 199)	Mayo Clinic[41] (N = 85)
Sex, % women	56	62
Age, mean ± SD, y	55 ± 14	53 ± 14
Current smokers	6	2
Symptoms		
Dyspnea	98	93
Cough	91	65
Flulike symptoms	34	33
Chest discomfort	35	24
Signs		
Crackles	87	56
Wheezes	16	13
Digital clubbing	21	5
Causes		
Not identified	1.5	25
Avian antigens	66	34
Farmer's lung	19	11
Hot tub lung	0	21
Molds	13	9
Pulmonary function		
Obstructive pattern	1	16
Restrictive pattern	64	53
Mixed pattern (both obstructive and restrictive)	1	Not reported
Nonspecific abnormalities	1	12
Normal	34	10

CHEST / 142 / 1 / JULY 2012

Predictors of HP

Variables	OR	95% CI
Exposure to a known offending antigen	38.8	11.6-129.6
Positive precipitating antibodies	5.3	2.7-10.4
Recurrent episodes of symptoms	3.3	1.5-7.5
Inspiratory crackles	4.5	1.8-11.7
Symptoms 4-8 h after exposure	7.2	1.8-28.6
Weight loss	2.0	1.8-28.6

CHEST / 142 / 1 / JULY 2012

Clinical Behavior

- Most of the cases examined fit best into a two-cluster model.
- Subacute HP difficult to define
- Overlap features with both the “acute” and “chronic”components.
- ***Acute and chronic do not describe pathogenic pathways and do not imply that chronic HP follows acute HP, which remains uncertain***

Lacasse Y, et al.Int Arch Allergy Immunol 2009

Classification of HP

- Cluster 1: recurrent systemic symptoms (chills, body aches) and normal chest X-rays
- ***Cluster 1: classical acute form of HP, tends to occur in individuals exposed to thermophilic actinomycete species or fungi (e.g., farmer's lung).***
- Cluster 2: more features of chronic and severe disease (i.e., clubbing, hypoxemia, restrictive patterns on PFTs, and fibrosis on HRCT.
- ***Cluster 2: Chronic form of HP, tends to occur in individuals with bird antigen exposure***

Lacasse Y, et al.Int Arch Allergy Immunol 2009

CLINICAL PRESENTATION OF HP

- ✓ ACUTE HP
- ✓ SUBACUTE HP
- ✓ CHRONIC HP
- ✓ ACUTE EXACERBATIONS

ACUTE EXACERBATIONS OF HP

Seems to occur mainly in:

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

Pathology: DAD+OP

Acute HP

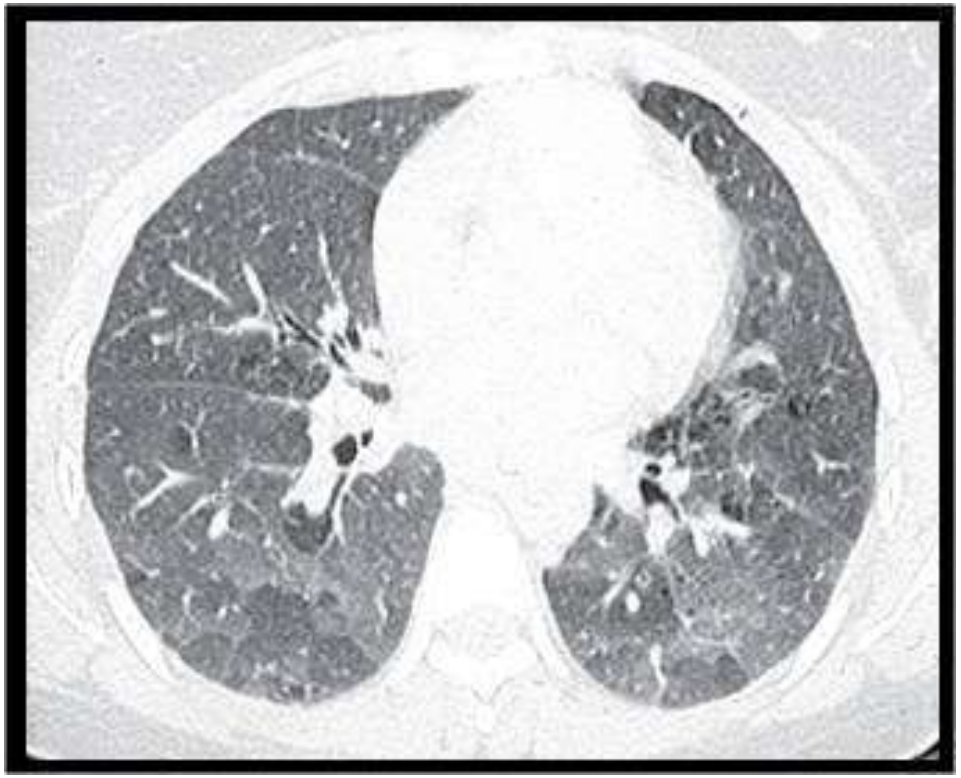
- Influenza-like syndrome occurring a few hours after a (usually) substantial exposure.
- Symptoms gradually decrease over hours/days but often recur with reexposure.
- Acute episodes can be indistinguishable from an acute respiratory infection caused by viral or mycoplasmal agents.
- *Occasionally, respiratory symptoms in acute HP are mild or absent.*
- The acute form is nonprogressive and intermittent, with spontaneous improvement after antigen avoidance.
- *Some patients with recurrent acute episodes of farmer's lung may develop an obstructive lung disease with centrilobular emphysema instead of fibrosis*.

