Hypersensitivity pneumonitis

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scope

- Epidemiology
- Clinical manifestration
- Diagnosis
- management

epidemiology

- ILD 30/100000
- HP less than 2% of incident cases
- Definition of dis
- Definite diagnosis
- Classification of resp. tract dis
- Geographic variable
- In general =>prevlence 0.5-3% of exposure

TABLE I. Causative agents of hypersensitivity pneumonitis

Agent*	Source	Disease
Microbes		
Thermophilic actinomycetes	Moldy plant materials	Farmer's lung
Saccharopolyspora rectivirgula ***(Micropolyspora faeni)***	Moldy hay	
Thermoactinomyces vulgaris	Moldy hay, compost	Farmer's lung, mushroom-worker's lung, composter's lung
Thermoactinomyces sacchari	Sugar cane residue	Bagassosis
Bacillus subtilis	Detergent enzymes	Detergent-worker's lung
Aspergillus clavatus	Moldy grains	Malt-worker's lung
Aspergillus versicolor	Animal bedding	Dog house disease
Aspergillus species	Tobacco mold	Tobacco-worker's lung
Penicillium casei	Cheese mold	Cheese-washer's lung
Penicillium frequentans	Moldy cork	Suberosis
Penicillium chrysogenum	Moldy wood dust	Woodworker's lung
Cryptostroma corticale	Moldy maple bark	Maple bark–stripper's lung
Aureobasidium pullulans	Moldy sequoia dust	Sequoiosis
Aureobasidium species	Contaminated water	Sauna-taker's disease
Alternaria species	Wood or wood pulp	Woodworker's lung
Merulius lacrymans	—	Dry rot lung
Botrytis cinerea	Grape mold	Winegrower's lung or Späetlase lung
Trichosporon cutaneum	Mold in Japanese homes	Summer-type HP
Cephalosporium	Sewage	Sewage-worker's lung
Mucor stolonifer	Paprika	Paprika-splitter's lung
Candida albicans	Saxophone mouthpiece	Sax lung
Mycobacterium avium-intracellulare	Contaminated water	Hot tub lung
Mixed ameba, fungi, and bacteria	Cold mist and other humidifiers, air conditioners	Nylon plant or office worker's or air conditioner's lung, ventilation pneumonitis
Bacteria and fungi	Contaminated metal-working fluids	Machine-operator's lung

TABLE I. Causative agents of hypersensitivity pneumonitis

Agent*	Source	Disease
Animals		
Avian proteins	Bird excreta, blood, or feather	Bird-breeder's lung, bird-fancier's lung, pigeon-breeder's lung
Rat proteins	Rat urine or serum	Rodent-handler's lung
Gerbil proteins	Gerbil	Gerbil-keeper's lung
Animal fur protein	Animal fur	Furrier's lung
Ox and pork protein	Pituitary snuff	Pituitary snuff–taker's lung
Mollusk shell protein	Mollusk shell dust	Oyster shell lung
Fish	Fish meal dust	Fishmeal-worker's lung
Wheat weevil	Flour	Miller's lung
Silk worm la		
Plants		
Soybean		
Coffee		
Lycoperdon s		
Chemicals		
Isocyanates		
Anhydrides		, plastic-worker's lung
Pauli's reage		
Bordeaux mi		
Pyrethrum	Insecticides	Insecticide lung
Metals		
Cobalt	—	Hard metal lung disease
Beryllium	—	Berylliosis

*The more frequent causative agents are listed in bold type.

Medications or Drugs

Amiodarone, clozapine, cyclosporin, gold, procarbazine, minocycline, chlorambucil, sulfasalazine, nitrofurantoin, HMG-CoA reductase inhibitor, methotrexate, beta blockers, intranasal heroin, intravesicular BCG, mesalamine, fluoxetine	Medications	Drug-induced HP

Amoebae		
Naegleria gruberi	Contaminated ventilation system	Ventilation pneumonitis
Acanthamoeba castellani		

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NOVEMBER 2001

Diagnostic criteria

- **Several diagnostic criteria have been published**
- **The most widely used => Richerson et al**
- **Criteria => not validate**

unknown diagnostic accuracy

Richerson et al. (25)

1. The history and physical findings and pulmonary function tests indicate an interstitial lung disease
2. The X-ray film is consistent
3. There is exposure to a recognized cause
4. There is antibody to that antigen

2. The X-ray film is consistent
3. There is exposure to a recognized cause
4. There is antibody to that antigen

Allergy 2009: 64: 322–334

TABLE II. Diagnostic criteria for hypersensitivity pneumonitis*

Major criteria

1. History of symptoms compatible with hypersensitivity pneumonitis that appear or worsen within hours after antigen exposure
2. Confirmation of exposure to the offending agent by history, investigation of the environment, serum precipitin test, and/or bronchoalveolar lavage fluid antibody
3. Compatible changes on chest radiography or high-resolution computed tomography of the chest
4. Bronchoalveolar lavage fluid lymphocytosis, if bronchoalveolar lavage performed
5. Compatible histologic changes, if lung biopsy performed
6. Positive "natural challenge" (reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment) or by controlled inhalational challenge

Minor criteria include:

1. Basilar crackles
2. Decreased diffusion capacity
3. Arterial hypoxemia, either at rest or with exercise

*Adapted from Schuyler and Cormier.[66]

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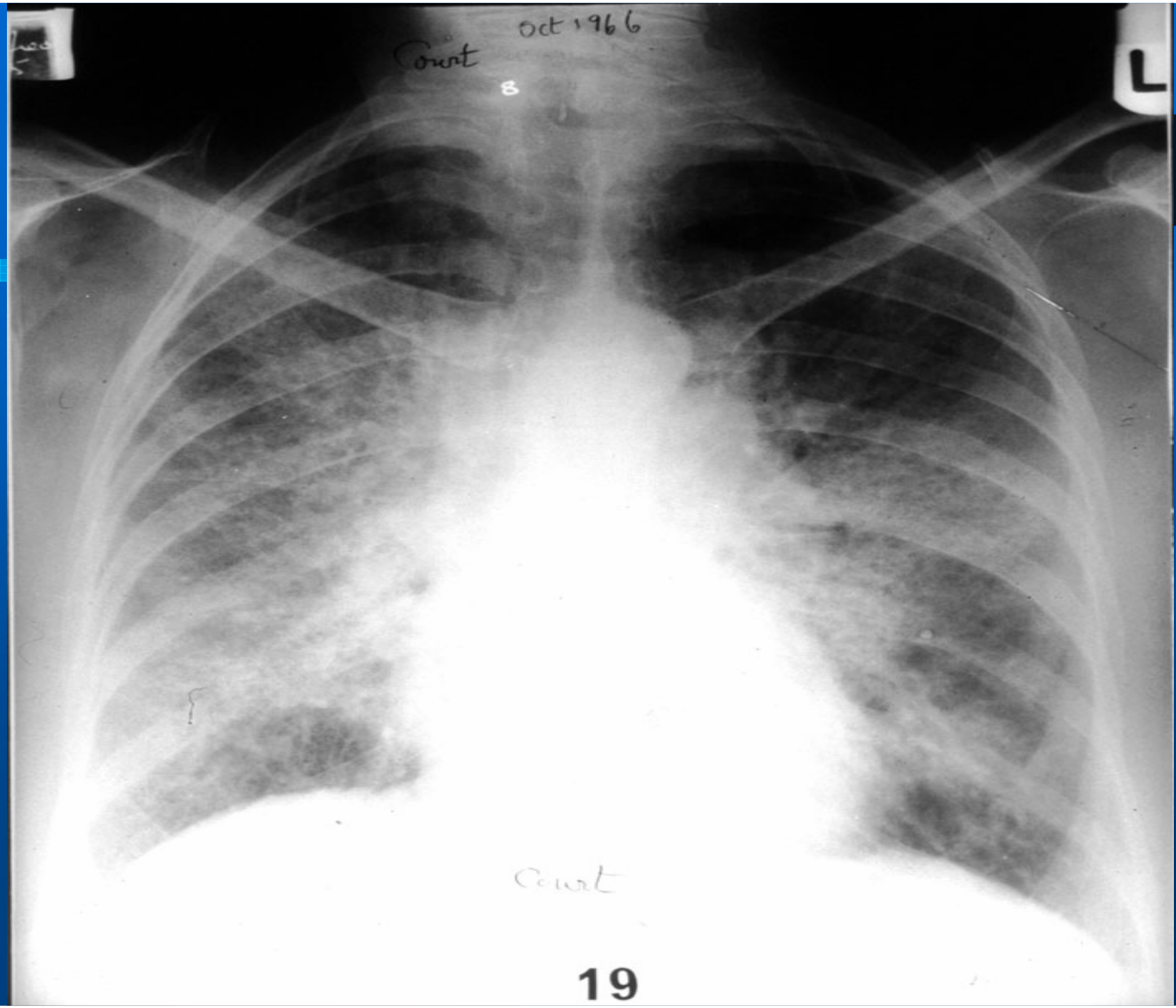
NOVEMBER 2001

Diagnostic method

- **CXR**

  - in acute HP => *fine ground-glass appearance nodular, straited patchy opacity*
  - in subacute HP => *spare lung base,linear shadow,small nodule*
  - in chronic HP => *loss lung volume,Reticular infiltration,interstitial fibrosis,predominant upper & middle lung zone*
  - 20% normal CXR

Pleural effeusion & hilar adenopathy are rare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- **CT scan**

  pattern not specific but suggestive HP

ground glass appearance!

Poorly defined ,centrilobular micronodule ,mosaic pattern and expiratory airtrap. increase propability of HP

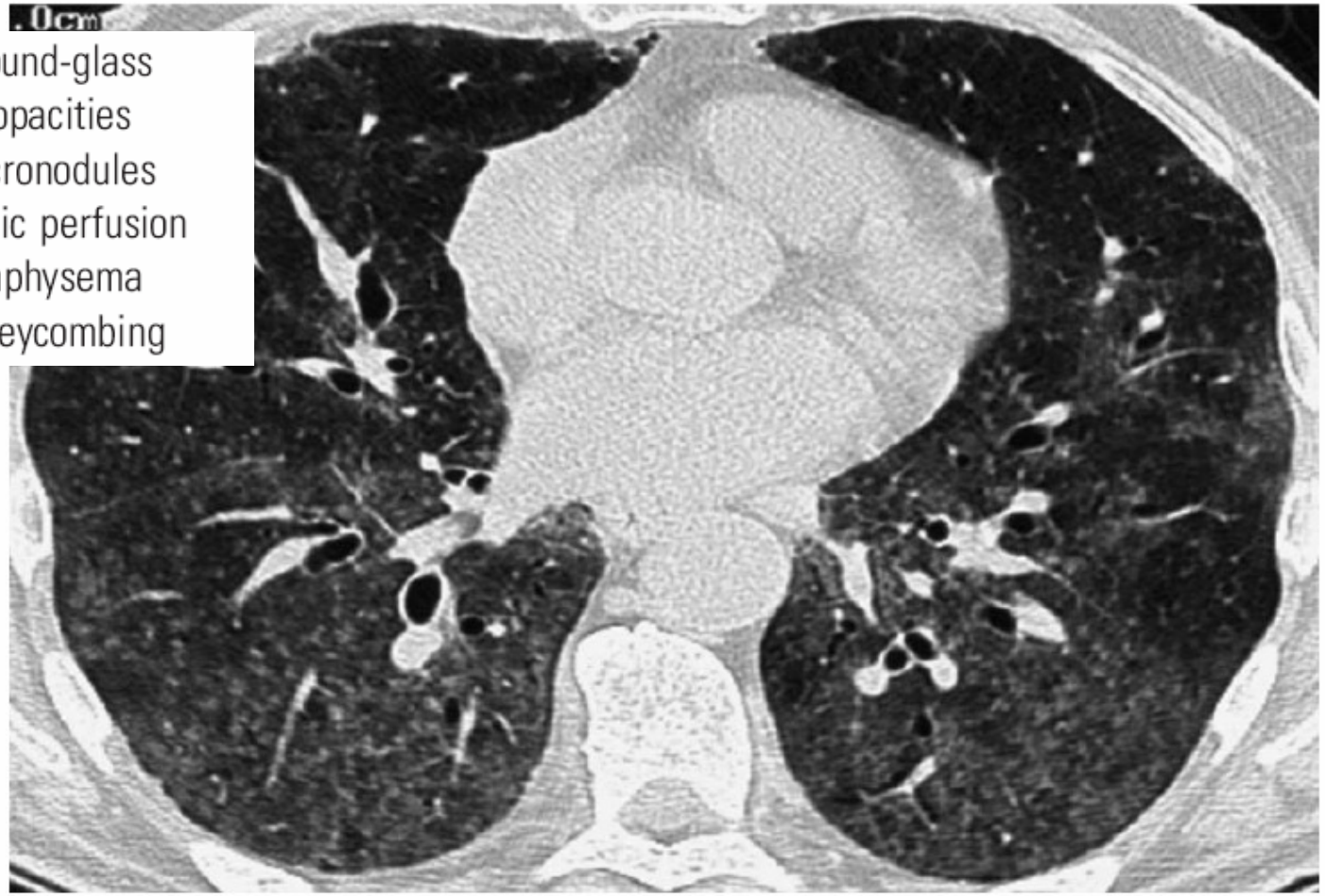
Table 4. High-resolution CT findings in hypersensitivity pneumonitis

Stage of disease	References	Sample size	Findings
Acute	Cormier et al. (41)	*n* = 20 (farmer's lung)	Ground-glass opacities Micronodules Mosaic perfusion Emphysema Honeycombing Mediastinal lymphadenopathies
Subacute	Hansell and Moskovic (42)	*n* = 17 (including 9 with pigeon breeder's disease and 4 with farmer's lung)	Generalized increase in attenuation of the lung Nodular pattern Reticular pattern Patchy air space opacification
	Remy-Jardin et al. (43)	*n* = 21 (pigeon breeder's disease)	Micronodular pattern (<5 mm in diameter) Ground-glass attenuation Emphysematous changes Honeycombing
Chronic	Adler et al. (44)	*n* = 16 (antigen = ?)	Fibrosis Ground-glass attenuation Nodules
	Remy-Jardin et al. (43)	*n* = 24 (pigeon breeder's disease)	Honeycombing Ground-glass attenuation Micronodules emphysema

The findings are ranked according to their decreasing order of prevalence in the study population.

