Hypersensitivity Pneumonitis: Epidemiology and Classification

Ulrich Costabel, MD
University of Duisburg-Essen, Ruhrlandklinik
Department of Pneumology/Allergy

Objectives

- Definitions, Etiology
- Epidemiology
- Classification

Hypersensitivity Pneumonitis (Extrinsic Allergic Alveolitis)

- Complex Syndrome rather than a single well-defined disease
  - Response to agricultural dusts, feathers, microorganisms, chemicals, *and …. Unknown*
  - Variable clinical presentation
  - Variable natural history

Types of HP and antigens (incomplete)

Farmer‘s lung	T. vulgaris, Saccharospora rectivirgula, Aspergillus spp.
Bird-keeper‘s lung pigeon breeder‘s budgerigars	Proteins in avian droppings, in serum, and on feathers
Mushroom-worker‘s lung	see farmer‘s lung
Humidifier lung	various moulds and bacteria
Malt-worker‘s lung	Aspergillus spp.
Cheese-washer‘s lung	Penicillium casei
Wood-worker‘s lung	Alternaria spp.
Hot-tub lung	Mycobacterium avium complex

Disease	*Antigen*	*Source*
Fungal and bacterial		
Farmer's lung	*Faeni 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 (ie, bagasse)
Mushroom worker's lung	*T. sacchari*	Moldy mushroom compost
Suberosis	*Thermoactinomyces viridis 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
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	*Cladosporium* spp.	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, *F. 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	*Pseudomona fluorescens, mycobacterium* spp.!?	Aerosolized metalworking fluid
Amebae		
Humidifier lung	*Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani*	Contaminated water
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* (ie, wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

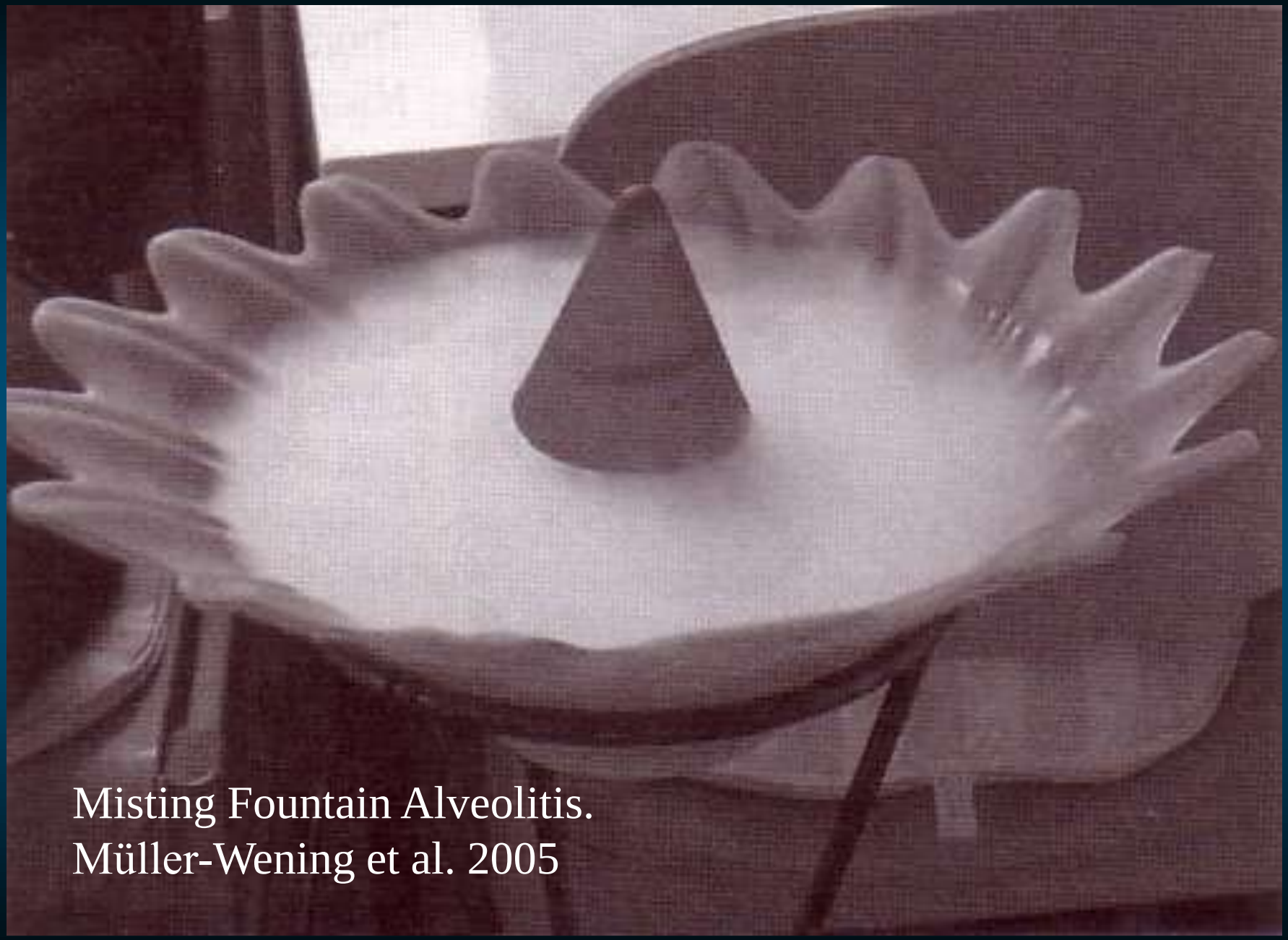
Disease	*Antigen*	*Source*
Chemical		
Pauli's reagent alveolitis	Sodium diazobenzene sulfate	Laboratory reagent
Chemical worker's lung	Isocyanates; trimellitic anhydride	Polyurethane foams, spray paints, elastomers, special glues
Vineyard sprayer's lung	Copper sulfate	Bordeaux mixture
Pyrethrum HP	Pyrethrum	Pesticide
Epoxy resin lung	Phthalic anhydride	Heated epoxy resin
Unknown		
Bible printer's lung		Moldy typesetting water
Coptic lung (mummy handler's lung)		Cloth wrappings of mummies
Grain measurer's lung		Cereal grain
Coffee worker's lung		Coffee bean dust
Tap water lung		Contaminated tap water
Tea grower's lung		Tea plants
Mollusk shell HP		Sea snail shell
Swimming pool worker's lung		Aerosolized endotoxin from pool water sprays and fountains