HRCT findings in Acute HP

- **HRCT is useful in separating the clinical forms of HP.**
- **HRCT may be normal in patients with symptomatic acute HP.**
- **Predominant findings: ground-glass opacities or poorly defined small nodules.**
- **Diffuse areas of dense air-space consolidation may be associated with groundglass opacities.**

HRCT in acute phase of HP

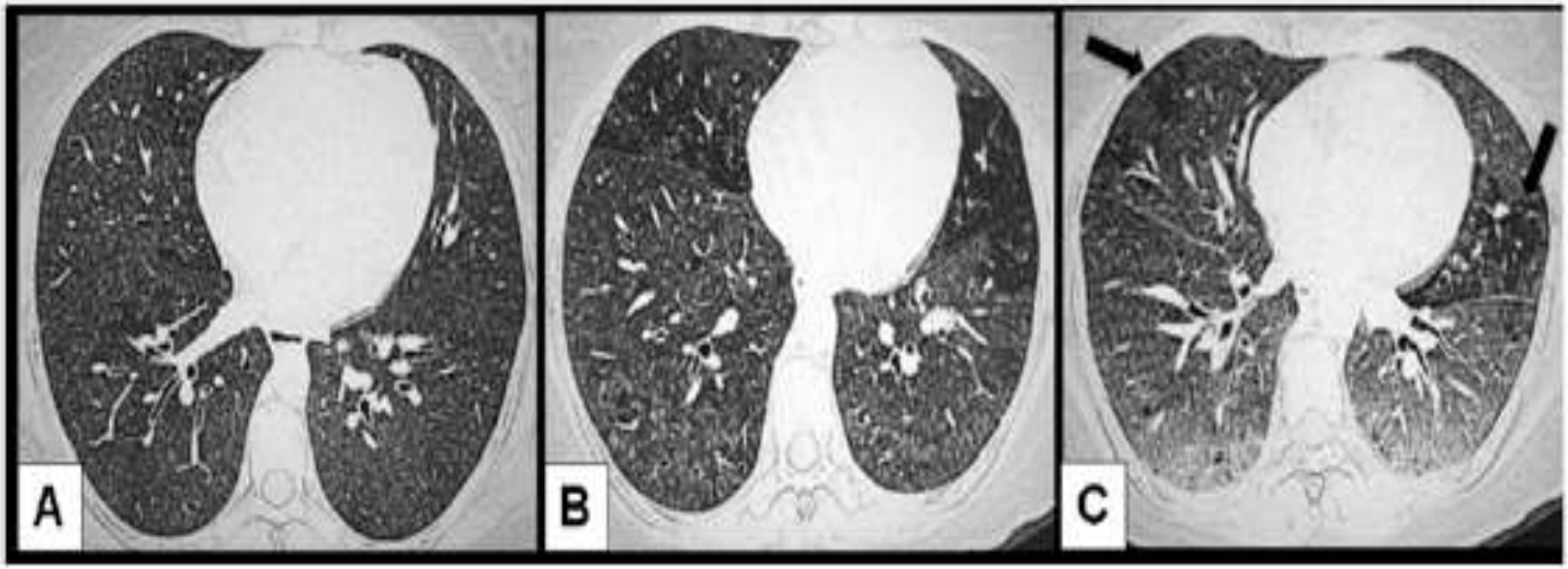
- **GGO during the acute phase of HP.**
- **Several secondary pulmonary lobules are spared and appear as darker areas in both lower lobes *(air-trapping).***
- **End expiratory HRCT is helpful.**
- ***Courtesy of Paul Stark, MD.***



Subacute HP

- May result from repeated low-level exposure to inhaled antigens.
- insidious onset of dyspnea, fatigue, and cough that develops over weeks to a few months.
- as a nonspecific febrile disorder until respiratory symptoms become visible.
- ***In general, subacute HP is a progressive disease, with coughing and dyspnea becoming persistent.***

HRCT in subacute HP

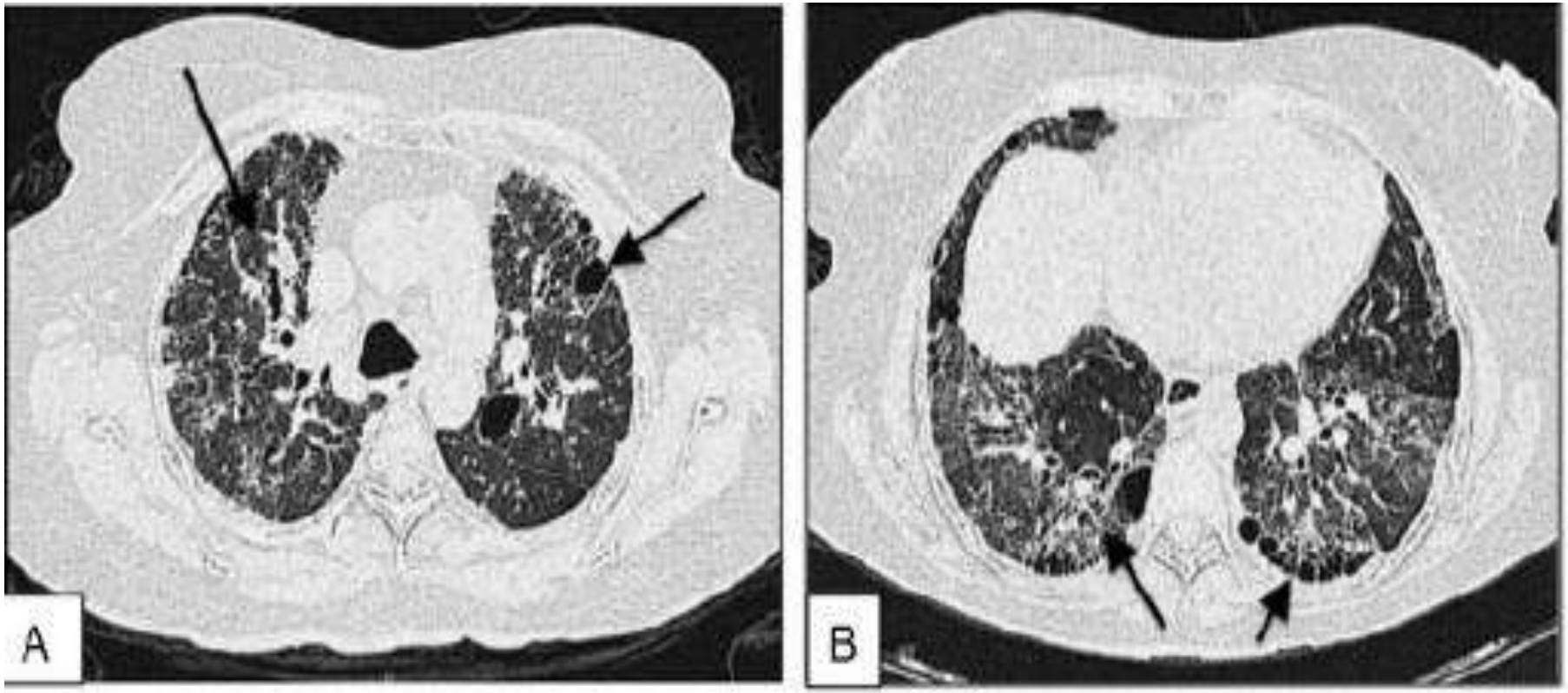


(A) 40-year-old woman exposed to birds, numerous ill-defined nodules.
(B) A 53-year-old woman exposed to birds: patchy ground-glass opacities, ill-defined nodules, and patchy areas of mosaic perfusion.
(C) Expiratory image demonstrating the prominence of the attenuation differences supporting the presence of air trapping