Figure 1. High resolution computed tomography of acute hypersensitivity pneumonitis

Ground-glass opacities
Micronodules
Mosaic perfusion
Emphysema
Honeycombing

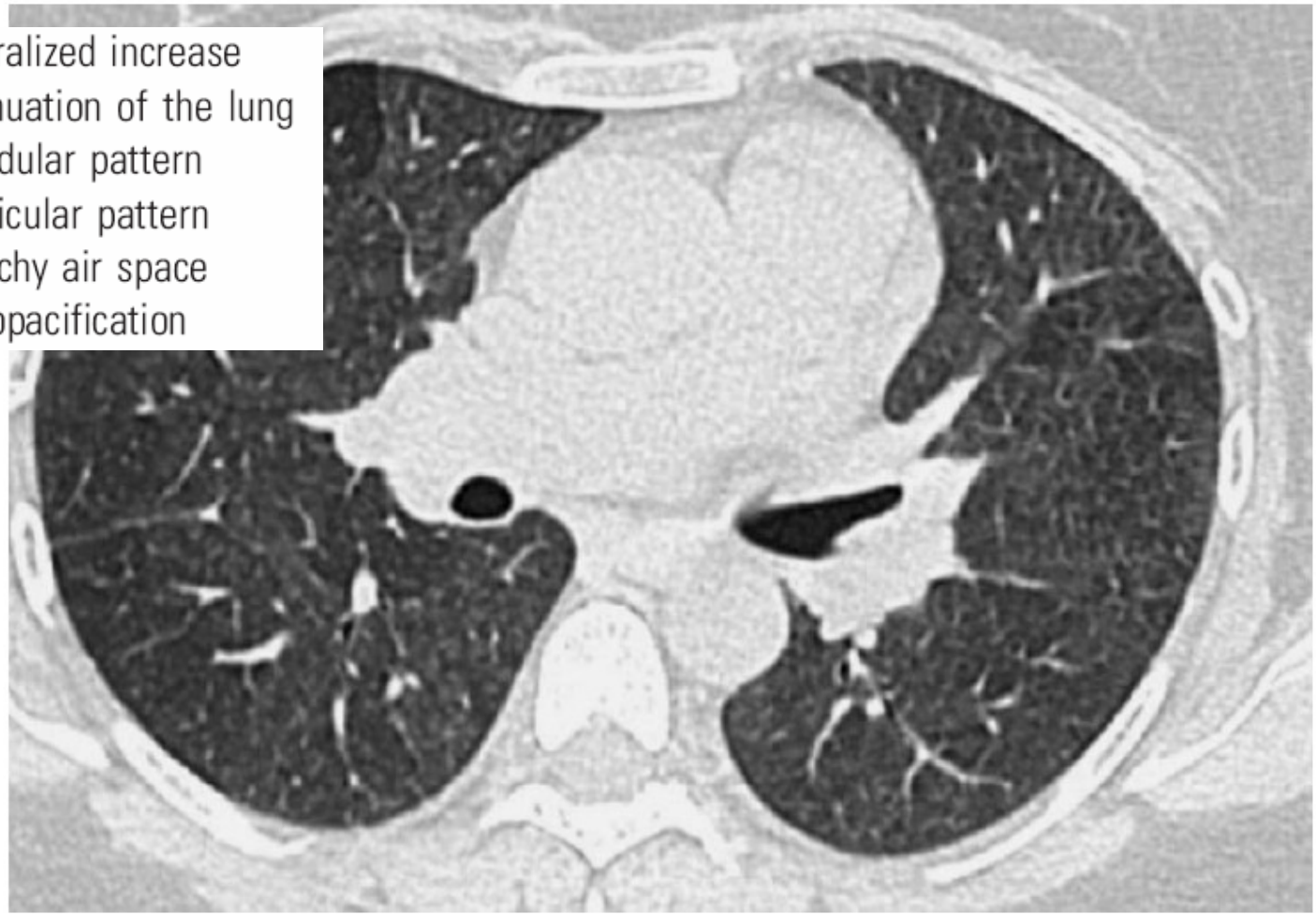


High resolution computed tomography of acute HP, showing scattered ground-glass opacities, which consist of multiple small nodules.

Current Opinion in Pulmonary Medicine 2004, 10:401–411

Figure 2. High resolution computed tomography of an advanced case of subacute hypersensitivity pneumonitis

Generalized increase
in attenuation of the lung
Nodular pattern
Reticular pattern
Patchy air space
opacification

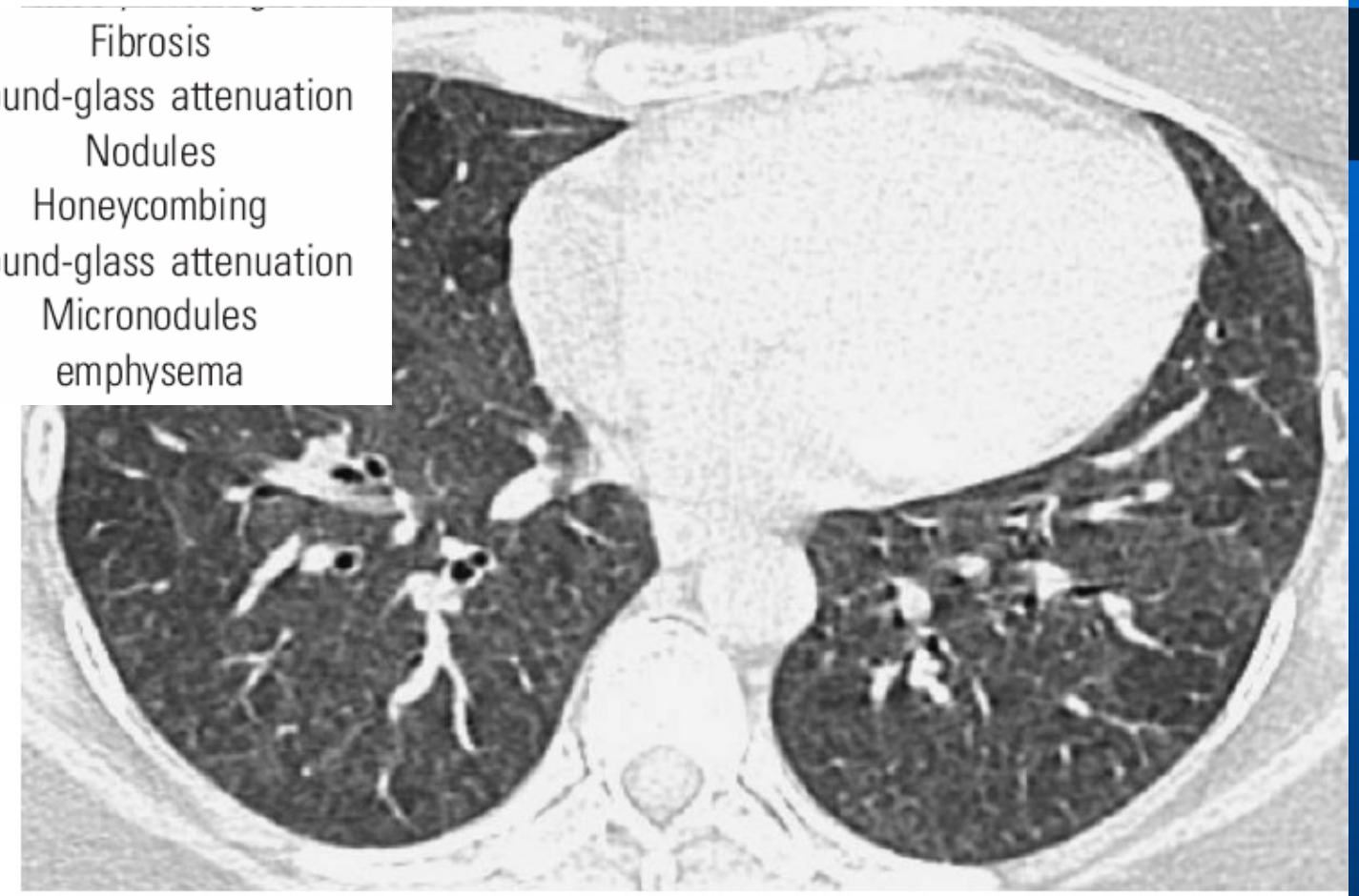


High resolution computed tomography of an advanced case of subacute HP showing multiple micronodules and scattered areas of mild fibrosis.

Current Opinion in Pulmonary Medicine 2004, 10:401–411

Figure 3. High resolution computed tomography of chronic hypersensitivity pneumonitis

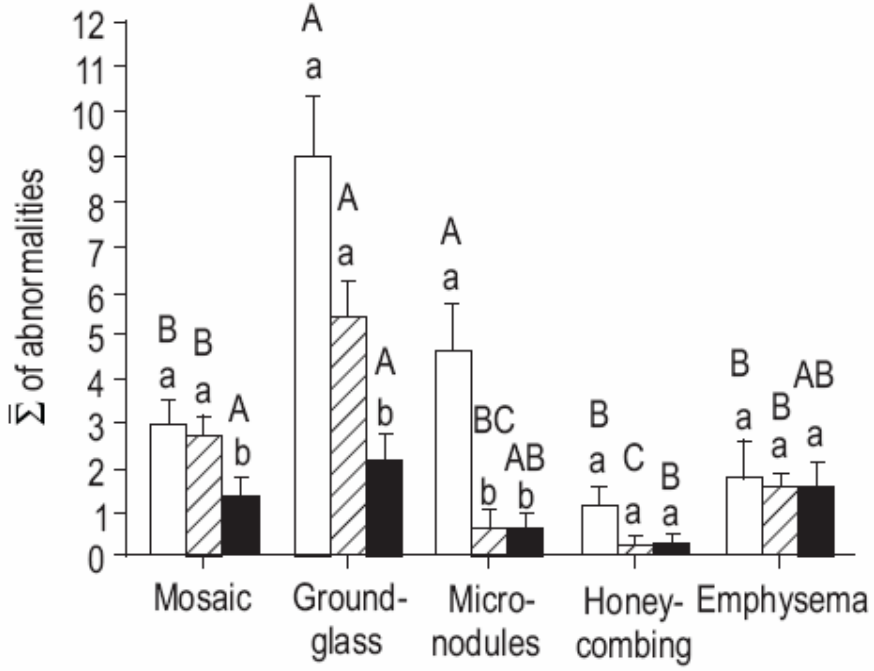
Fibrosis
Ground-glass attenuation
Nodules
Honeycombing
Ground-glass attenuation
Micronodules
emphysema



High resolution computed tomography of chronic HP showing pulmonary fibrosis with several areas of honeycombing. Areas of increased radiolucency are seen among scattered ground-glass opacities. These are thought to represent hyperinflated pulmonary lobules caused by partially obstructed bronchioles.

Current Opinion in Pulmonary Medicine 2004, 10:401–411

High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up



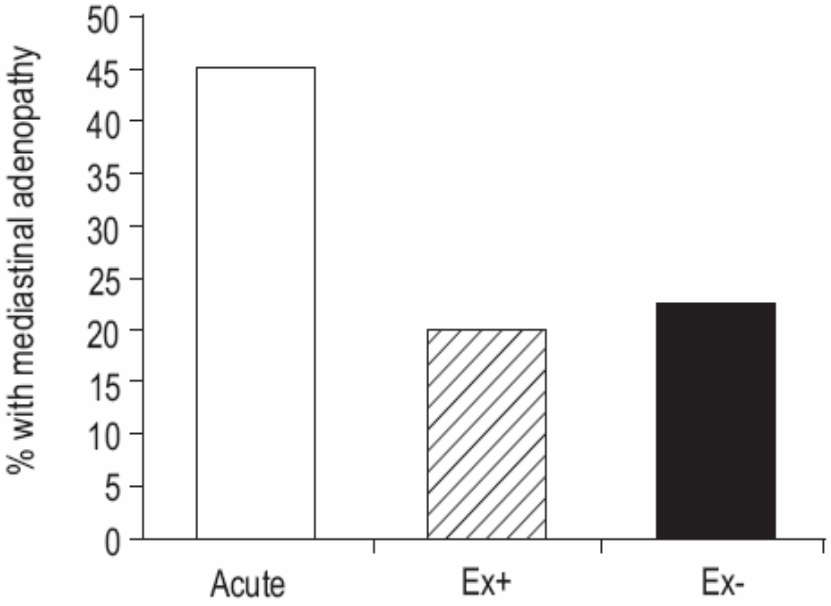


Fig. 3. – Percentage of subjects from the three groups studied with enlarged mediastinal lymph nodes (smaller diameter >1 cm).

Eur Respir J 2000; 16: 56–60

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		*p*
	Chronic HP (*n* = 19)	UIP (*n* = 33)	
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

AJR 1995;165:807–811

- **PFTs**
  - guild to therapy
  - not useful for differentiating HP from other ILD
  - acute HP =>restrictive pattern with low DLCO
  - chronic pattern can be restrictive (Farmer lung show obstructive defect)
  - ABG wide A-a gradient, hypoxemia in some case
  - 22% normal DLCO at the time Dx

- **Specific antibodies**
  - not always present in HP
  - 1-15% +ve sAbs develop HP
  - use for supportive evidence
  - +ve sAbs is sig. predictor of HP
  - not all antigen are commercial available
  - ELISA is prefer

- Inhalation challenge
  - lack of standardization
  - further study was need

- **BAL**

- important role for Dx HP

- normal lymph number => rule out HP

- predominant CD8+, CD4+/CD8+ < 1

- what dis. that CD4+, CD4+/CD8+ > 1 ?