- **Fungal & Bacterial**
- **Animal Proteins**
- **Insect Proteins**
- **Chemical**
- **Unknown**

Selman in *Schwarz & King 4th ed*

Newer Entities

- Metalworking-fluid-associated HP
  Bernstein D, 1995; Tillie-Leblond I, 2011
- Hot tub lung
  Kahana LM, 1997; Hanak V, 2006
- Swimming pool alveolitis
  Koschel D, 2006
- Misting fountain alveolitis
  Koschel D, 2003, Müller-Wening D, 2006



Misting Fountain Alveolitis.
Müller-Wening et al. 2005

Rare environments and causative agents

- Feather duvet lung
  (Koschel D et al, Int Arch Allergy Immunol 2010)

- Chacinero‘s lung- HP due to dry sausage dust
  [Penicillium frequentans and other moulds]
  (Morell F et al, Scand J Work Environ Health 2010)

- Saxophone player‘s lung
  [fungi]
  (Metzger F et al, Chest 2010)

- Cheiropodist‘s lung
  [fungi in foot skin and nails]
  (Lingenfelser et al, Allergologie 2010)

Epidemiology

- Geographic variations

  - budgerigar (parakeet) in Europe

  - pigeon breeder´s in Mexico

  - summer-type HP in Japan

- Different climate, local customs, local working conditions

- Farmer´s lung more prevalent in cold and wet regions; silage making has reduced the incidence

Prevalence estimates

- Farmer‘s lung 1 to 19% of exposed farmers

  (Gruchow 1981; Terho 1987; Depierre 1988)

- Pigeon breeder’s lung 6 to 20% of exposed

  (Rodriguez 1993)

- Budgerigar’s lung 0.5 to 7.5% of exposed, which is 10 to 12% of the UK population

  (Hendrik 1978)

Smoking

- Protective against the development of HP
- Nonsmokers have higher levels of serum precipitins than smokers
- Cigarette smoking suppresses lymphocyte and macrophage function
- Smoking may inhibit the alveolar macrophage function to take up, process and present the inhaled antigen to lymphocytes

Clinical Features in 85 Patients with Hypersensitivity Pneumonia

TABLE 1. **Demographic Data and Clinical Presentation**

Characteristic	No. (%) of patients (N=85)
Women	53 (62)
Mean ± SD age (y)	53±14
Smoking history	
Never	49 (58)
Previous	34 (40)
Current	2 (2)
Median duration of symptoms (mo) (interquartile range)	14 (5-43)
Symptoms	
Dyspnea	79 (93)
Cough	55 (65)
Flulike symptoms	28 (33)
Chest discomfort	20 (24)
Signs	
Crackles	48 (56)
Wheezes	11 (13)
Inspiratory squeaks	8 (9)
Digital clubbing	4 (5)

TABLE 2. **Pulmonary Function Test Results at Presentation**

Type of abnormality	No. (%) of patients (n=83)*
Obstruction	13 (16)
Mild	4
Moderate	5
Severe	4
Restriction	44 (53)
Mild	23
Moderate	10
Severe	11
Nonspecific abnormality	10 (12)
Isolated reduction in diffusing capacity	8 (10)
Normal	8 (10)

Hanak et al. 2007 *Mayo Clin Proc 82:812-6*

Hypersensitivity pneumonitis: clinical classification

- Acute
- Subacute/Intermittent
- Chronic/Progressive

Richerson, et al. 1989

Clinical forms of HP

- **Acute HP**

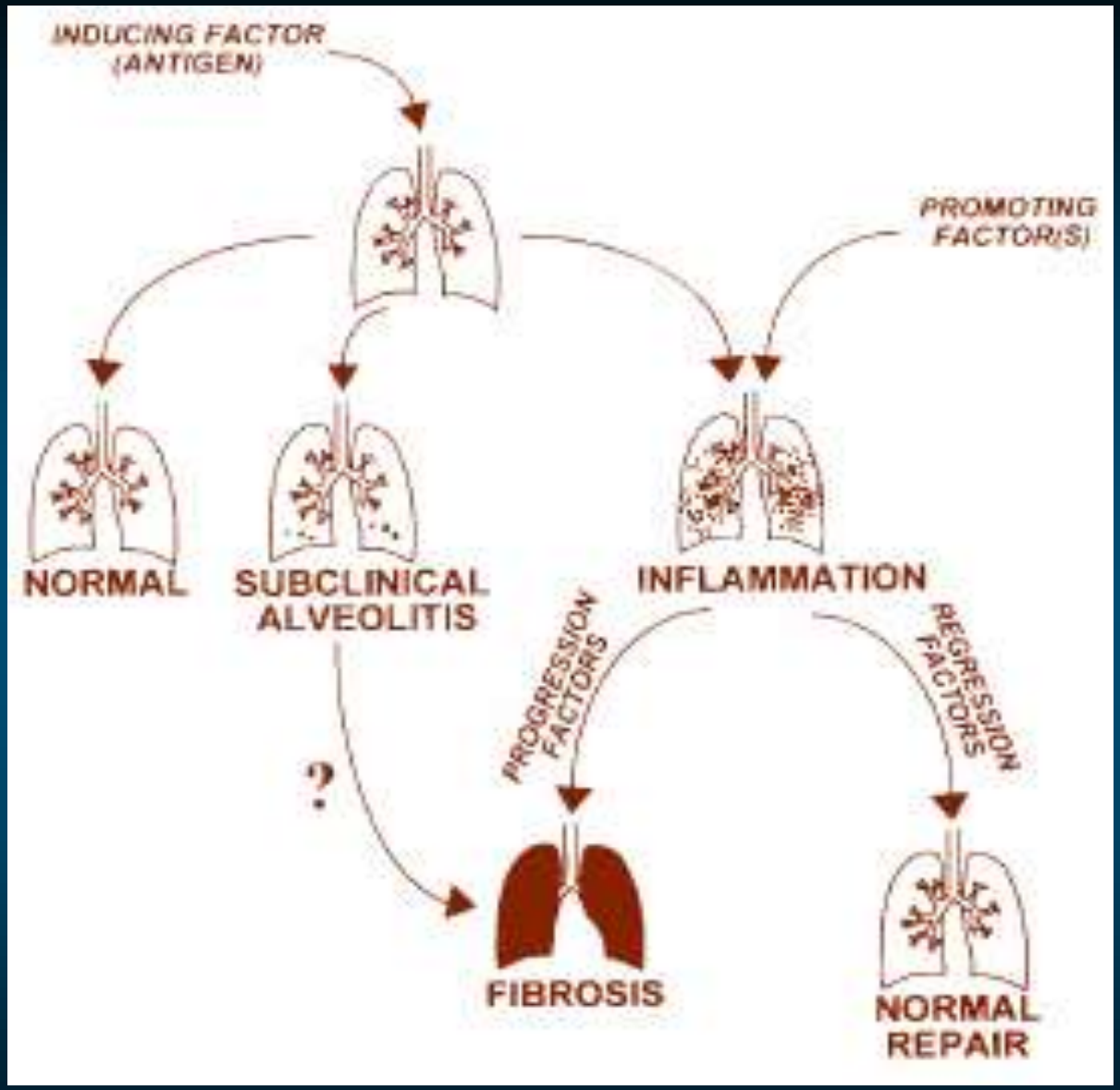
  - intermittent high-level exposure
  - symptoms occur 4 to12 hours
  - flu-like symptoms and respiratory symptoms