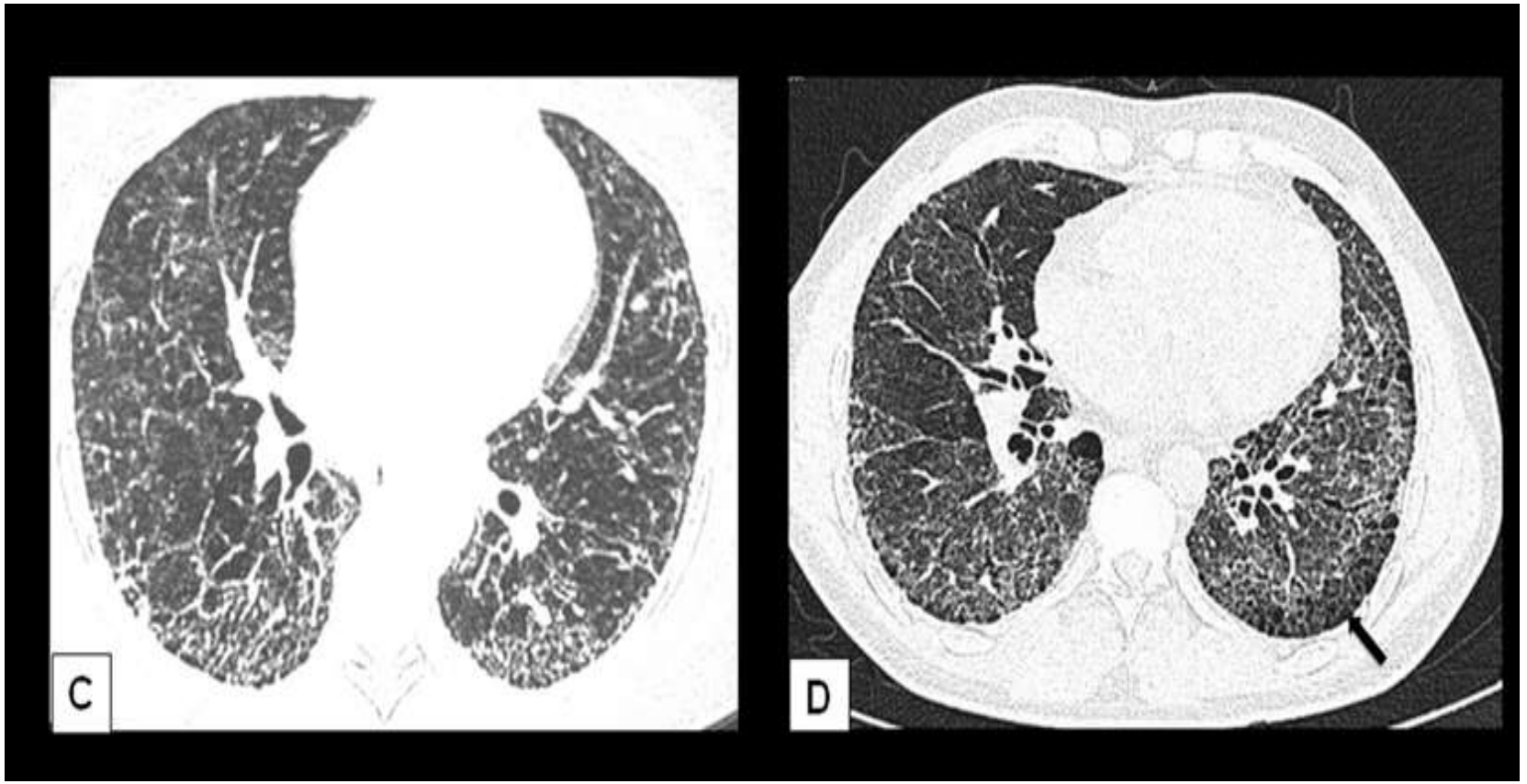
Chronic HP

- **Unrecognized and untreated acute/subacute episodes may evolve to chronic HP.**
- **many patients with chronic HP have no recognizable acute episodes**
- **present as a slowly progressive (insidious) chronic respiratory disease (bird exposure).**
- **The progressive dyspnea, cough, fatigue, malaise, and weight loss.**
- **Digital clubbing may be present and predicts clinical deterioration.**

HRCT in chronic phase of HP



- **Extensive reticular opacities, traction bronchiectasis and honeycombing.**
- ***Selman and Buendia-Roldan. Sem Respir Crit Care Med 2012***



(C) Subpleural predominant distribution of scattered nodules, ground-glass and reticular opacities, and traction bronchiectasis.

(D) Irregular reticular and ground-glass opacities with architectural distortion, traction bronchiectasis, and honeycombing (arrow) in a peripheral distribution simulating the UIP-like pattern.

Chronic hypersensitivity pneumonitis: HRCT patterns and pulmonary function indices as prognostic determinants

- Key points:
- HRCT is increasingly used to assess chronic fibrotic HP.
- HRCT patterns are superior to pulmonary function tests for predicting mortality.
- ***Extensive traction bronchiectasis strongly predicts poor survival in chronic HP.***

Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Eur Radiol 2012

HRCT in chronic phase of HP

- **Features favoring HP over IPF or NSIP:**
  - lobular areas with decreased attenuation and vascularity,
  - centrilobular nodules,
  - lack of lower zone predominance of abnormalities.

- **TABLE 1: Accuracy of CT Diagnosis of Idiopathic Pulmonary Fibrosis (IPF) and Hypersensitivity Pneumonitis (HP)**

CT Diagnosis	Level of Confidence	No. of Cases	Pathologic Diagnosis		Correct Diagnoses (%)
			IPF	HP	
IPF	Definite	26	23	3	88
IPF	Probable	6	4	2	66
IPF	Possible	2	1	1	50
HP	Definite	13	1	12	92
HP	Probable	12	5	7	58
HP	Possible	4	2	2	50

LYNCH et al. AJR 1995;165:807-811

Can CT Distinguish Hypersensitivity Pneumonitis from Idiopathic Pulmonary Fibrosis?