Sarcoidosis (ratio >4 100% PPV for DDx)

Keyword of cell in BAL

in acute phase CD4 predominant and increase CD4/CD8 ratio and then follow

by predominant CD8+ Tcell and decrease CD4/CD8 ratio in chronic phase

Is that true ?

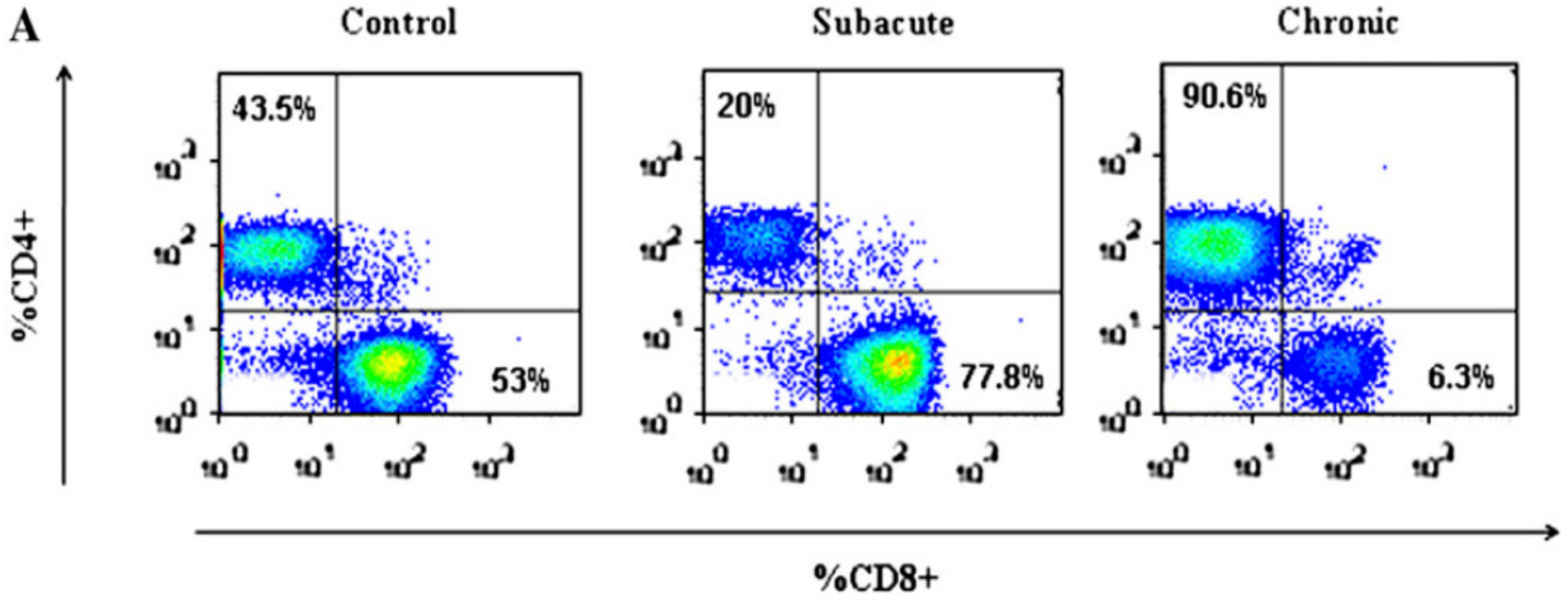
Depend on - dose and type of inhaled antigen

- stage of disease

- other nonspecific stimulation

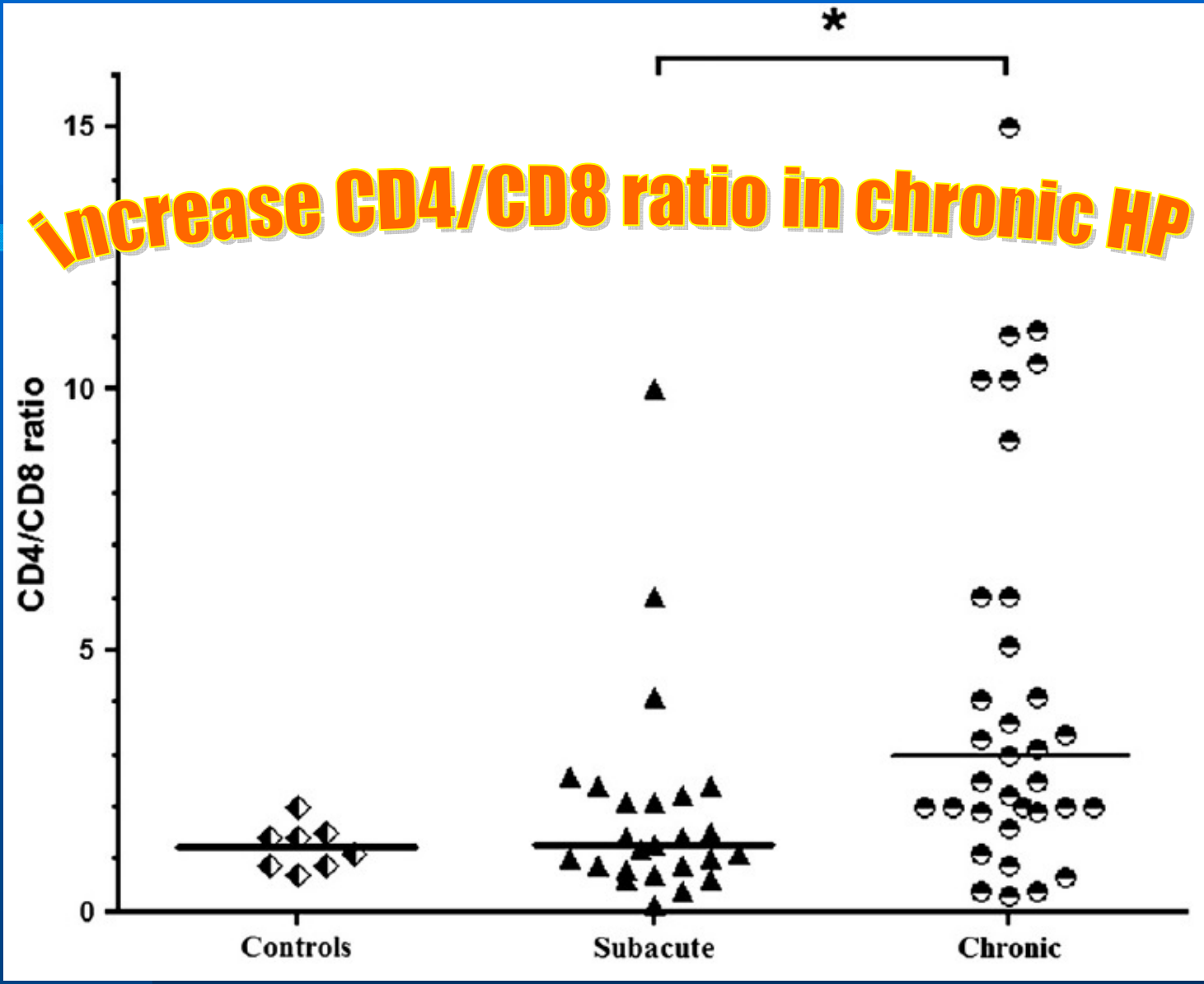
Functional Diversity of T-Cell Subpopulations in Subacute and Chronic Hypersensitivity Pneumonitis

n=8 n=25 n=30



Am J Respir Crit Care Med Vol 177. pp 44–55, 2008

Increase CD4/CD8 ratio in chronic HP



Am J Respir Crit Care Med Vol 177. pp 44–55, 2008

Extrinsic allergic alveolitis: comparative study of the bronchoalveolar lavage profiles and radiological presentation

Table 5 Subjects' characteristics before the clinical presentation of the disease and to the exposure to the causative antigen at the time of the diagnosis

	Subacute	Chronic	Exposure+	Exposure −
Increased IgG	71%	14%	57%	29%
Normal IgG	2[illegible]%	[illegible]%	[illegible]%	71%
[illegible]	[illegible]%	4[illegible]%	[illegible]%	[illegible]
[illegible]				
Normal BAL lymphocyte count	29%	57%	14%	71%
Decreased CD4/CD8	86%	43%	86%	43%
Normal CD4/CD8	14%	57%	14%	57%
Increased HLA-DR +	100%	57%	86%	71%
Normal HLA-DR +	0%	43%	14%	29%
HRCT alveolar	2.9	1.6	3.5	1.4
HRCT interstitial	1.7	2.6	1.7	2.6

decrease CD4/CD8 ratio in acute HP

Postgrad Med J 2006;**82**:598–601

Lung biopsy

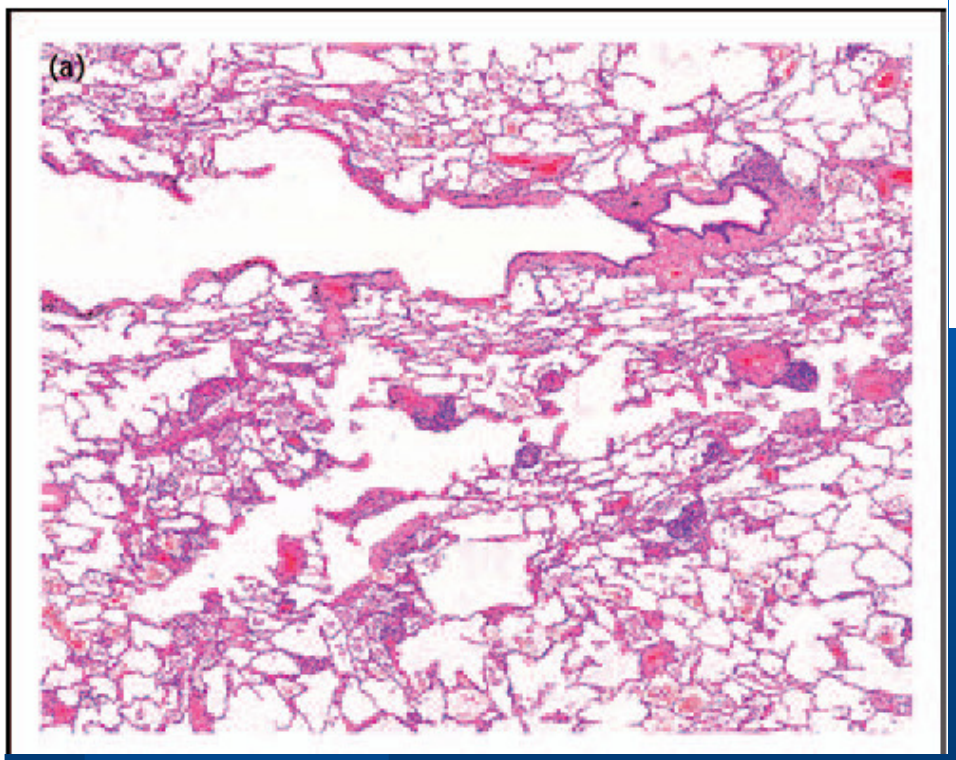
- **Acute**
  - **PMN,Eo infiltrate in alveolar space**
  - **DAD**
  - **Ig and complement deposition in vss.**

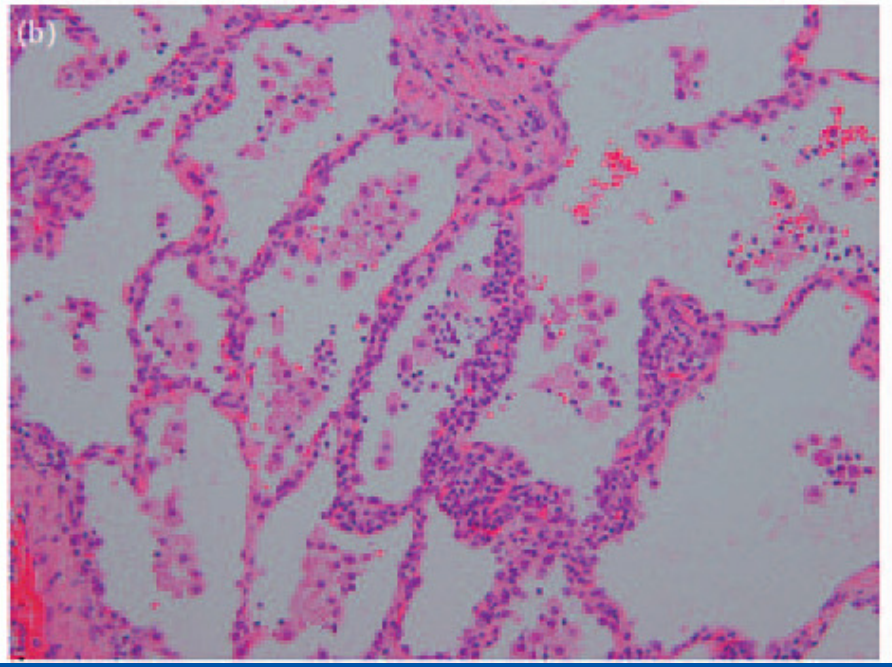
Current Opinion in Pulmonary Medicine 2008, 14:440–454