- **Subacute HP**

  - acute episodes with fever superimposed on a background of exertional dyspnea, fatigue and cough

- **Chronic HP**

  - continuous low-level exposure
  - insidious onset
  - dyspnea on exertion, dry cough, weight loss, malaise



Selman in *Schwarz & King 4th ed*

Clinical diagnosis of HP (1)

Lacasse et al, 2003

- Patients with ILD from 7 centers
- Derivation cohort: 400 (116 with HP)
- Validation cohort: 261 (83 with HP)

Clinical diagnosis of HP (2)

Lacasse et al, 2003

Logistic regression model identified 6 significant predictors of HP

- Exposure to known antigen
- Positive precipitating antibody
- Recurrent episodes of symptoms
- Inspiratory crackles
- Symptoms 4 to 8 h after exposure
- Weight loss

If all 6 are present, probability of having HP is 98%!

Classification of HP- a hypothesis generated by cluster analysis

- Cluster 1 (41 patients):

  recurrent systemic symptoms (chills, body aches),

  a few hours following antigen exposure;

  X ray normal in 30%

- Cluster 2 (127 patients):

  advanced ILD, inspir. crackles, clubbing one third,

  restriction, fibrotic changes on HRCT

Internal validation: only 3.6% misclassification rate

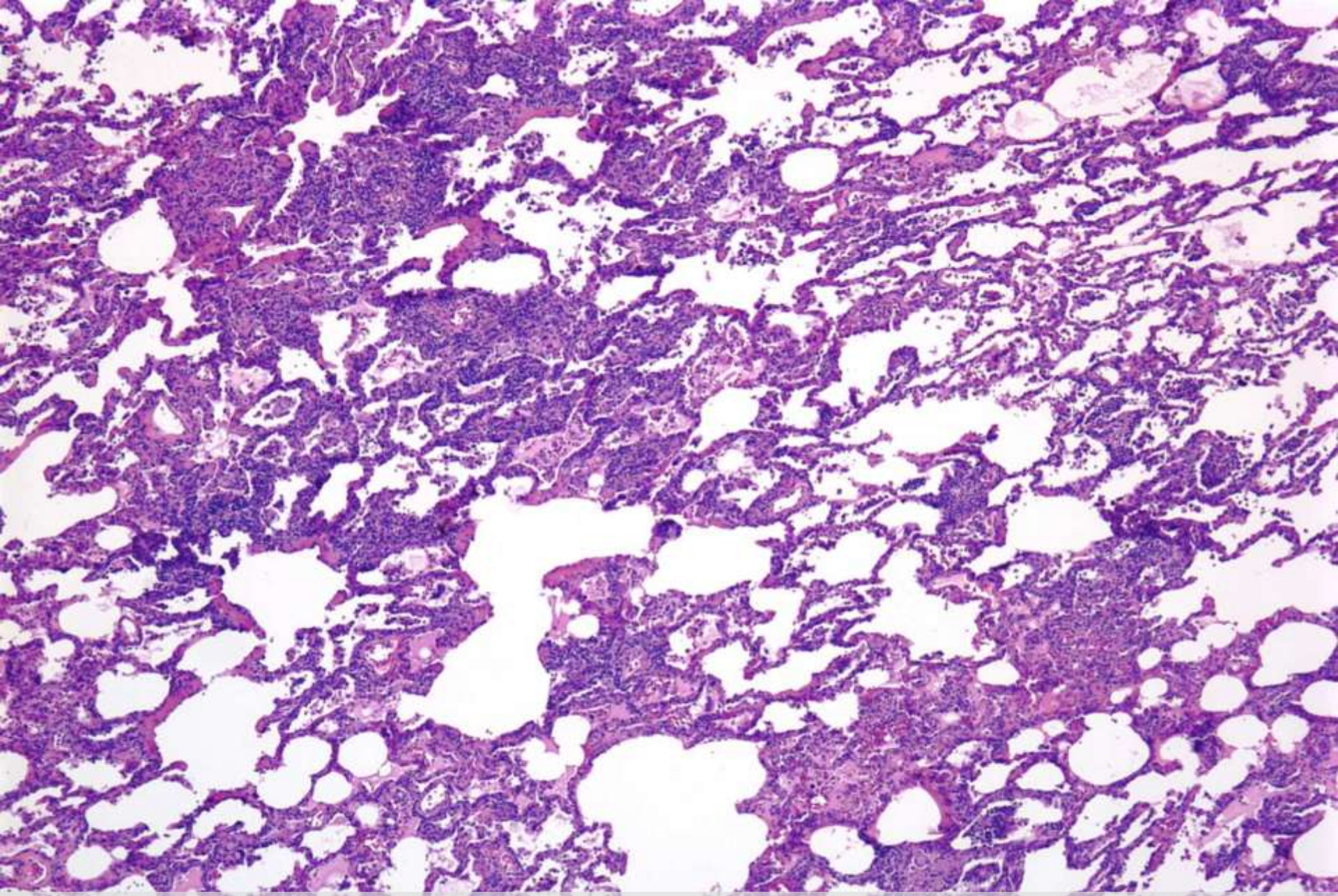
Lacasse et al 2009

Histopathology of HP

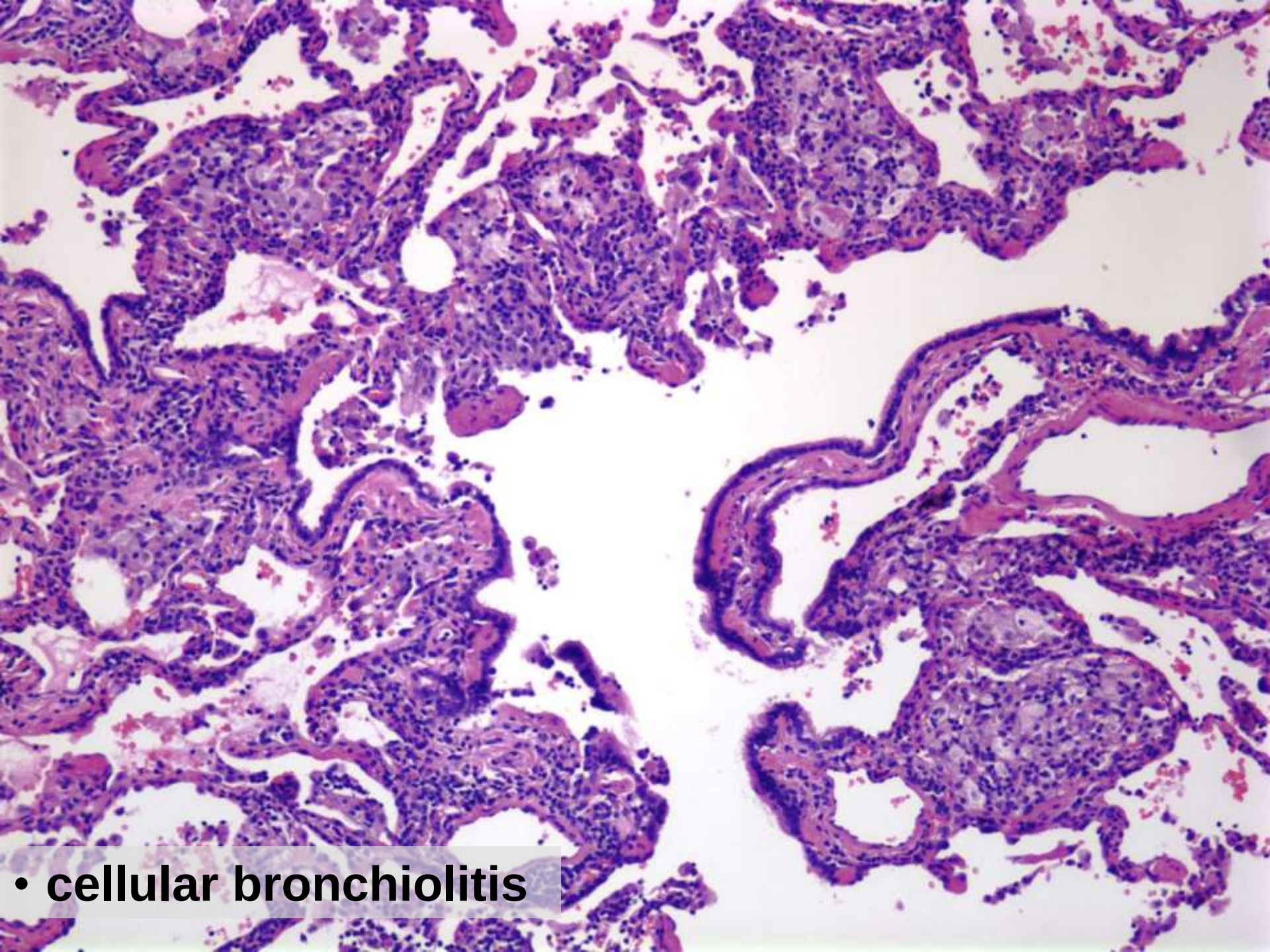
Partly depends on acute, subacute or chronic nature

- Interstitial inflammatory infiltrate (cellular interstitial pneumonitis = NSIP)
- Cellular bronchiolitis
- Granulomatous inflammation

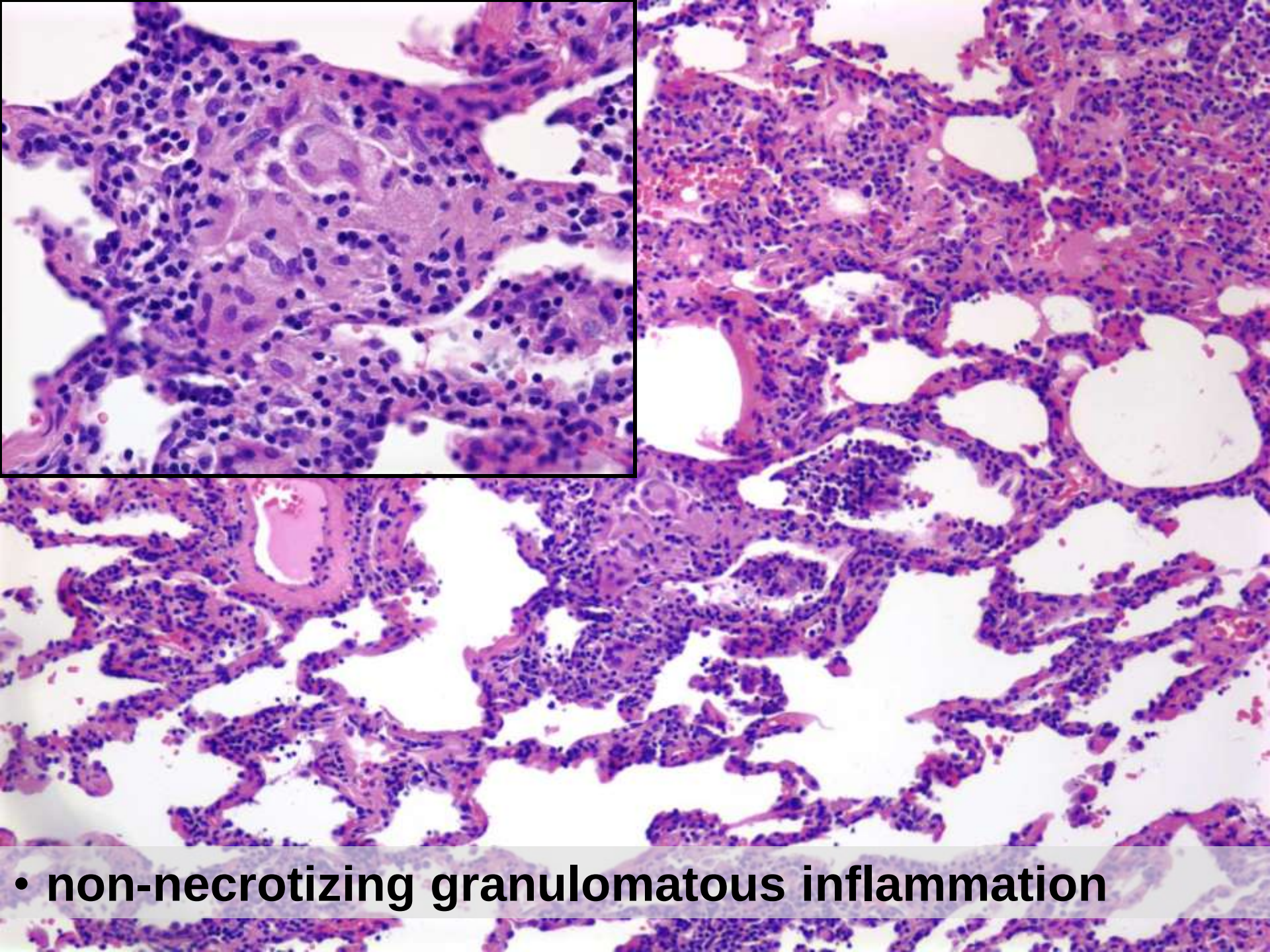
⇒ This histologic triad is seen in no more than 75% of cases.