TABLE 2: CT Features of Patients with Chronic Hypersensitivity Pneumonitis (HP) and Usual Interstitial Pneumonia (UIP)

	No. (%) of Patients		
	Chronic HP (n = 19)	UIP (n = 33)	p
Honeycombing	3 (16)	29 (88)	<.0001
Traction bronchiectasis	10 (53)	28 (85)	.012
Micronodules	8 (42)	2 (6)	.002
Extensive ground-glass attenuation	6 (32)	4 (12)	.087
Irregular lines	16 (84)	32 (97)	.096
Parenchymal distortion	15 (79)	30 (91)	.224
Air-space opacity	2 (11)	6 (18)	.461
Overall extent of isolated ground-glass attenuation (mean ± standard error of the mean)	32 ± 5	26 ± 4	.350
Upper zone predominance	3 (16)	1 (3)	.096
Middle zone predominance	3 (16)	2 (6)	.252
Lower zone predominance	8 (42)	27 (81)	.003
No zone predominance	5 (26)	3 (9)	.097
Peripheral predominance	10 (53)	30 (91)	.002
Peripheral and lower zone predominance	5 (26)	25 (76)	.001
Relative sparing of lower half of lower zone	13 (48)	3 (8)	<.001

LYNCH et al. AJR 1995;165:807-811

Chronic Hypersensitivity Pneumonitis: Differentiation from Idiopathic Pulmonary Fibrosis and Nonspecific Interstitial Pneumonia by Using Thin-Section CT[1]

Radiology

Table 2

Diagnostic Criteria for Chronic HP, IPF, and NSIP at Thin-Section CT

Diagnosis	Level of Confidence: Confident	Level of Confidence: Probable
Chronic HP	Centrilobular nodules, lobular areas of decreased attenuation and vascularity, mild to moderate extent of GGO away from fibrosis, no or minimal honeycombing, relative basal sparing	Mild to moderate extent of GGO, predominant peribronchovascular distribution and/or upper or middle zone predominance, no or minimal honeycombing, cysts
IPF	Reticulation in all lobes, extensive honeycombing, no or minimal GGO, peripheral and basal predominance	Bilateral reticulation, minimal honeycombing, minimal to moderate GGO, peripheral and basal predominance
NSIP	Extensive GGO, no or only mild reticulation, traction bronchiectasis, no honeycombing, basal predominance, relative subpleural sparing	Moderate GGO, moderate reticulation, traction bronchiectasis, no or minimal honeycombing, basal predominance

Advances in Knowledge

- The thin-section CT findings most helpful in differentiating chronic hypersensitivity pneumonitis (HP) from idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) are lobular areas with decreased attenuation and vascularity, centrilobular nodules, and lack of lower zone predominance of abnormalities.
- The thin-section CT findings allow confident distinction of chronic HP from IPF and NSIP approximately 50% of the time.

ROLE OF PRECIPITINS/INHALATION CHALLENGES IN HP

- **Serum IgG ab specific to an identified antigen should be undertaken.**
- **Antibodies may be found in exposed but asymptomatic individuals,**
- **False-negative mainly in chronic cases.**
- **The presence of *precipitins* only indicates exposure and a humoral response (*up to 50% of asymptomatic pigeon breeders and 2–10% of asymptomatic farmers).***
- **INHALATION CHALLENGES- not routinely, limited to specific research centers.**

BRONCHOALVEOLR LAVAGE IN HP

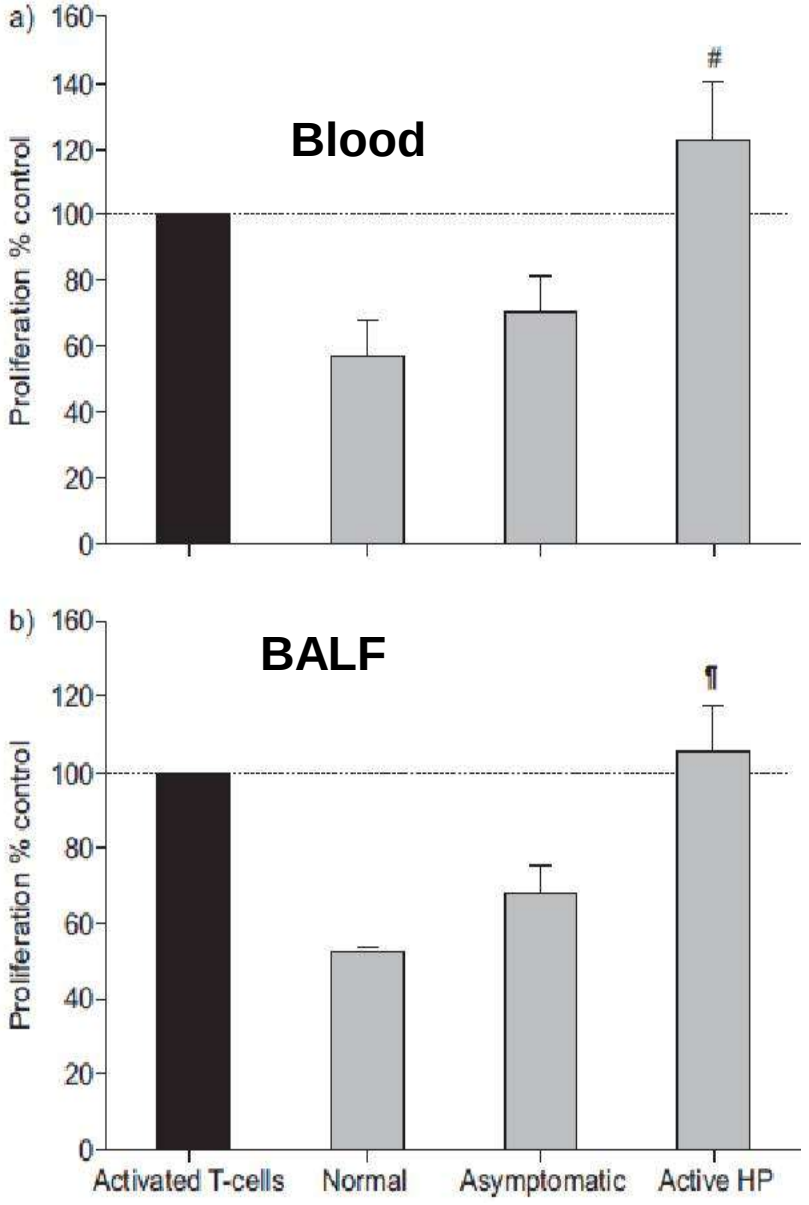
- Increase of total and % of lymphocytes, T cells, mast cells.
- Also in asymptomatic HP.
- CD4:CD8 ratio measurement is not recommended.
- Increase of neutrophils together with lymphocytes characterizes the acute attacks.