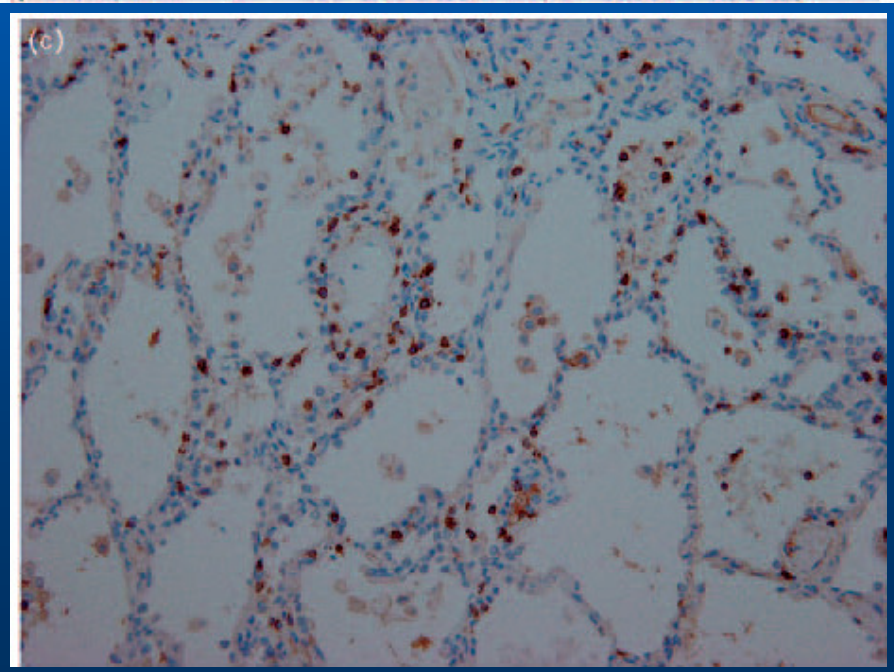
- **Subacute**
  - lymphocyte dominant interstitial infiltration
  - poorly formed nonnecrotizing granuloma
  - cellular bronchiolitis
  - intra-alveolar fibrosis
  - NSIP

Current Opinion in Pulmonary Medicine 2008, 14:440–454

Figure 1 Lymphocytic alveolitis in subacute hypersensitivity pneumonitis







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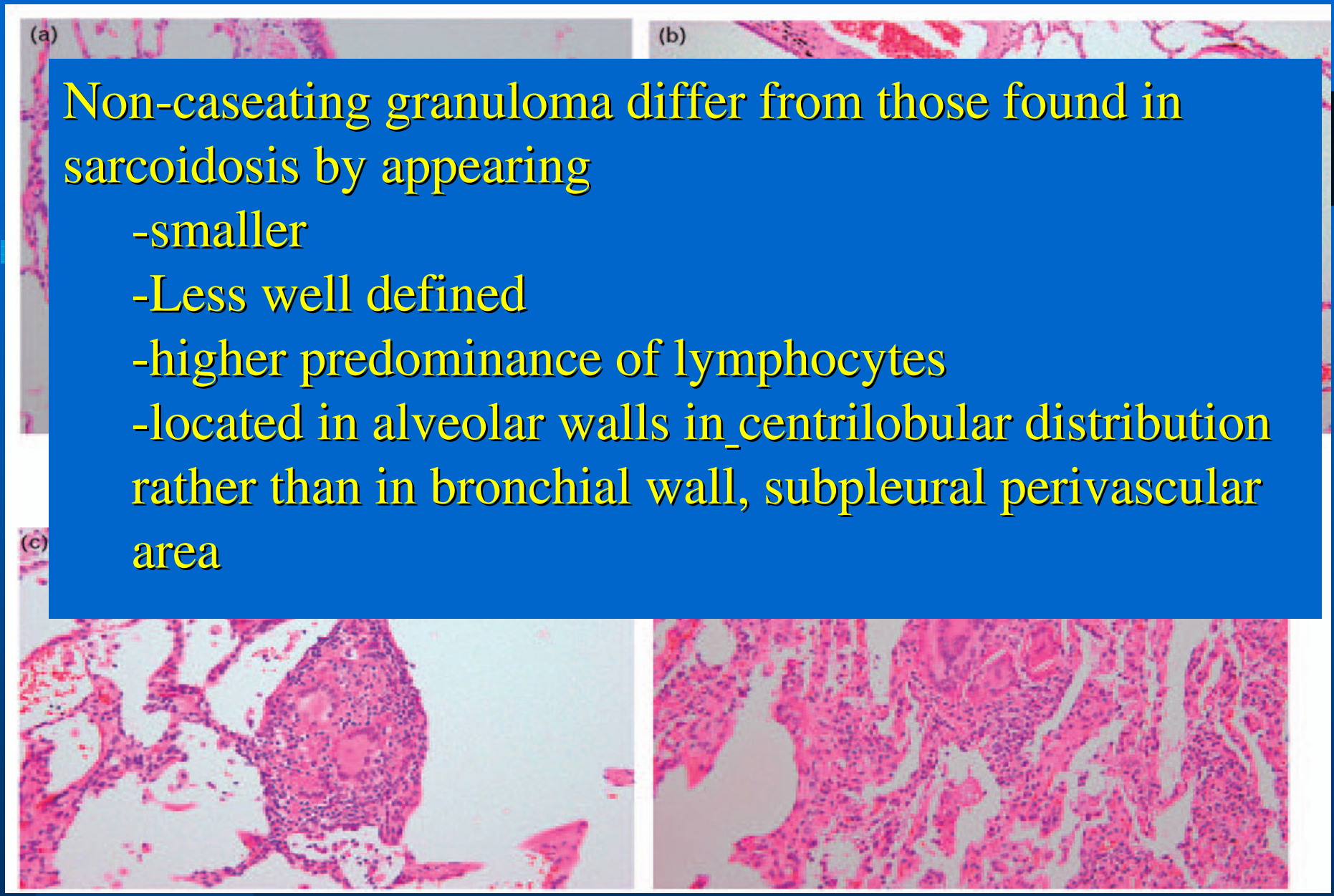


Non-caseating granuloma differ from those found in sarcoidosis by appearing

-smaller

-Less well defined

-higher predominance of lymphocytes

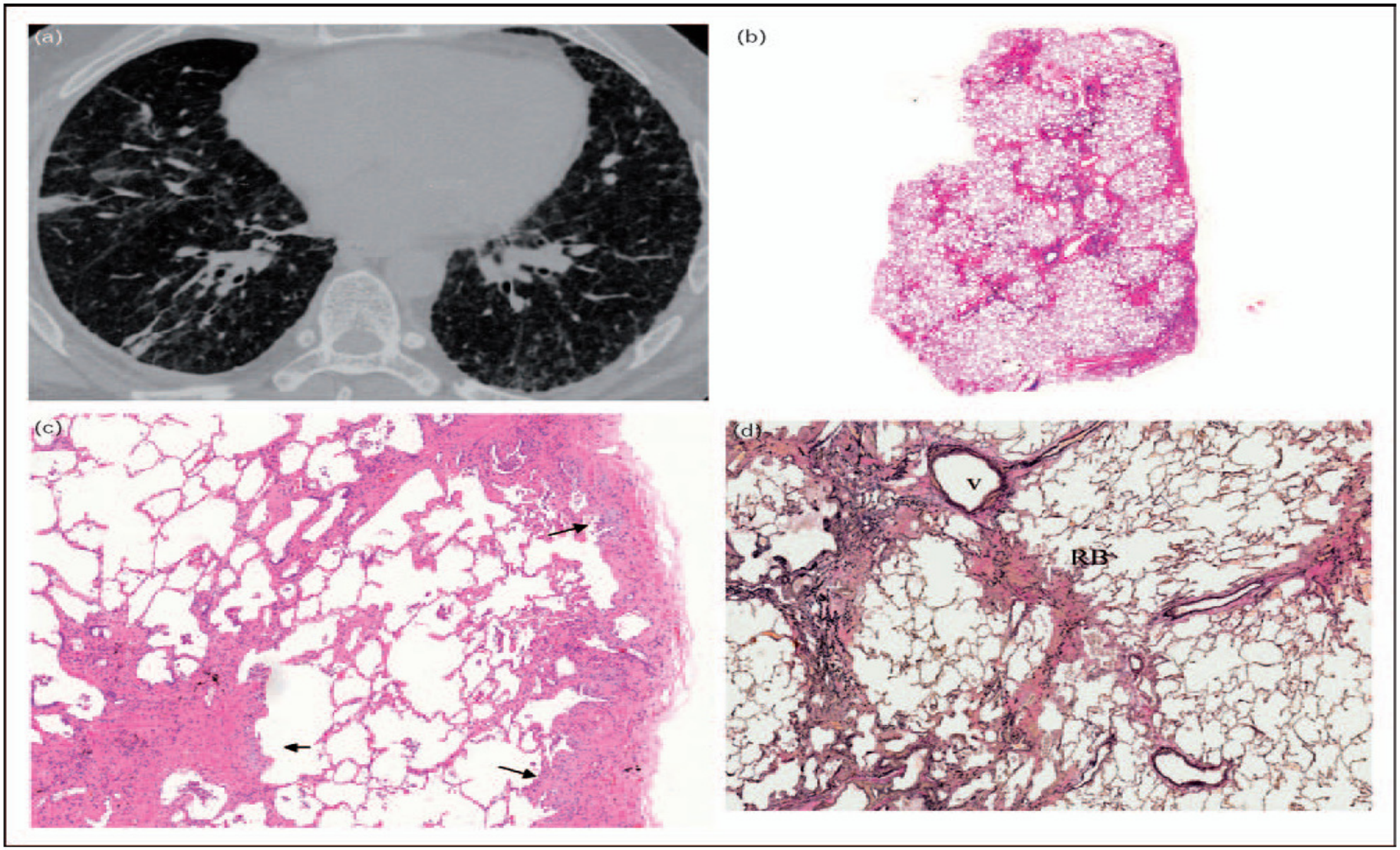
-located in alveolar walls in centrilobular distribution rather than in bronchial wall, subpleural perivascular area

Current Opinion in Pulmonary Medicine 2008, 14:440–454

- Chronic
  - UIP-liked pattern
  - NSIP-liked pattern
  - organizing pneumonia pattern
  - centrilobular fibrosis with or without granuloma

Current Opinion in Pulmonary Medicine 2008, 14:440–454

Figure 7 Bridging fibrosis seen in chronic bird fancier's lung disease in a 33-year-old man



(a) Computed tomography (CT) shows traction bronchiectasis and centrilobular small nodular opacity. (b) Lower power view reveals centrilobular fibrosis and patchy subpleural fibrosis. (c) Centrilobular fibrosis is extending to the subpleural area and small fibroblastic foci (arrows) are located at the edge of the centrilobular and subpleural fibrosis (HE, ×4). (d) Bridging fibrosis is located between respiratory bronchiole and interlobular septa (Elastica van Gieson, ×4). RB, respiratory bronchiole; V, interlobular vein.

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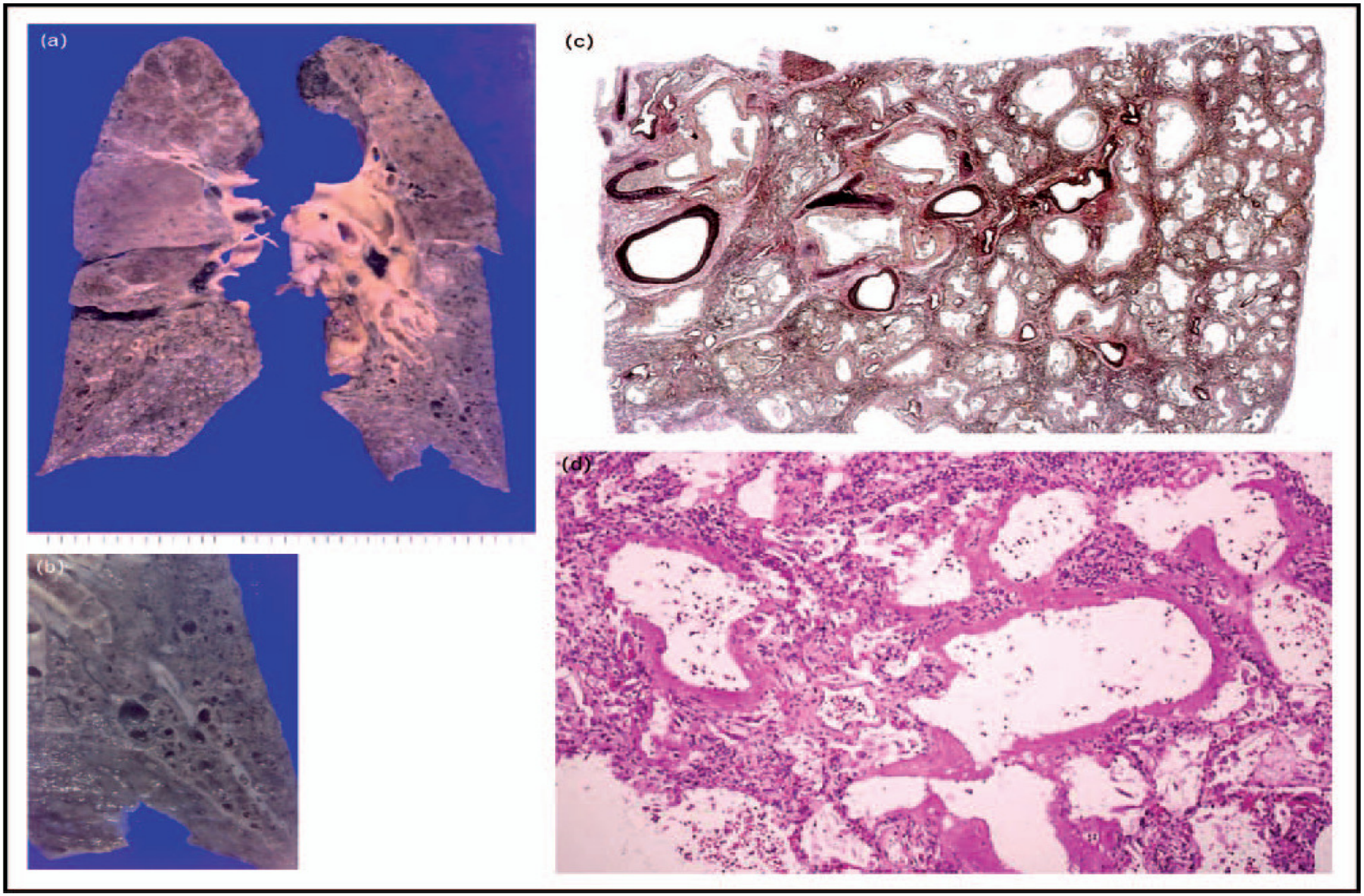
Figure 12 Autopsy lung of a case of chronic bird fancier's lung with insidious course



(a) The lungs showed lower lobe contraction with honeycomb change, mimicking usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF). (b) Small size honeycomb change of the lower lobe. (c) Microscopic appearance of honeycomb change in the lower lobe (EvG, ×1). (d) Hyaline membrane formation in the upper lobe of the same case (HE, ×20).