- **cellular chronic interstitial pneumonia (“NSIP-like”)**



- **cellular bronchiolitis**



- **non-necrotizing granulomatous inflammation**

Histopathological classification of HP

Chronic bird fancier‘s lung: histopathological and clinical correlation. An application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias

Y Ohtani, S Saiki, M Kitaichi, Y Usui,

N Inase, U Costabel, Y Yoshizawa

Thorax 2005;60:665-671

Diagnostic criteria for chronic bird fancier's lung- *Thorax 2005;60:665-671*

- A history of avian contact
- Antibodies and /or lymphocyte proliferation to avian antigens
- Reproduction of symptoms of HP by an environmental provocation or laboratory controlled inhalation of avian antigens, either
- Evidence of pulmonary fibrosis with or without granulomas on histopathological analysis, or honeycombing on CT scans
- Progressive deterioration of a restrictive impairment on pulmonary function over 1 year, and
- Respiratory symptoms related to HP of >6 months

Clinical features of the patients
- *Thorax 2005;60:665-671*

Chronic bird fancier's lung was clinically divided into two subgroups:

- **Recurrent:** 10 patients

  reproduction of symptoms by environmental provocation at the beginning of the disease process

- **Insidious:** 16 patients

  a positive result following a laboratory controled inhalation provocation test but not following environmental exposure

Clinical features of the patients (cont.)
- *Thorax 2005;60:665-671*

Before the first visit to the hospital, 11/26 patients with chronic bird fancier's lung had been diagnosed as having IPF, and 1/26 as having idiopathic NSIP.

Histopathological characteristics of surgical lung biopsy specimens in chronic bird fancier's lung

Thorax 2005;60:665-671

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
n	7	8	11
Cellular bronchiolitis, %	100	50	27
Honeycombing,%	0	75	91
Fibroblastic foci, %	0	75	100
Lymphoid follicles, %	100	63	64

Histopathological characteristics of surgical lung biopsy specimens in chronic bird fancier's lung

Thorax 2005;60:665-671

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
n	7	8	11
Interstitial infiltrates of chronic inflammatory cells, %	100	88	100
Intraalveolar foamy histiocytes, %	29	25	36
Cholesterol clefts, %	57	38	46
Multinucleated giant cells, %	71	75	73
Granulomas, %	43	25	0

Clinical characteristics and histological pattern in chronic bird fancier's lung – *Thorax 2005;60:665-671*

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
n	7	8	11
Age, yrs	57	58	65
Cases of recurrent acute episode , %	86	50	0
Exertional dyspnoea, %	86	100	91
Duration of symptoms before surgical lung biopsy, months	19	46	24
Exposure periods, yrs	12	18	11
Finger clubbing, %	0	50	82

Lab and PFT characteristics and histological pattern in chronic bird fancier's lung

Thorax 2005;60:665-671

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
n	7	8	11
Anti-PDE or BDE antibodies, %	86	63	18
Antigen induced lymphocyte proliferation, %	100	88	91
VC, % pred	80	61	75
TLco, % pred	59	49	52

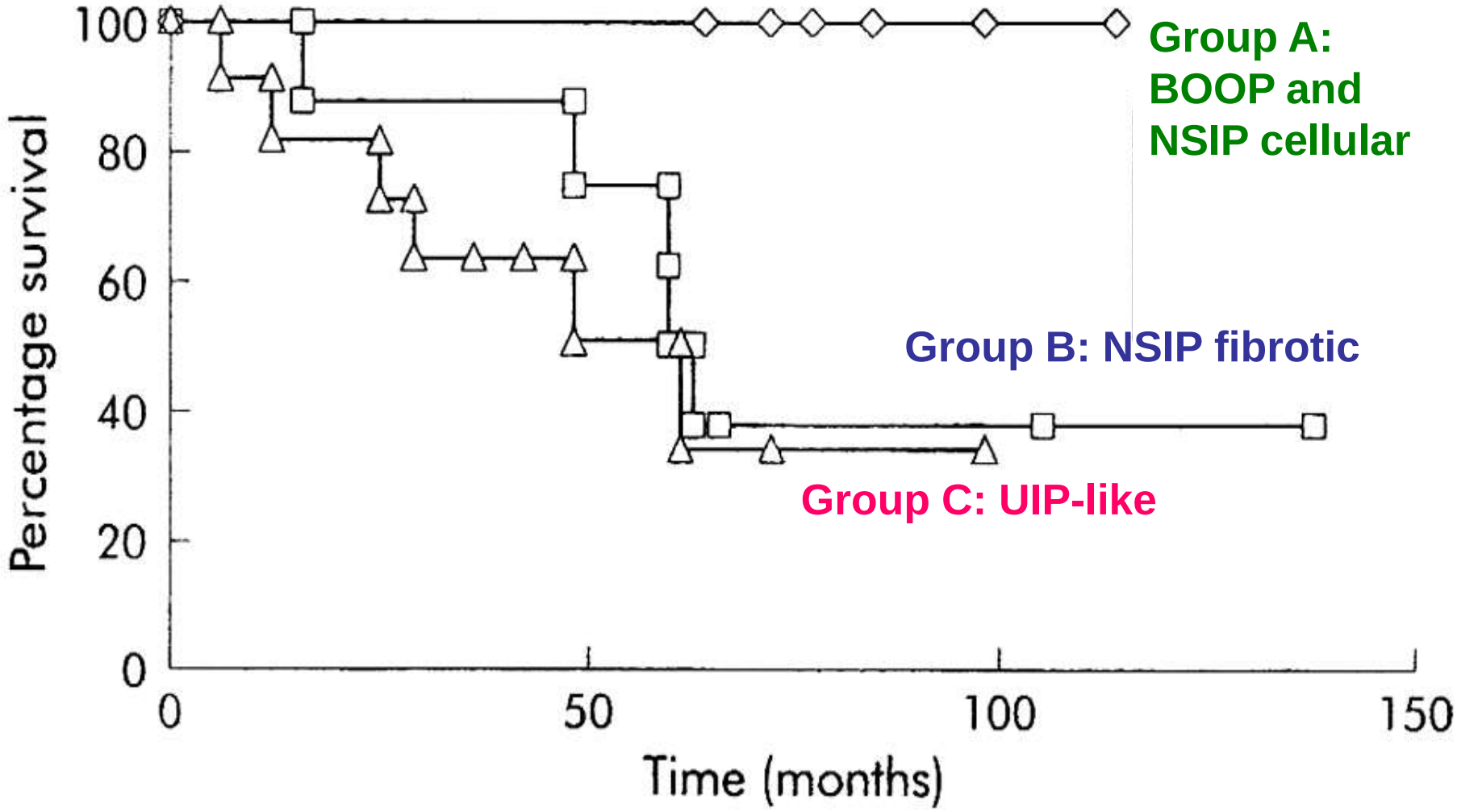
HRCT and BAL characteristics and histological pattern in chronic bird fancier's lung