BRONCHOALVEOLAR LAVAGE IN HP

TABLE 1 Cells recovered from bronchoalveolar lavage (BAL) of normal individuals, asymptomatic subjects and hypersensitivity pneumonitis (HP) patients

	Normal	Asymptomatic	HP patients
Subjects n	4	4	6
Total inflammatory cells $\times 10^6$	29.82	35.63	134.57
Macrophages $\times 10^6$	24.72	28.58	72.13
Lymphocytes $\times 10^6$	3.97	7.20	51.00
Treg cells $\times 10^6$	0.12	0.17	2.81
Neutrophils $\times 10^6$	0.37	0.24	11.84
Eosinophils $\times 10^6$	0	0	0

Girard et al. ERJ 2011



Clinical Evidence of Acute Diffuse Infiltrative Lung Disease
(dyspnea, diffuse infiltrates, hypoxemia, no known prior lung disease, illness ≤4 weeks duration)

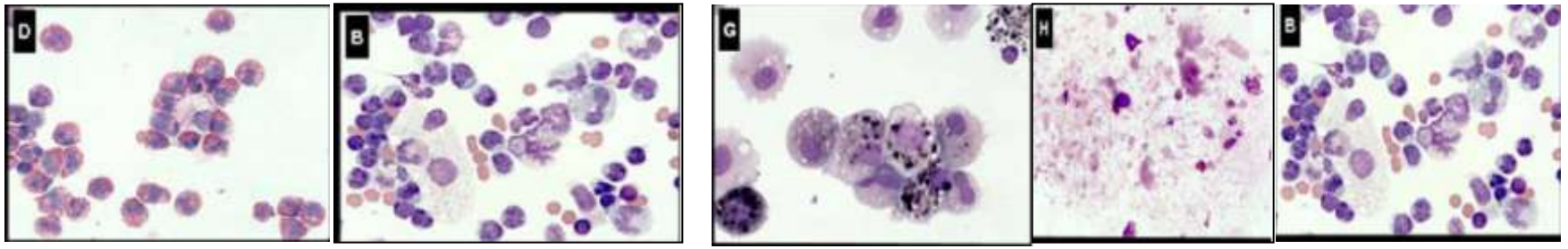
ATS BAL GUIDELINES, AJRCCM 2012

High-Resolution CT Scan*

Diffuse Ground Glass Opacities
(±superimposed on chronic changes)

Bronchoalveolar Lavage

Eosinophils ≥25%	Lymphocytes ≥50%	Bloody lavage (persists and/or increases on sequential aliquots)	Other findings
Eosinophilic Pneumonia	Consider Drug Reaction, Acute HP	Diffuse Alveolar Hemorrhage	**Specific Diagnosis** / **Non-diagnostic**



DIAGNOSTIC CRITERIA FOR HP

ACUTE	SUBACUTE	CHRONIC
EXPOSURE [Hx, Ab]	EXPOSURE [Hx, Ab]	EXPOSURE [Hx, Ab]
FLULIKE SYNDROME	PROGRESSIVE DYSPNEA	CONSISTENT CHRONIC CLINICAL BEHAVOR
BALF INCREASE NEU+LYMP	BALF LYMP>40%	BALF LYMPHOCYTOSIS
	COMPATIBLE HRCT *[GGO, CENTRILOBULAR NODULES, MOSAIC, AIR TRAPPING]*	HRCT RETICULAR ON SUBACUTE CHANGES
	RESTRICTIVE PFTs+ HYPOXEMIA+ LOW DIFFUSION	RESTRICTIVE PFT+ HYPOXEMIA+LOW DIFFUSION
IMPROVEMENT ON REMOVING, WORSENING AFTER REEXPOSURE	IMPROVEMENT ON REMOVING, WORSENING AFTER REEXPOSURE	LUNG BIOPSY IF NEEDED

SELMAN 2012

DIFFERENTIAL DIAGNOSIS OF HP

- **ACUTE HP**
  - Bronchial asthma
  - Acute RTI
  - Acute endotoxin exposure
  - Organic dust toxic syndrome
  - ABPA
  - Aspiration pneumonitis
  - AIP
  - Goodpasture's syndrome
- **CHRONIC HP**
  - IPF/CPFE
  - NSIP
  - Sarcoidosis
  - MAC complex disease
- **SUBACUTE HP**
  - Recurrent RTI
  - APBA
  - Vasculitis *[GPA, MPA, Churg-Strauss]*
  - Sarcoidosis
  - Berylliosis
  - Silicosis / Talcosis
  - PLCH
  - DIP/RB-ILD, COP

4 major pathological features of HP

1. Interstitial mononuclear cell infiltrates
2. Small, often poorly formed, non caseating granulomas- absent in ~ 1/3 of cases.
3. Bronchiolitis- frequently similar to BO, *peribronchiolar,* usually *lymphocyte-dominant.*
4. Interstitial fibrosis/honeycombing- indistinguishable from UIP.