Current Opinion in Pulmonary Medicine 2008, 14:440–454

Table 3 Comparison of histological features between hypersensitivity pneumonitis, sarcoidosis, lymphoid interstitial pneumonitis, NSIP and UIP

	HP	Sarcoidosis	LIP	NSIP	UIP
Granuloma morphology	Poorly formed	Well formed	Well formed or poorly formed	Absent	Absent
Distribution	Random, peribronchiolar	Lymphangitic	Random		
Interstitial infiltrate of inflammatory cells	Prominent peri-bronchiolar	Minimal	Extensive, diffuse	Diffuse, moderate	Minimal
Intraluminal fibrosis	Moderate	Minimal	Absent	Moderate	Absent, rare
Cellular bronchiolitis	Frequent	Minimal	Minimal	Minimal	Minimal
Fibrosis interstitial	Frequent in chronic	In advanced cases	Unusual	Frequent	Frequent
CLF	Frequent in chronic	Occasional	Absent	Minimal	Minimal
Honeycomb	Frequent in chronic	Occasional in advanced cases	Absent	Occasional in fibrotic NSIP	Frequent
Fibroblastic foci	Occasional	Absent	Absent	Occasional	Frequent

CLF, centrilobular fibrosis; HP, hypersensitivity pneumonitis; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Current Opinion in Pulmonary Medicine 2008, 14:440–454

Keyword in histopathology

-Diffuse interstitial infiltrate, scattered noncaseating granuloma and cellular inflammation of the bronchioles

- Generalized vasculitis and/or necrotizing granulomata are absent

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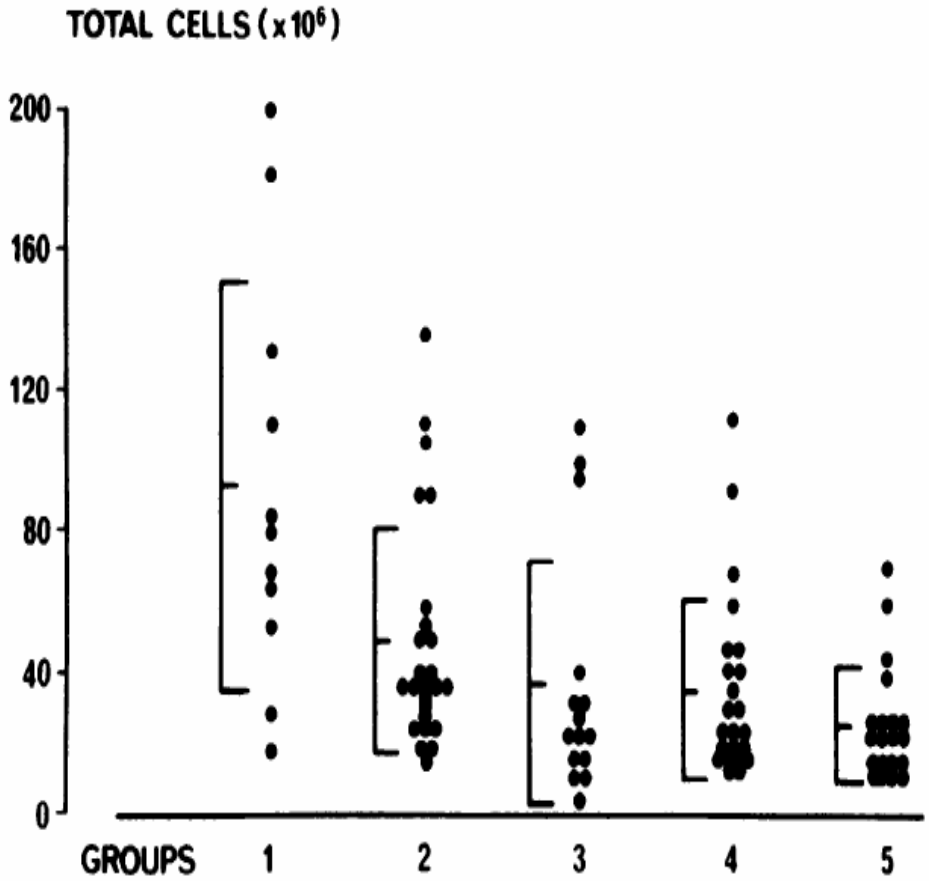
Relationships between radiographic change, pulmonary function, and bronchoalveolar lavage fluid lymphocytes in farmer's lung disease



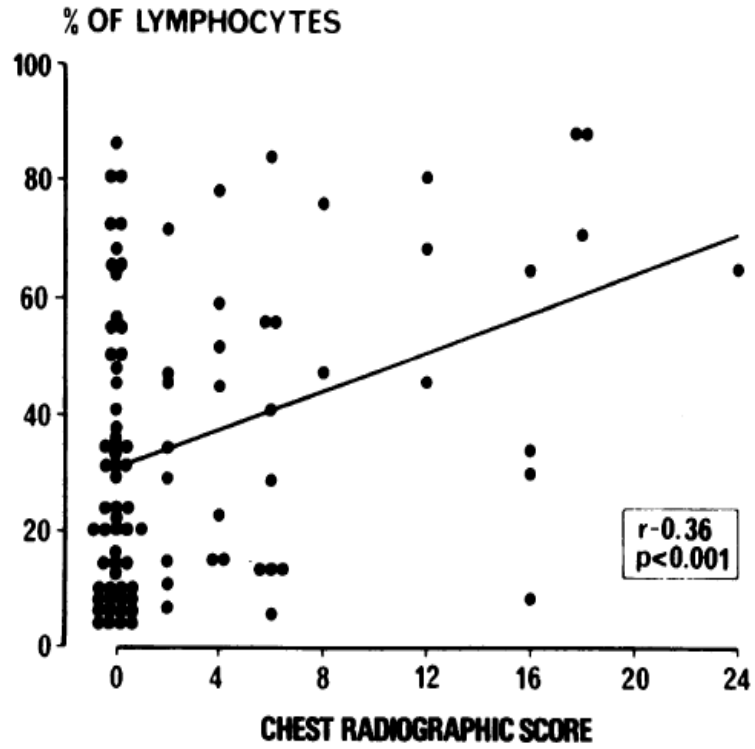
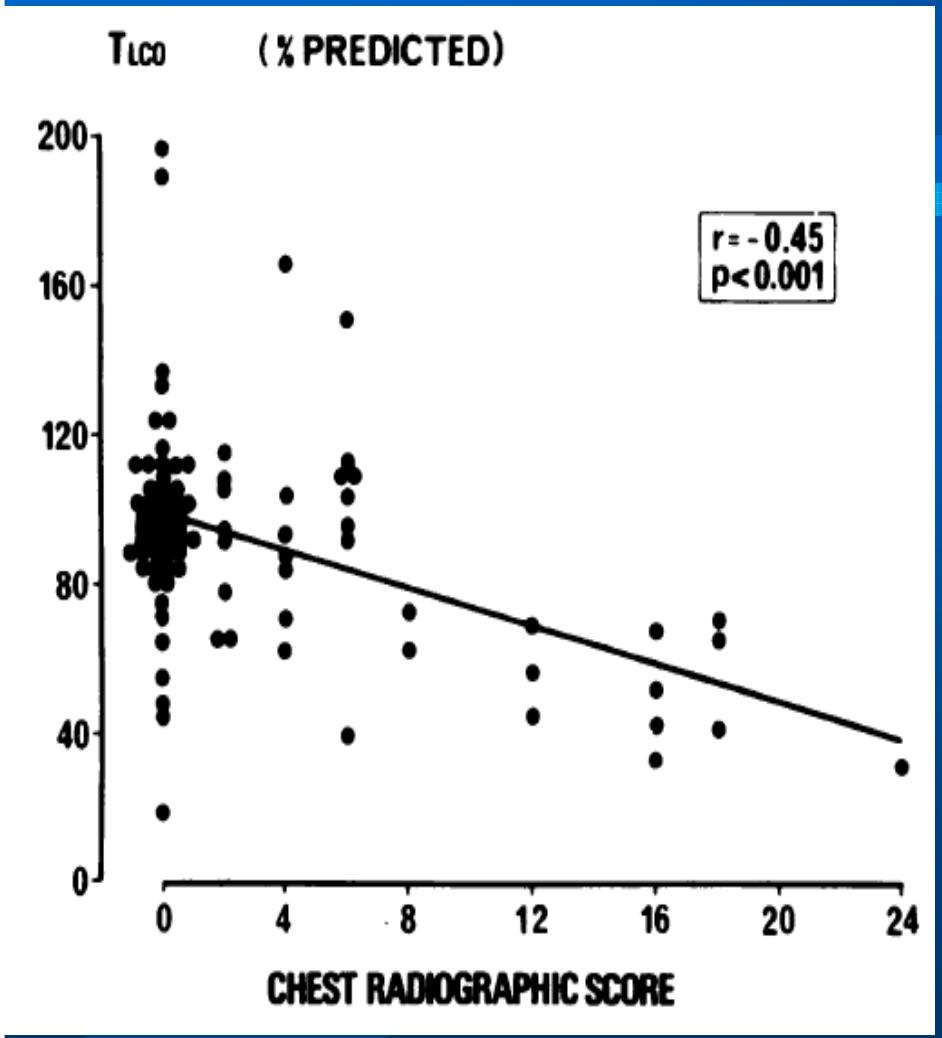
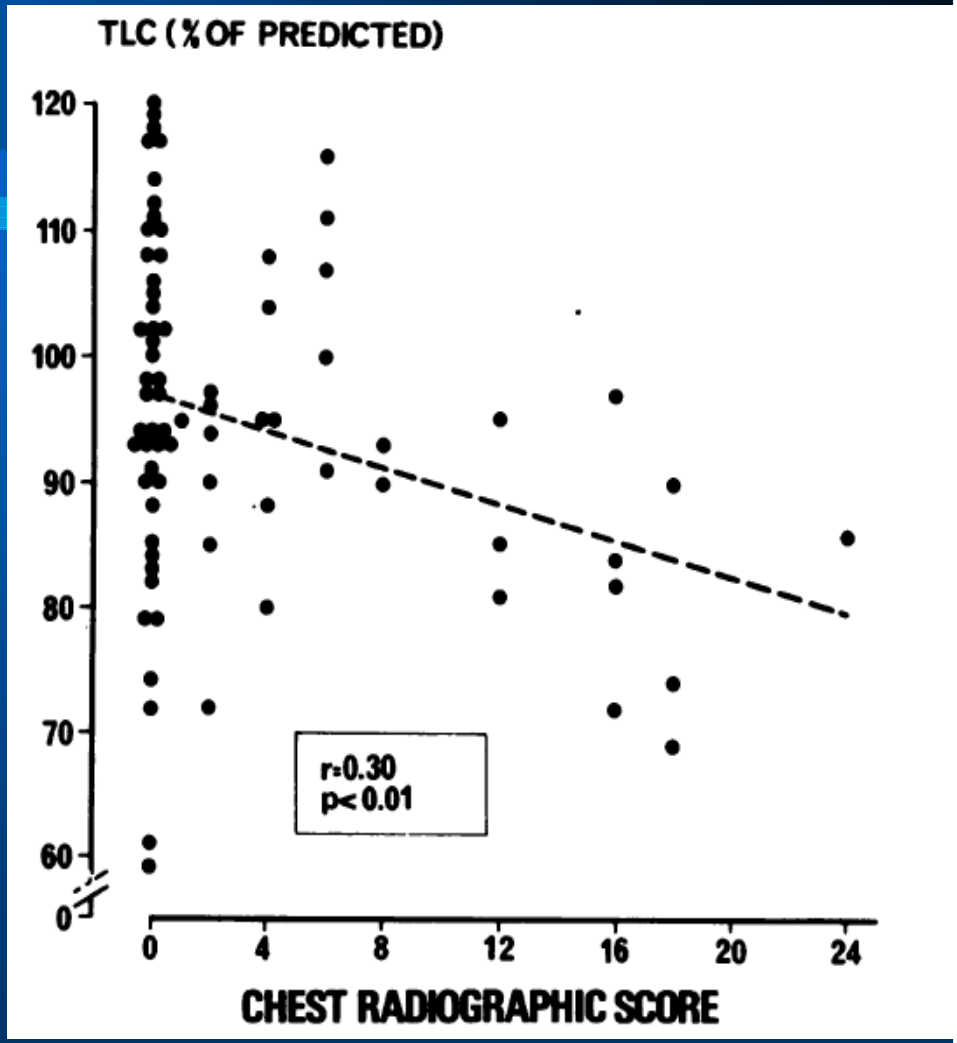


Fig 3 *Correlation between the percentage of lymphocytes found in bronchoalveolar lavage fluid and the radiographic score.*

Thorax 1986;**41**:28–33





Thorax 1986;**41**:28–33

Significant predictor of HP

Variables	Odds ratio (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 (1.0–3.9)

Allergy 2009: 64: 322–334

TABLE 4. PROBABILITY OF HAVING HYPERSENSITIVITY PNEUMONITIS

Exposure to a Known Offending Antigen	Recurrent Episodes of Symptoms	Symptoms 4–8 h After Exposure	Weight Loss	Crackles, %			
				+		−	
				Serum Precipitins		Serum Precipitins	
				+	−	+	−
+	+	+	+	98	92	93	72
+	+	+	−	97	85	87	56
+	+	−	+	90	62	66	27
+	+	−	−	81	45	49	15
+	−	+	+	95	78	81	44
+	−	+	−	90	64	68	28
+	−	−	+	73	33	37	10
+	−	−	−	57	20	22	5
−	+	+	+	62	23	26	6
−	+	+	−	45	13	15	3
−	+	−	+	18	4	5	1
−	+	−	−	10	2	2	0
−	−	+	+	33	8	10	2
−	−	+	−	20	4	5	1
−	−	−	+	6	1	1	0
−	−	−	−	3	1	1	0

All the predictors are dichotomous variables: '−' indicates absent; '+' indicates present.