Thorax 2005;60:665-671

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
Micronodules on HRCT, %	57	25	0
Traction bronchiectasis on HRCT, %	29	100	100
Honeycombing on HRCT, %	0	50	91
BAL lymphocytes, %	77	41	19

Prognosis and histological pattern in patients with chronic bird fancier's lung – *Thorax 2005;60:665-671*

	Group A: BOOP-like or cellular NSIP-like lesions	Group B: fibrotic NSIP-like lesions	Group C: UIP-like lesions
Favourable response to treatment, %	7/7	1/7	1/9
No response to treatment, %	0/7	5/7	6/9
Alive/dead	7/0	4/4	5/6



Ohtani, Saiki, Kitaichi, et al,2005

Chronic bird fancier‘s lung: histopathological and clinical correlation

- BOOP 2
- NSIP, cellular 5

} recurrent episodes, good outcome

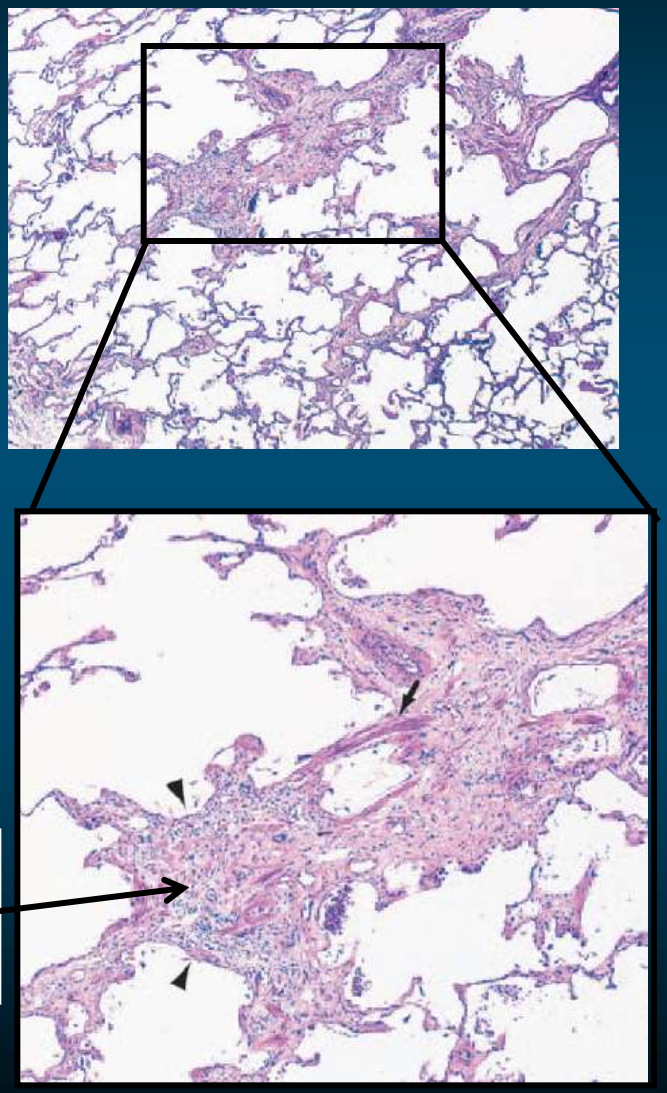
- NSIP, fibrotic 8
- UIP-like 11

} insidious onset, unfavorable outcome

Total n = 26

Histopathologic findings in IPF vs chronic HP

- Autopsy findings in 16 well defined CHP and 11 IPF
  - Honeycomb change in all
  - Granulomas in none
  - Macroscopic changes more common in upper lobes of CHP (44%) than IPF (0%)
  - Centrilobular fibrotic lesions more common in CHP