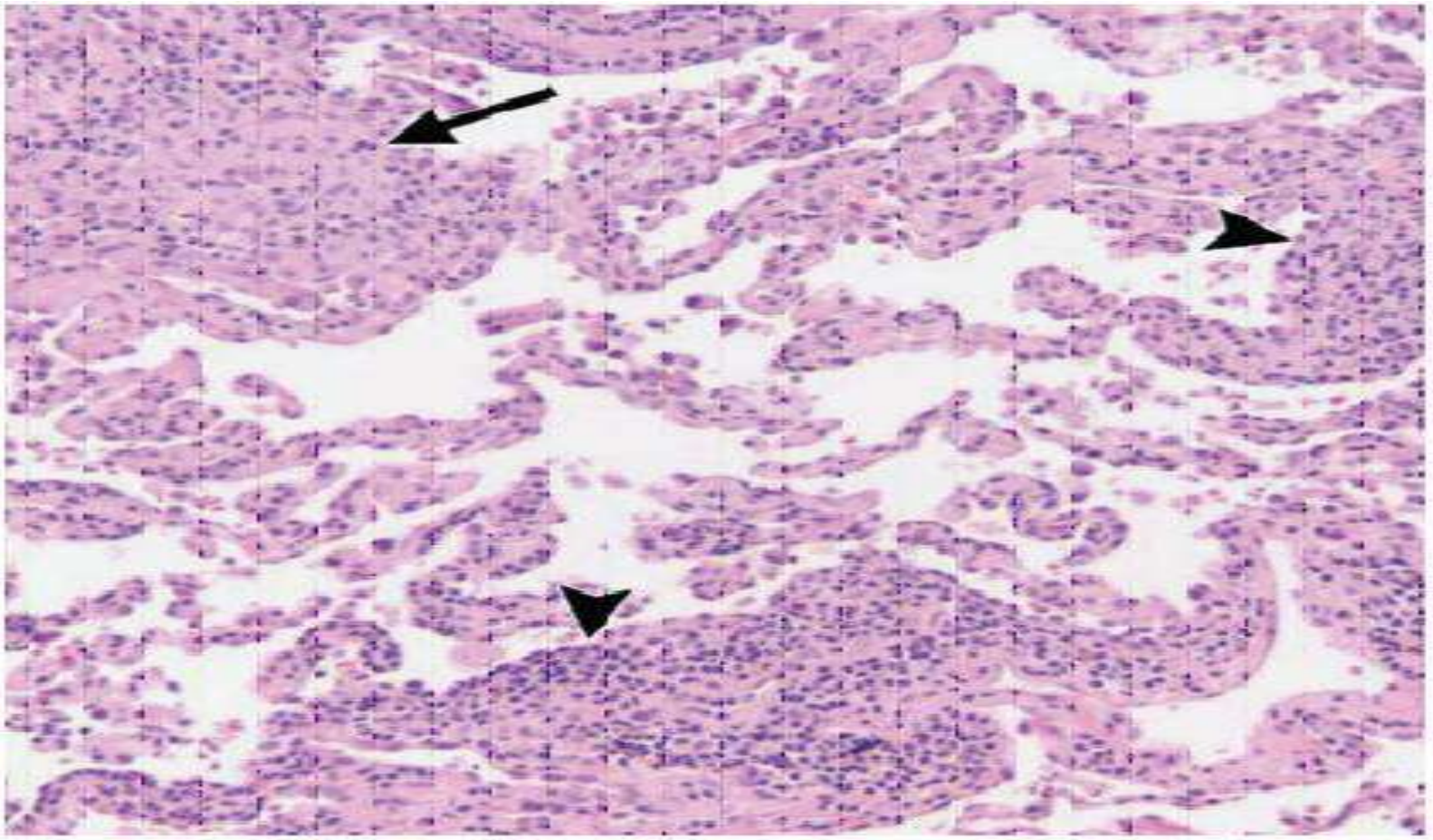
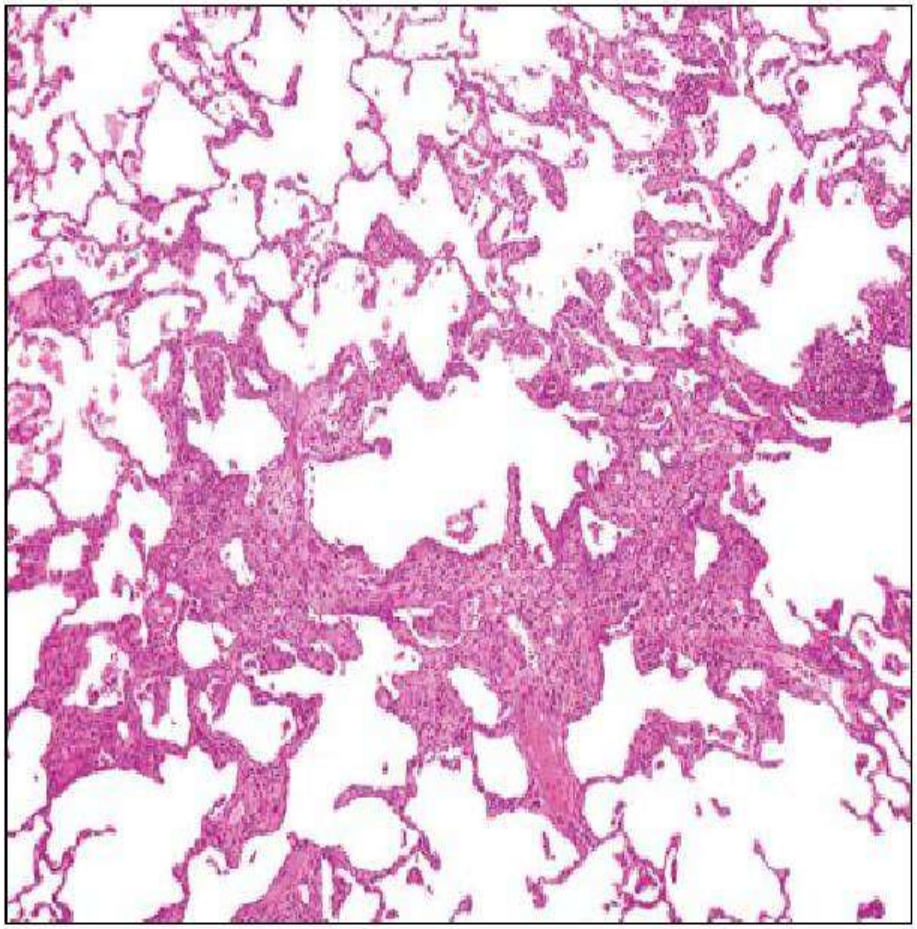
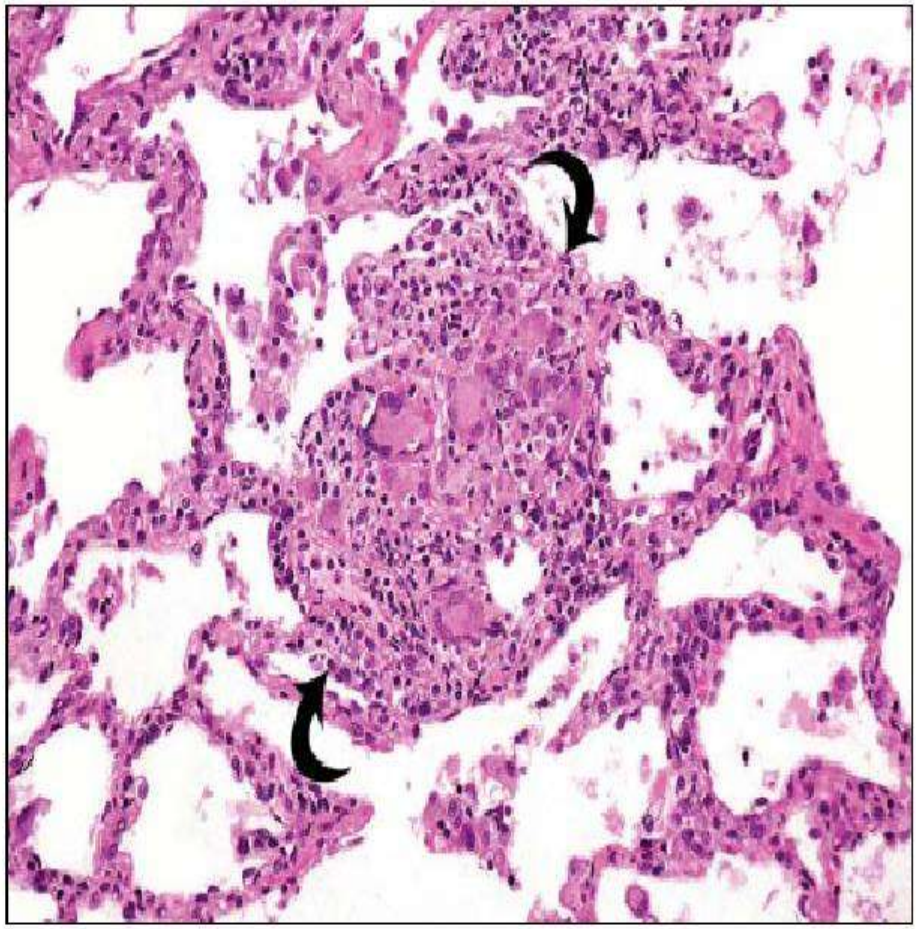