Classification of HP

- **Acute**
  - **influenza-like symptom begin 2-9 hrs after exposure**
  - **peak typically 6-24 hrs**
  - **cough,dyspnea are common but not universal**
  - **spontaneous resolve in 2-5 dys**
  - **recurrent symptom when expose to causative agent**
  - **PE => crackle**

- **Subacute**
  - gradually onset over several days to weeks
  - marked dyspnea and cough may progress to severe dyspnea and cyanosis,leading to urgent hospitalization
  - Mild symptoms
  - Extend over 10-14 days
  - Usually reversible

- **Chronic**
  - **incidious onset over a peroid of months with increasing cough and exertional dyspnea.**
  - **Fatigue and Wt. loss may be prominent symptoms**
  - **no fever**
  - ***absent clubbing of finger***

Differential diagnosis

Acute stage

- Acute tracheobronchitis, bronchiolitis, or pneumonia
- Acute endotoxin exposure
- Organic dust toxic syndrome
- Allergic bronchopulmonary aspergillosis
- Reactive airways dysfunction syndrome
- Pulmonary embolism/infarction
- Aspiration pneumonitis
- Bronchiolitis obliterans organizing pneumonia
- Diffuse alveolar damage

Subacute stage

- Recurrent pneumonia
- Allergic bronchopulmonary aspergillosis
- Granulomatous lung diseases
- Infection—mycobacteria, fungi
- Berylliosis
- Silicosis
- Talcosis
- Langerhans' cell histiocytosis
- Churg-Strauss syndrome
- Wegener's granulomatosis

Chronic stage

- Idiopathic pulmonary fibrosis
- Chronic obstructive pulmonary disease with pulmonary fibrosis
- Bronchiectasis/bronchiolectasis
- *Mycobacterium avium* complex pulmonary disease

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pathophysiology

- **Immune complex mediated reaction**
- **Cell mediated reaction=> granuloma formation**

Hypersensitivity reaction

type III and IV reaction

Promoting and protective factors

- Etiological agents
  - many HP offending agents are small slowly degradable particles
- Viral infection
  - viral antigen express in HP more than normal subject
  - possible mechanism => increase CD86 molecule on APC

Common Respiratory Viruses in Lower Airways of Patients with Acute Hypersensitivity Pneumonitis

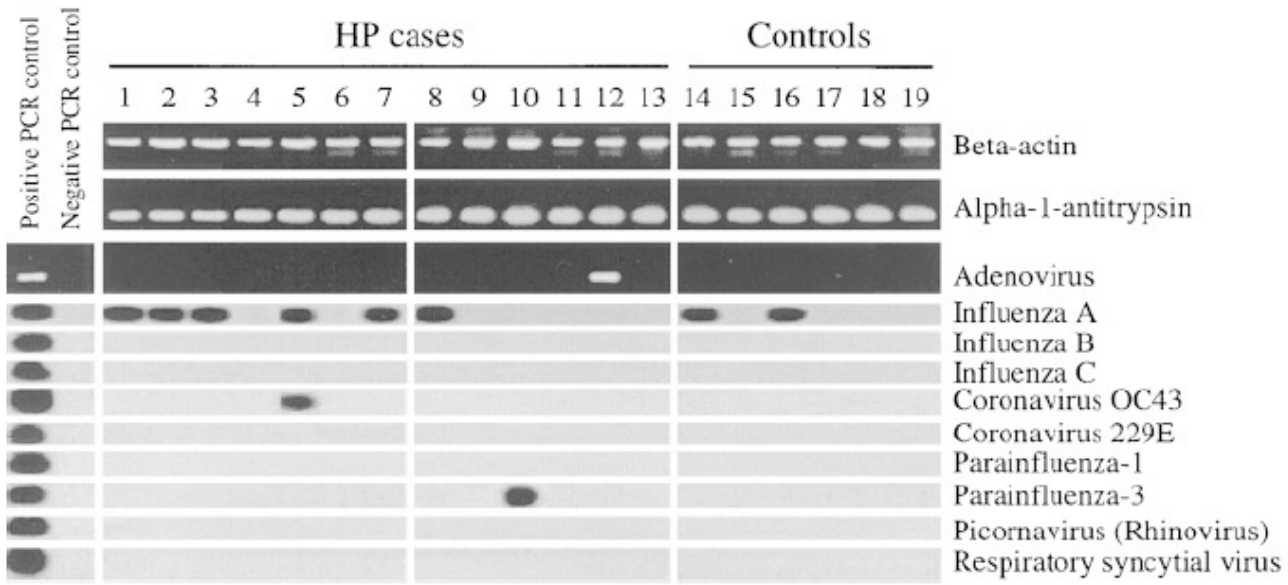


Figure 1. Representative agarose gels and southern blots showing specific PCR products of common respiratory viruses and housekeeping genes detected in BAL cells obtained from patients with HP (Subjects 1 to 13) and unexposed healthy volunteers (Subjects 14–19).

R= 0.7

AM J RESPIR CRIT CARE MED 1999;159:1316–1322.

- Genetic predisposition

  - TNF-α $^{-308}$ associate with high TNF in Bird-fancier lung
  - some MHC class II

- Nicotine
- Suppressive cell => Treg

Inh. Immunological process,decrease

-lymphocyte in BAL

-Decrease costi mol.

-Inh. Macrophage

Major Histocompatibility Complex and Tumor Necrosis Factor- Polymorphisms in Pigeon Breeder's Disease

- HLA-DRB1*1305 ($p < 0.001$, OR = 15.4, 95% CI = 3.18-102.6)
- HLA-DQB1*0501 ($p < 0.05$, OR = 2.93, 95% CI = 1.21-7.15)
- A decrease of HLA-DRB1*0802 ($p < 0.05$).
- Haplotype analysis increase of DRB1*1305-DQB1*0301 and a decrease of DRB1*0802-DQB1*0402.
- increased frequency of TNF-2 308 ($p < 0.05$).
- Patients exhibiting the TNF-2 308 allele were younger and more lymphocytes in their BAL ($p<0.05$)

Am j res crit care med . 2001 , 1528-33

immunopathogenesis

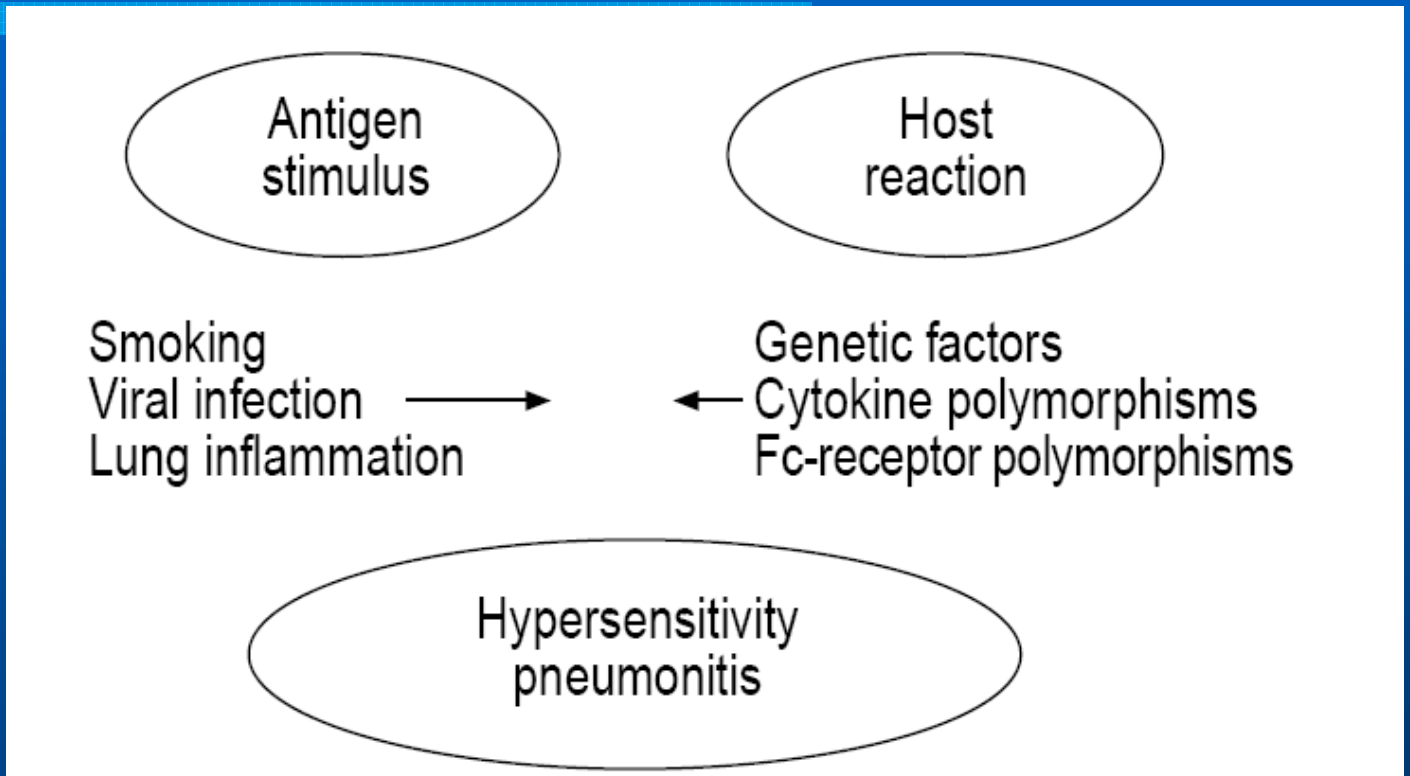


Fig. 1.–In hypersensitivity pneumonitis, the interaction between the external antigen and the host's immune response is influenced by both genetic and environmental factors. Fc: fragment crystallizable.

Eur Respir J 2001; 18: Suppl. 32, 81s–92s.

immunopathogenesis

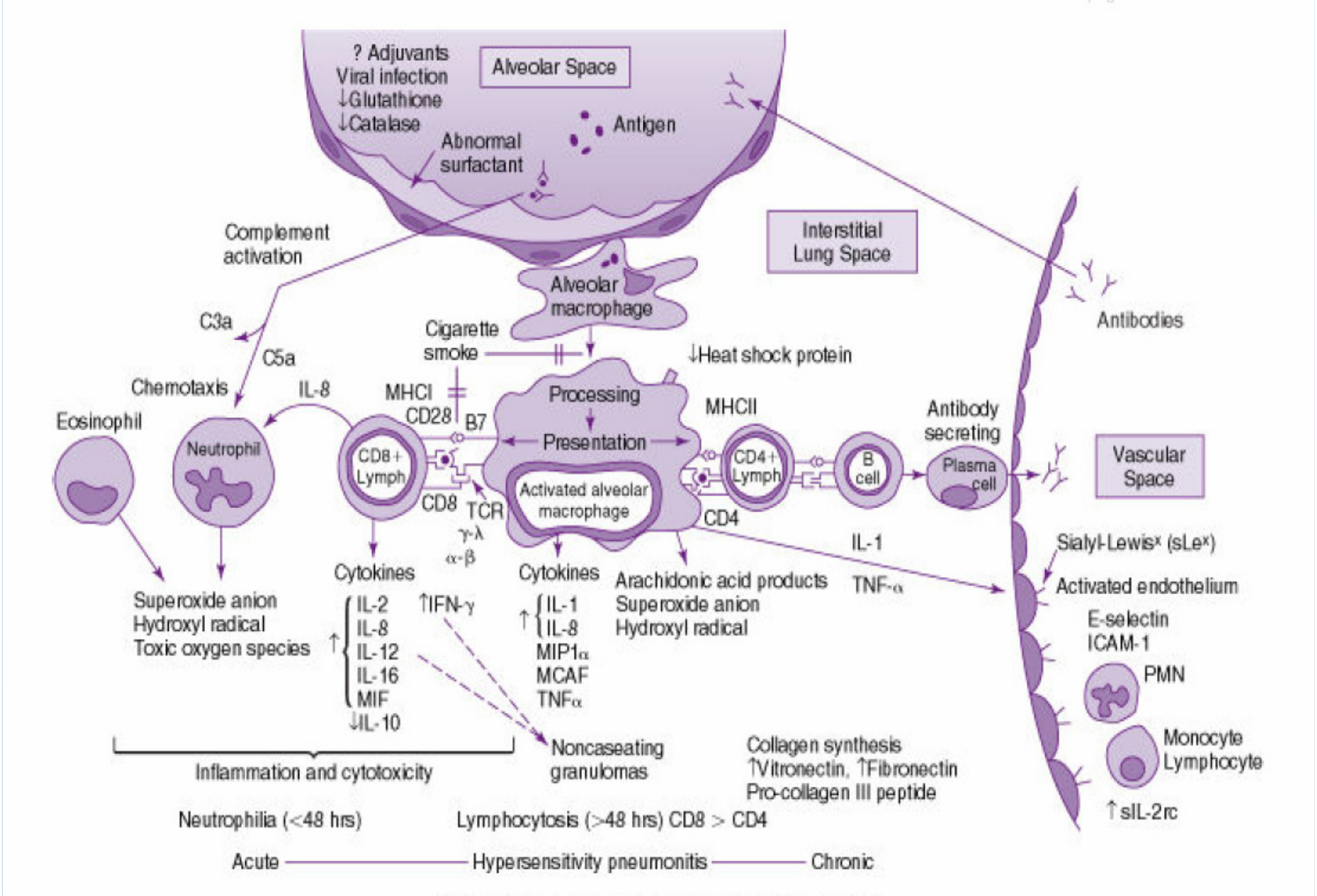
- Proliferation of CD8+ T cell
- production of antibody by proliferation of plasma cell stimulated by TH1 cell
- Both pathways begin after inhaled antigen-carrying particles are ingestd by Macrophage
- 3 phase of HP overlap in immunopathogenesis
- Greater production of TNF-α(TNF A2 alle)
- CD8+ Tcell in lung have increase usage of Vβ regions of T cell receptor gene