„Bridging fibrosis“

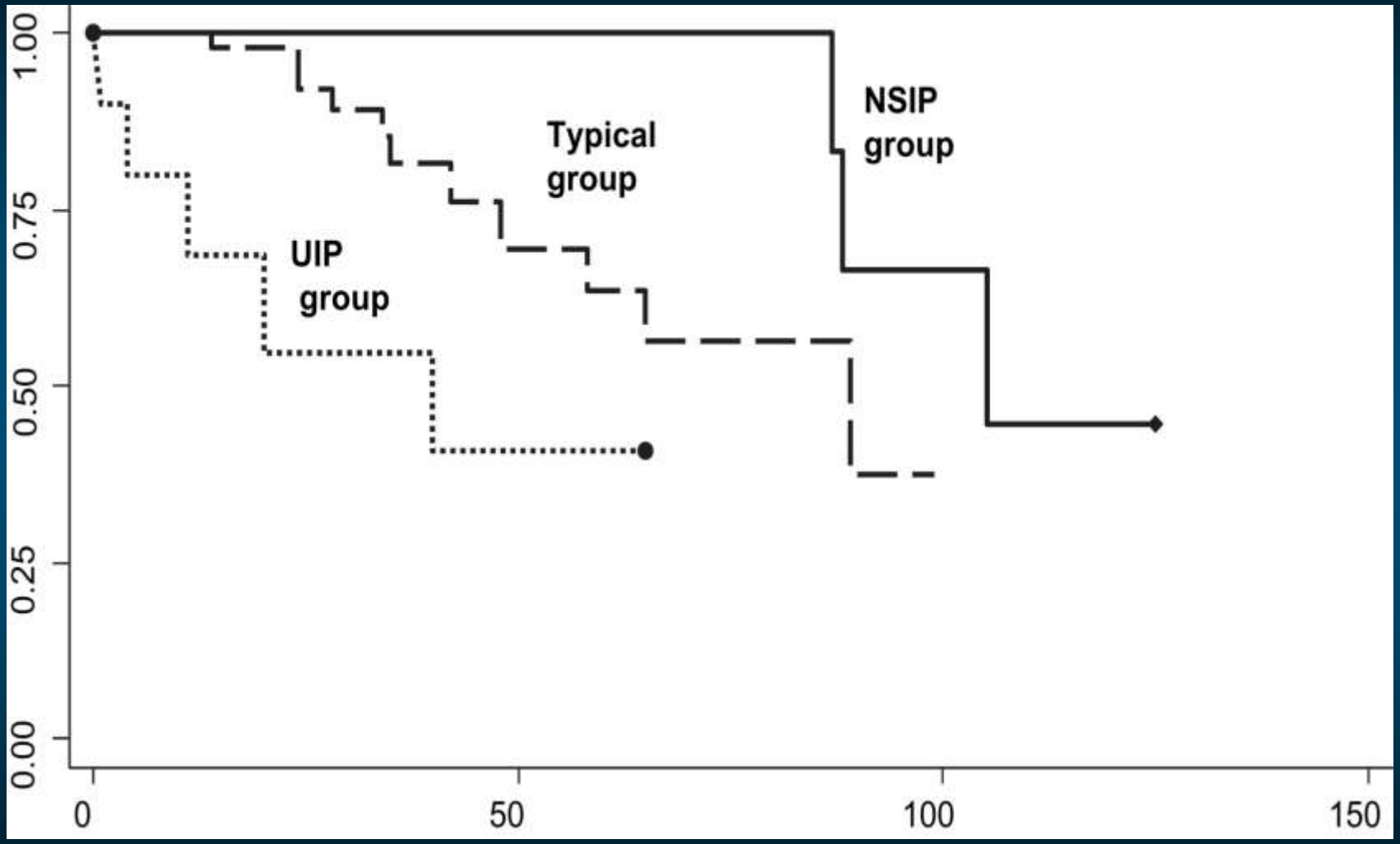
Akashi et al. *Am J Clin Pathol* 2009; 131: 405-15

Histological pattern in chronic pigeon breeder's disease: correlation with clinical data

	Typical pattern *n* = 58	NSIP pattern *n* = 22	UIP-like pattern *n* = 10	*p*
Finger clubbing	30/56 (53)	10/21 (47.6)	8/10 (80)	0.26
BAL lymphocytes %	65 ± 21	52 ± 23	36 ± 23	0.0011
BAL macrophages %	34 ± 20	45 ± 23	59 ± 18	0.0028
BAL eosinophils %	1 (0–9)	0 (0–13)	2 (0–13)	0.11
BAL neutrophils %	0 (0–10)	1 (0–10)	1 (0–4)	0.61
HRCT				
Inflammation (%)	30/40 (75)	11/16 (69)	1/7 (14)	<0.007
Fibrosis (%)	10/40 (25)	5/16 (31)	6/7 (86)	<0.007

Gaxiola M et al, Respir Med 2011

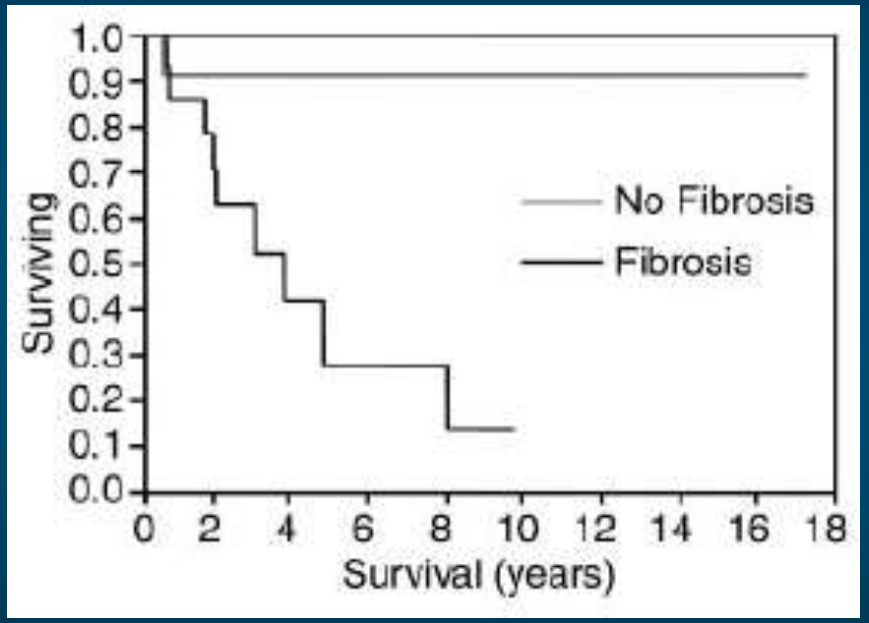
Survival rate according to histological pattern



Gaxiola M et al, Respir Med 2011

HRCT Features in Relation to Fibrosis on Biopsy

	Fibrotic HP (n=15)	Non-Fib HP (n=11)	p value
Onset (yrs)	5	3	0.08
UIP pattern	6(40)	0	0.02
Honeycomb	8(53)	0	0.007
Tr Bronchiec.	8(53)	0	0.007
Reticular >25%	11(73)	2(18)	0.02



No difference in GGO, Centrilobular nodules, emphysema, Mosaic attenutaion

Sahin et al. 2007 *Radiology* 244:591-8

Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants

Simon L. F. Walsh · Nicola Sverzellati ·
Anand Devaraj · Athol U. Wells · David M. Hansell