Figure 1. Photomicrograph shows the two most common and most characteristic histopathologic features of hypersensitivity pneumonitis: lymphocytic infiltrates within the interstitium, sometimes referred to as cellular interstitial pneumonitis (arrowheads), and a poorly formed granuloma (arrow). (Image courtesy of Rodney A. Schmidt, MD, Department of Pathology, University of Washington Medical Center, Seattle, Wash.)



A



B

Fig. 1—35-year-old woman with subacute hypersensitivity pneumonitis (bird fancier's lung).
A, Photomicrograph of histopathologic specimen obtained at surgical lung biopsy shows moderate, diffuse, bronchiolocentric chronic lymphocytic inflammatory infiltrate. (H and E, ×60)
B, Magnified view of different area from A shows poorly formed granuloma (*arrows*) and chronic interstitial inflammatory infiltrate. (H and E, ×200)

Pathological differentiation of chronic HP from IPF/UIP

- ***More frequent in HP than in IPF***:
- Bronchiolitis,
- Centrilobular fibrosis,
- Bridging fibrosis
- Organizing pneumonia,
- Granulomas
- Giant cells
- Lymphocytic alveolitis

Takemura T, et al. Histopathology 61, 1026–1035 (2012)

Usual interstitial pneumonia-*pattern* fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology

Maxwell Smith,[1] Mercedes Dalurzo,[2] Prasad Panse,[3] James Parish,[4] Kevin Leslie[1]

Table 1 UIP in IPF

Clinical features	Radiological features	Histopathological features
▶ Age greater than 60 years ▶ More frequent in men ▶ Smoking history common ▶ Dyspnoea longer then 3 months ▶ Dry, non-productive cough ▶ Restrictive pattern of respiratory impairment common ▶ Inhalational exposures uncommon ▶ Digital clubbing, common in advanced disease ▶ Oxygen desaturation with exercise common	▶ Subpleural and basal predominance ▶ Progressive gradient toward bases ▶ Reticular abnormalities ▶ Traction bronchiectasis ▶ Subpleural honeycomb cysts (necessary for confident radiological diagnosis) ▶ Minimal ground-glass opacities: common in areas of reticulation, but never extensive	▶ Spatial heterogeneity ▶ Temporal heterogeneity ▶ Fibroblastic foci common ▶ Peripheral lobular distribution commonly present ▶ Microscopic honeycomb remodelling ▶ Smooth muscle in fibrosis

IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

Table 3 UIP in CHrHP

Clinical features	Radiological features	Histopathological features
▶ Middle age to older individuals ▶ Slowly progressive dyspnoea ▶ Cough frequent, often productive ▶ Exposure history, frequent, with focused questioning or home visit ▶ Positive precipitin antibodies, inconsistent	▶ Reticular pattern with traction bronchiectasis ▶ Ground-glass opacities, common ▶ Mid and upper lung zones commonly affected in a bronchovascular distribution with resulting micronodules ▶ Non-basilar distribution common ▶ Mosaic attenuation ▶ Irregular bronchovascular bundles ▶ Subpleural honeycomb cysts, not always basilar	▶ Patchy fibrosis along the bronchovascular bundle with rare fibroblast foci ▶ Individual interstitial giant cells, some with cholesterol clefts. ▶ Honeycomb cysts (lower and upper lobes) ▶ Extensive peribronchiolar metaplasia. ▶ Bridging fibrosis across lobules

CHrHP, chronic hypersensitivity pneumonitis; UIP, usual interstitial pneumonia.