- **Acute phase**

- soluble Ag bind to IgG Ab=>immune complex
- initiate complement cascade=>C5
- macrophage activation
- PMN, T cell, Monocyte recruitment
- **MIP-1α** (chemotactic factor for MØ,monocyte,Tcell)& IL-8
- IFN-γ(develop granuloma),IL-1,**TNF**-α,IL-12(TH1)
- IL-6(from activated MØ induce B cell, CD8+ T cell)
- CD80/86,CD28
- early phase Th1 and later CD8+

- **Subacute phase**
  - granuloma formation
  - MIP-1=> MØ =>epitheliod cell and multinucleated giant cell
  - lymphoid follicles containing plasma cells also develop in lesions
  - Th1bearing CD 40ligand => activate B cell

- **Chronic phase**
  - collagen formation by myofibroblast
  - over express of TGF-β by alveolar MØ=> fibrosis and angiogenesis
  - Fas and CD 4o ligand are also involved
  - mast cell => increase procollagen type III



Middleton :6th edition

Interleukin 12, interleukin 18, and tumor necrosis factor α release by alveolar macrophages: acute and chronic hypersensitivity pneumonitis

Qiao Ye, MD*†; Shinobu Nakamura, MD‡; Rafael Sarria, MD§; Ulrich Costabel, MD*; and Josune Guzman, MD‡||

Table 2. Bronchoalveolar Lavage Fluid Cell Differentials[a]

	Patients with acute HP (n = 6)	Patients with chronic HP (n = 16)	Controls (n = 11)
Total cells, $\times 10^4$/mL	29 (4)[b]	23 (4)[b]	8 (2)
Macrophages, %	18 (6)[b]	17 (2)[d]	90 (1)
Lymphocytes, %	73 (5)[b]	77 (2)[d]	8 (1)
Neutrophils, %	4 (2)	2.6 (0.5)	2 (0.4)
Eosinophils, %	2 (0.4)[c]	3 (0.8)[b]	0.13 (0.05)
Mast cells, %	1.9 (0.6)[d]	0.6 (0.2)[b]	0.04 (0.02)
Plasma cells, %	0.4 (0.2)	0.1 (0.07)	0
$CD8^+$ lymphocytes, %	38 (10)	32 (5)	39 (4)
$CD4^+/CD8^+$ ratio	2.5 (0.8)	3.2 (0.5)	1.4 (0.3)
HLA-DR^+ lymphocytes, %	21 (9)[c]	33 (6)[b]	5 (0.5)

Abbreviation: HP, hypersensitivity pneumonitis.

[a] Data are presented as mean (SE).

[b] $P < .01$: acute or chronic forms of HP vs controls.

[c] $P < .05$: acute or chronic forms of HP vs controls.

[d] $P < .001$: acute or chronic forms of HP vs controls.

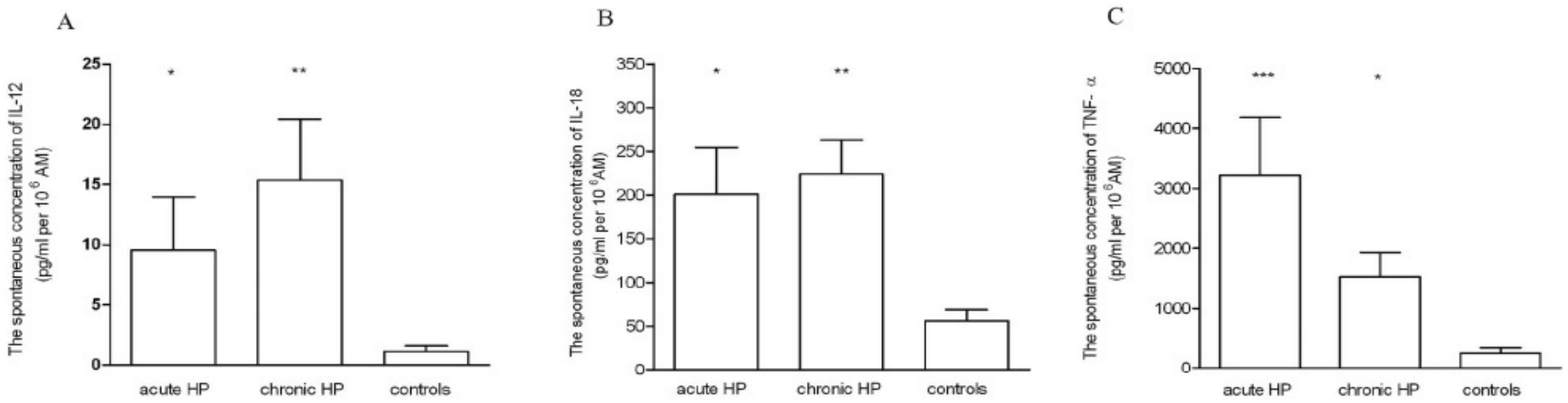


Figure 1. Spontaneous release of interleukin (IL) 12 (A), IL-18 (B), and tumor necrosis factor α (TNF-α) (C) from bronchoalveolar lavage macrophages in patients with acute and chronic hypersensitivity pneumonitis (HP) and controls. The columns indicate mean (SEM) ($^*P < .05$, $^{**}P < .01$, $^{***}P < .001$ compared with controls). AM indicates alveolar macrophage.

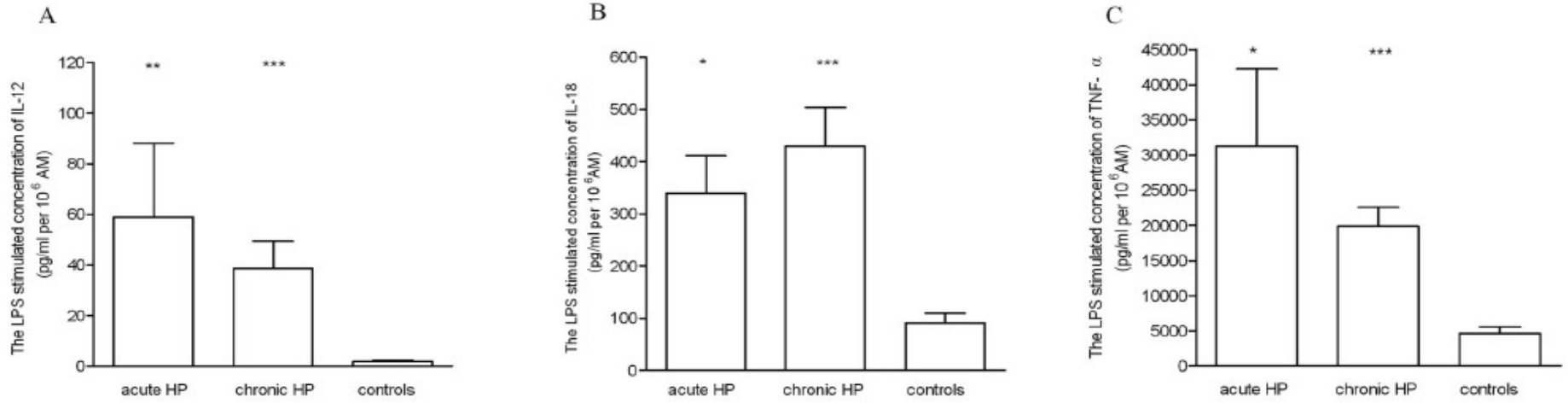


Figure 2. Lipopolysaccharide (LPS)–stimulated release of interleukin (IL) 12 (A), IL-18 (B), and tumor necrosis factor α (TNF-α) (C) from bronchoalveolar lavage (BAL) macrophages in patients with acute and chronic hypersensitivity pneumonitis (HP) and controls. The columns indicate mean (SEM) ($^*P < .05$, $^{**}P < .01$, $^{***}P < .001$ compared with controls). AM indicates alveolar macrophage.

prognosis

Table 2 Results of univariate analysis of prognostic factors in patients with hypersensitivity pneumonitis.

Variables	Hazard ratio	95% CI	*p* value
Older age	1.05	1.00—1.09	0.049
Male sex	3.49	1.32—9.27	0.012
Duration of symptoms	1.01	0.99—1.02	0.562
Clubbing	1.02	0.33—3.13	0.978
Velcro crackles	7.15	1.63—31.45	0.009
Pulmonary function			
FVC, % predicted	0.98	0.96—1.01	0.180
FEV_1/FVC ratio, %	1.08	1.01—1.15	0.020
Higher oxygen saturation, %			
At rest	0.99	0.87—1.13	0.889
During exercise	0.92	0.86—0.99	0.025
HRCT findings			
Centrilobular nodules	1.47	0.56—3.86	0.437
Ground-glass opacities	1.66	0.58—4.71	0.343
Mosaic pattern/air trapping	0.26	0.07—0.90	0.034
Findings of fibrosis	8.14	1.08—61.61	0.042
Honeycombing	5.73	1.26—26.05	0.024
Typical HP*	1.75	0.64—4.76	0.274
Use of cytotoxic agents on treatment	3.58	1.26—10.16	0.017

Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; HRCT = High-resolution computed tomography; HP = hypersensitivity pneumonitis.

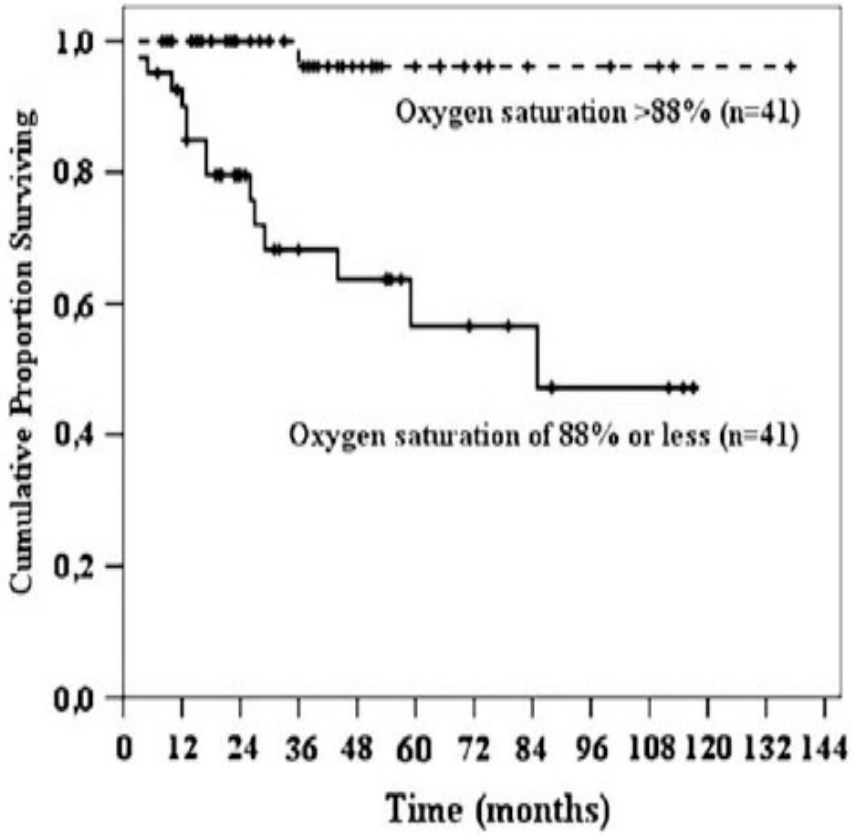
* Typical HP was defined as typical histological findings, including granulomas or giant cells.

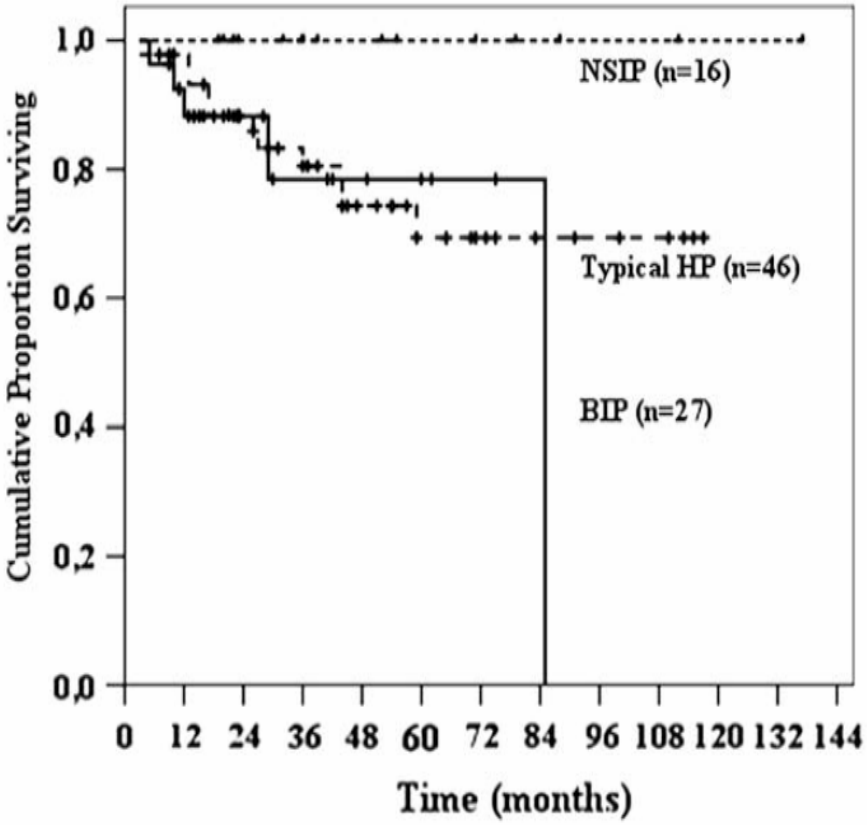
Table 3 Results of multivariate analysis of prognostic factors in patients with hypersensitivity pneumonitis.