Eur Radiol (2012) 22:1672–1679

Chronic HP:
HRCT patterns predict mortality

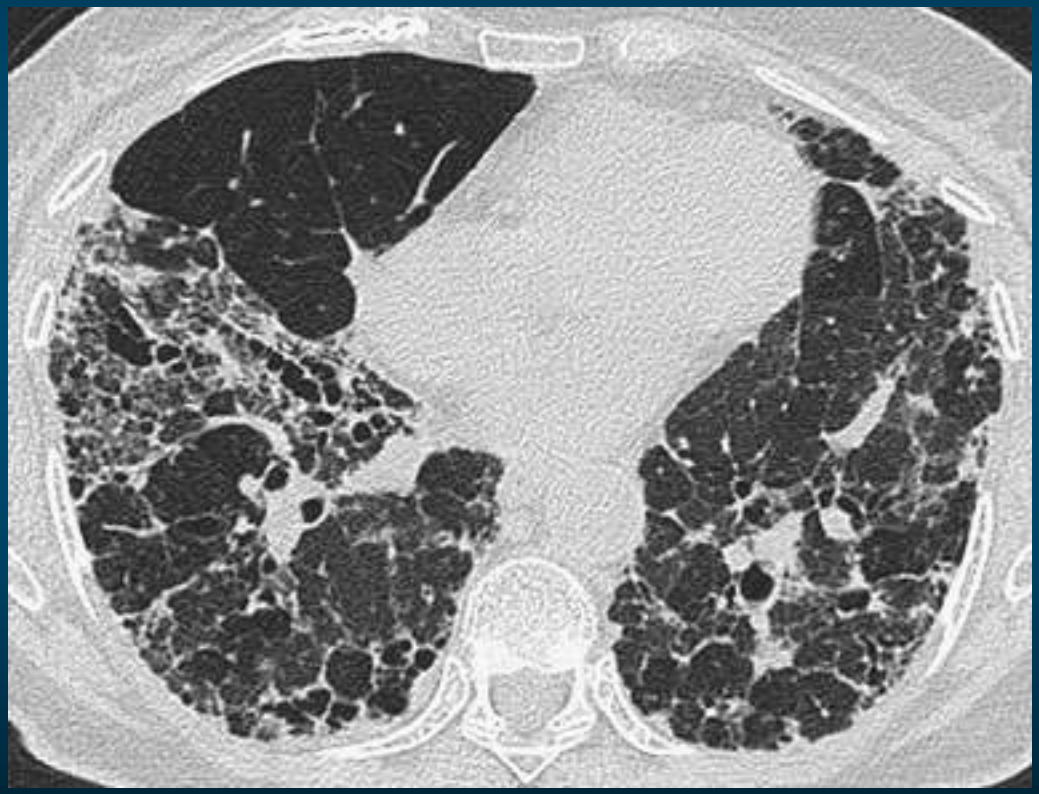
Chronic HP
n=92

↓

PFT, HRCT
Score

↓

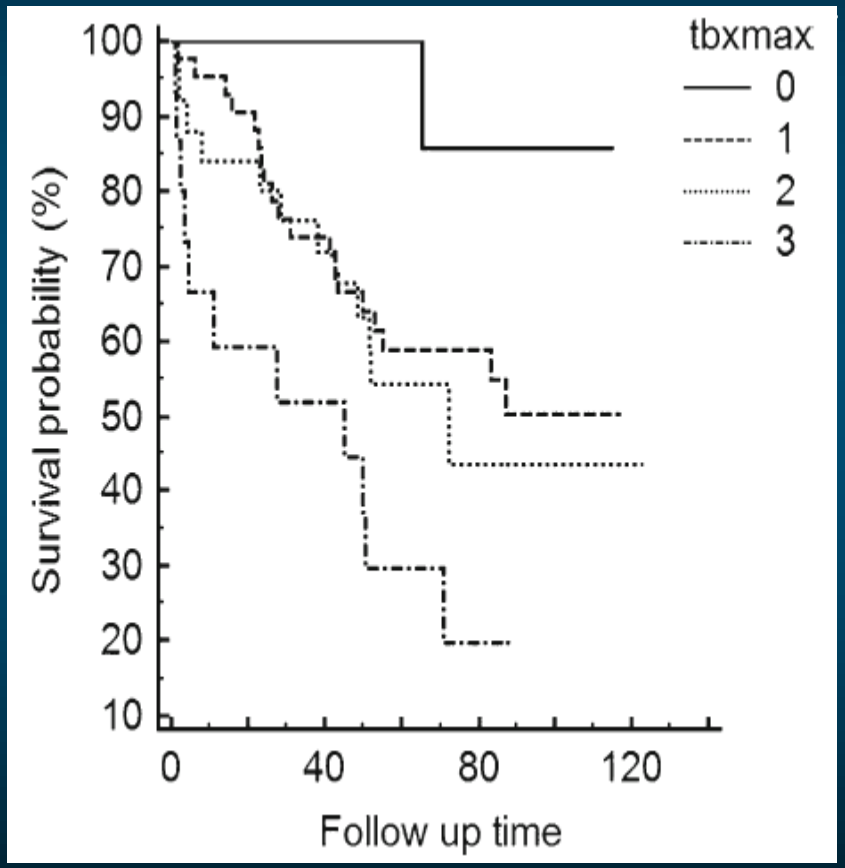
Correlate with
survival



Walsh et al, Eur Radiol 2012

HRCT patterns and mortality in HP

Variable	Hazards ratio	*P* value	95% CI
Total interstitial disease extent	1.02	0.02	1.00-1.03
Microcystic honeycombing	1.09	0.019	1.01-1.17
Macrocystic honeycombing	1.06	<0.01	1.01-1.10
Traction bronchiectasis	1.10	<0.001	1.04-1.16



*Each patient was assigned a maximum traction bronchiectasis score (Tbxmax) ranging from 0–3.

Walsh et al, Eur Radiol 2012

Conclusions from this study

- Superiority of HRCT patterns over pulmonary function for determining prognosis in chronic HP

- Increasing severity of traction bronchiectasis is the strongest determinant of mortality

Walsh et al, Eur Radiol 2012

Classification According to Disease Behavior

Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g. acute HP, many cases of RB-ILD)	Remove possible cause	Short-term (3-6 month) observation to confirm disease regression
Reversible disease with risk of progression (e.g. subacute HP, cellular NSIP and some fibrotic NSIP, COP)	Initially for a response & then rationalize longer term therapy	Short-term observation to confirm treatment response. Long term observation to ensure that gains are preserved
Stable with residual disease (e.g. inactive HP with some fibrotic residuals)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g. some chronic HP, some fibrotic NSIP)	To stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g. IPF, some chronic HP, some fibrotic NSIP)	To slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

ATS/ERS Update of Classification of IIPs 2013

Summary

- HP is a complex syndrome rather than a single disease
- Aetiological classification
- Clinical classification
- Histopathological classification
- HRCT classification
- Disease behavior classification

Thank you for your attention