J Clin Pathol 2013;

DIFFERENTIAL DIAGNOSIS from IIPs

- **IIPs are frequently confused with HP, and *vice versa*, except when the exposure is readily apparent.**

- **Up to 30% of subjects with histologic HP have no identifiable exposure.**
  - ***(AJRCCM 2013)***

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

Ferran Morell, Ana Villar, María-Ángeles Montero, Xavier Muñoz, Thomas V Colby, Sudhakar Pipvath, María-Jesús Cruz, Ganesh Raghu

- **20/46 (43%) IPF patients had subsequent diagnosis of chronic HP due to occult avian antigen *(feather bedding).***
  - ***9 BCT +8 IgG+, 6 SLB HP***
  - ***7 IgG+ plus SLB HP***
  - ***1 IgG+ plus BALF>20% lymph***
  - ***3 SLB subacute HP***

THE LANCET Respiratory Medicine **2013;Nov. 685-694**

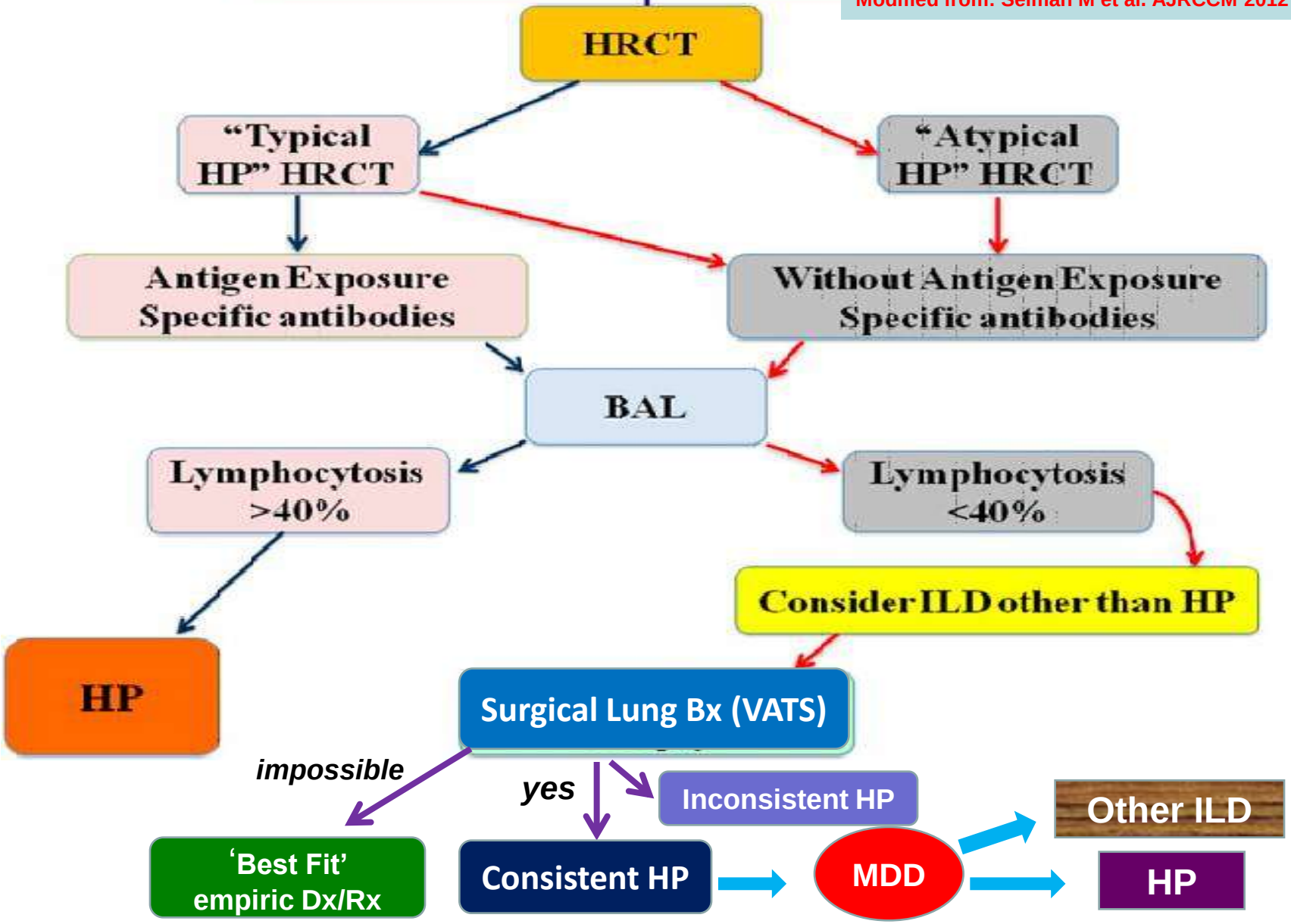
Chronic hypersensitivity pneumonitis in the setting of definite IPF: does the current study undermine IPF guideline recommendations?

Athol U Wells

- **More questions than it answers!!!**
- Is underlying chronic HP truly as prevalent in the setting of a UIP pattern on CT ?
- Does the report represent a unique referral centre cluster of chronic HP related to feather bedding?
- Does this report have major implications for future guideline statements?
- Will we have cause to regret the 2011 guideline recommendation that BAL is not warranted in the majority of patients with supposedly definite IPF?

DIAGNOSTIC ALGORITHM OF HP

Modified from: Selman M et al. AJRCCM 2012



CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Reversible & self-limited (e.g. RBILD) **ACUTE HP**	Remove possible cause	Short term (3-6 month) observation to confirm disease regression
Reversible disease with risk of progression (e.g. some NSIP, DIP, COP) **ACUTE HP/SUBACUTE**	Initial response & then rationalize longer term therapy	Short term observation to confirm Rx response. Long term observation to ensure that gains are preserved
Stable with residual disease (e.g. some NSIP) **INACTIVE HP(SUB ACUTE HP)**	Maintain status	Long term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g. some fibrotic**NSIP)** **SUB/CHRONIC HP**	To prevent progression	Long term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g. IPF, some fibrotic NSIP) **CHRONIC HP**	To slow progression	Long-term observation to assess disease course and need for transplantation or effective

TREATMENT OF HP

- **Antigen avoidance**
  - **of critical importance**
  - **usually results in regression of disease**
  - **prevents sensitization of other individuals**
  - **Not always possible/efficacious**
  - **Avian antigen was reported to persist in the patient's house 6 months after removal of all birds** ***(Craig T. 1992)***

TREATMENT OF HP

Glucocorticoids

- Accelerate initial recovery in severely ill
- Prednisone, 0.5 to 1 mg/kg of IBW/d (max 60 mg/d), each morning X1-2 wk. and tapered over 2-4 wk. to 10-15 mg/d maintenance.
- Long-term outcome appears unchanged.
- ICS may be effective in treating or preventing recurrence, but not well studied.

PROGNOSTIC FACTORS OF HP

- The duration/intensity of exposure
- Histopathologic changes (OP, cellular NSIP vs. fibrotic NSIP or a UIP-like pattern)
- The presentation (acute, subacute, or chronic HP)
- Digital clubbing predicts a worse outcome
- Older patients have a less complete recovery
- Neither the degree or type of PFTs nor CXR at the time of diagnosis correlate with outcome.
- HRCT patterns may predict prognosis of chronic HP

Conclusion

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