Characteristic	Hazard ratio	95% CI	*p* value
Older age	1.10	1.03—1.18	0.007
Higher oxygen saturation, %			
During exercise	0.88	0.80—0.96	0.003
HRCT findings			
Presence of mosaic pattern/air trapping	0.05	0.01—0.39	0.004

Definition of abbreviations: CI = confidence interval; HRCT = high-resolution computed tomography.

Respiratory Medicine (2009) **103**, 508—515





Respiratory Medicine (2009) 103, 508–515

TABLE IV. Key features of the stages of hypersensitivity pneumonitis

	Time frame	Clinical features	HRCT findings	Immunopathology	Prognosis
Acute	4-48 hr	Fever, chills, cough, hypoxemia, aches	Ground-glass infiltrates	Alveolitis, immune complex	Good
Subacute	Weeks to 4 mo	Dyspnea, cough, episodic flares	Micro-nodules, air trapping	Granulomas, bronchiolitis	Good
Chronic	4 mo to years	Dyspnea, cough, fatigue, weight loss	Fibrosis +/– honeycombing, emphysema	Lymphocytic infiltration and fibrosis, neutrophil-mediated air space destruction	Poor

HRCT, High-resolution computed tomography.

J ALLERGY CLIN IMMUNOL
NOVEMBER 2001

management

- **Contact avoidance**
- **Environmental control**
- **Oral corticosteroids**

  20-50mg/day or 0.5 mg/kg/d for 2-4 wks in acute and maybe longer in subacute and chronic HP

expert opinion !

Effect of Corticosteroid Treatment on the Recovery of Pulmonary Function in Farmer's Lung[1–3]

TABLE 1

RESULTS OF PULMONARY FUNCTION TESTS AT THE TIME OF DIAGNOSIS OF FARMER'S LUNG IN THE CORTICOSTEROID AND PLACEBO GROUPS*

	Prednisolone (*n* = 19)	Placebo (*n* = 16)
FVC		
L	2.95 ± 0.75	2.82 ± 0.63
% pred	79 ± 15	75 ± 11
FEV_1		
L	2.29 ± 0.66	2.26 ± 0.52
% pred	75 ± 17	73 ± 11
D_{LCO}†		
ml/min/mm Hg	13.2 ± 2.8‡	13.6 ± 3.5
% pred	59 ± 13	59 ± 17
Pa_{O_2}, mm Hg	68 ± 12	66 ± 10

* Values are mean ± SD.
† Equipment was Morgan Resparameter Mark 4.
‡ n = 18.

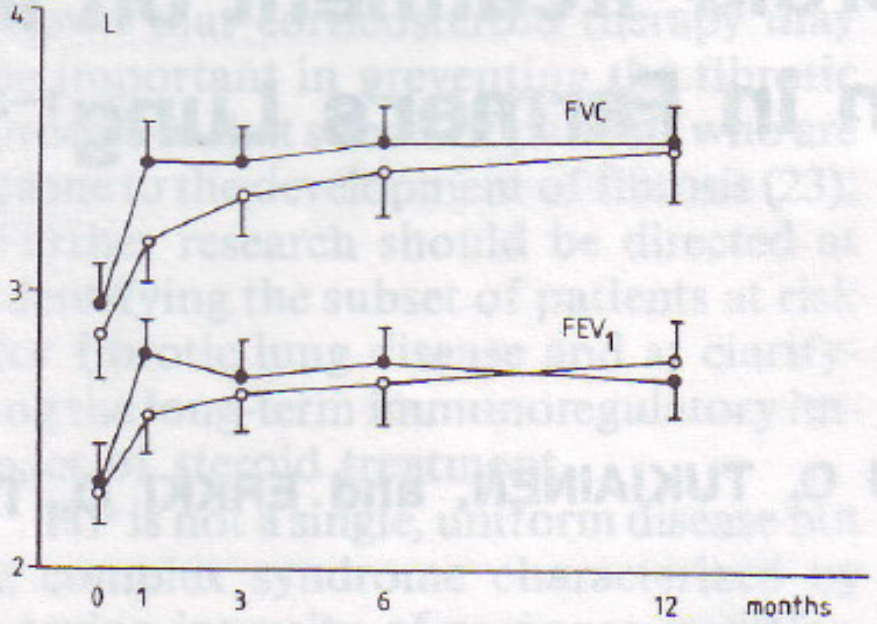


Fig. 1. FVC and FEV_1 (mean and SEM) during the first year of follow-up in the corticosteroid and placebo groups. Differences between the treatment groups at the 1-month follow-up were almost significant (FVC: p = 0.10; FEV_1: p = 0.06). Closed circles = prednisolone (n = 19); open circles = placebo (n = 15).

AM REV RESPIR DIS 1992; 145:3–5

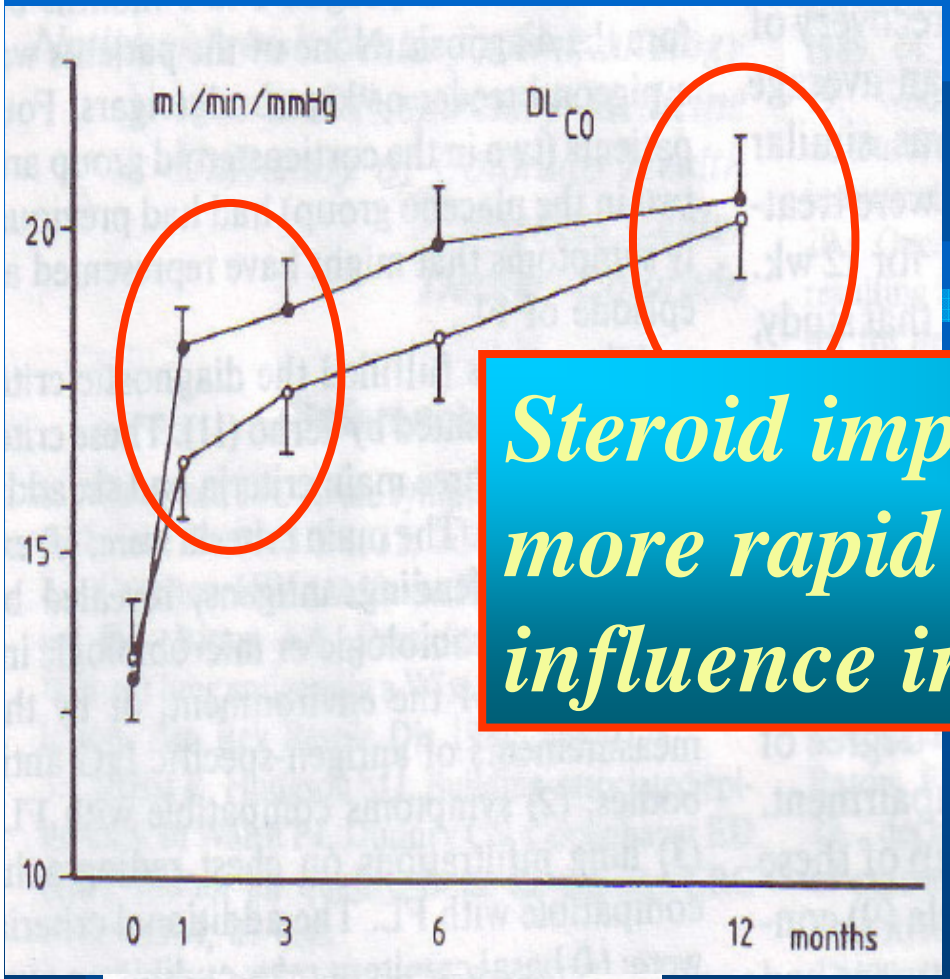


Fig. 2. D_{LCO} (mean and SEM) during the first year of follow-up in the corticosteroid and placebo groups. Difference between the treatment groups at the 1-month follow-up was significant ($p = 0.03$). Closed circles = prednisolone ($n = 17$); open circles = placebo ($n = 13$).

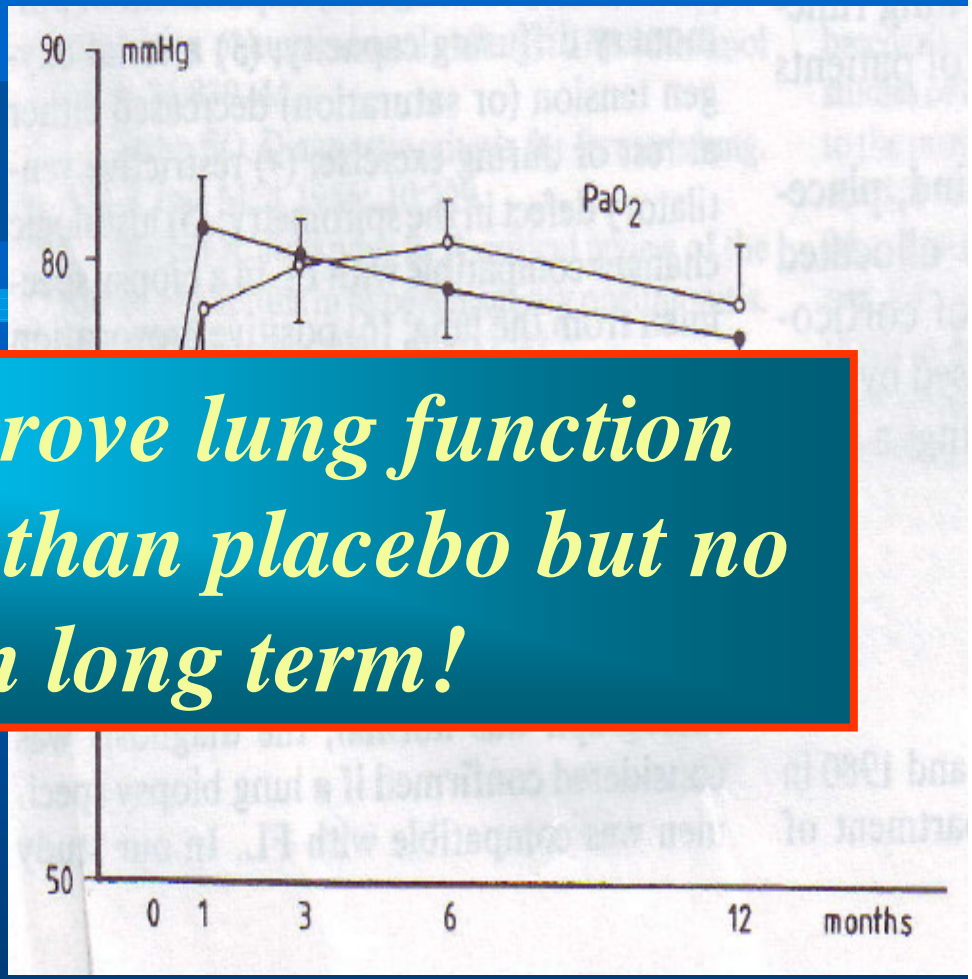


Fig. 3. Pa_{O_2} (mean and SEM) during the first year of follow-up in the corticosteroid and placebo groups. Difference between the treatment groups at the 1-month follow-up was not significant. Closed circles = prednisolone ($n = 16$); open circles = placebo ($n = 12$).

Steroid improve lung function more rapid than placebo but no influence in long term!

AM REV RESPIR DIS 1992; 145:3-5

quiz

1. All of the following agents have been shown to cause both occupational asthma and hypersensitivity pneumonitis EXCEPT:

   A. Toluene diisocyanate
   B. Trimellitic anhydride
   C. Micropolyspora faeni
   D. Bacillus subtilis
   E. Diphenylmethane diisocyanate

2. Which of the following groups of symptoms are common in the chronic form of Hypersensitivity Pneumonitis?

A. Progressive dyspnea, cough, fever
B. Malaise, weakness, fever
C. Cough, malaise, anorexia
D. Cough, weakness, myalgias

3. The immunologic basis of hypersensitivity pneumonitis appears to be:

A. Type 3 (immune complex)
B. Type 1 (IgE)
C. Type 4 (Cell mediated)
D. Combination of Type 3 and Type 4
E. Combination of Type 1 and Type 3

4. Which antigens are capable of inducing Hypersensitivity Pneumonitis?

A. Bacteria, rodent products, plant products, and prions
B. Bacteria, viruses, low molecular weight chemicals, and certain drugs
C. Fungi, amoebae, avian products, and certain drugs
D. Prions, viruses, bacteria, and fungi

5. Which of the following best represents CD4 and CD8 lymphocyte numbers found in bronchoalveolar lavage samples of patients with Hypersensitivity Pneumonitis vs. normal controls?

A. Increased CD4, increased CD8, decreased CD4/CD8 ratio
B. Decreased CD4, decreased CD8, decreased CD4/CD8 ratio
C. Decreased CD4, increased CD8, decreased CD4/CD8 ratio
D. Decreased CD4, decreased CD8, increased CD4/CD8 ratio

6. Which of the following is a major criterion for the diagnosis of Hypersensitivity Pneumonitis?

A. Bibasilar dry rales
B. Decreased diffusing capacity
C. Arterial hypoxemia
D. Lung larvage fluid lymphocytosis

7. Which type of Hypersensitivity Pneumonitis has been associated with exposure to amoebae?

A. Oyster shell lung
B. Tap water lung
C. Summer-type Hypersensitivity Pneumonitis
D. Ventilation pneumonitis

8. Which of the following is associated with Farmer's lung?

A. Histoplasmosis
B. Cryptococcus
C. Thermophilic actinomycetes
D. *Aspergillus fumigatus*

9. Which of the following scenarios is most indicative of sarcoidosis?

A. Restrictive pattern on PFT, increased ACE, increased T suppressor cells in BAL
B. Obstructive pattern on PFT, decreased ACE, increase in T helper cells in BAL
C. Restrictive pattern on PFT, increased ACE, increase in T helper cells in BAL
D. Obstructive pattern on PFT, increased ACE, increase in T suppressor cells in BAL

10. The most common form of Hypersensitivity Pneumonitis in the pediatric population is related to the inhalation of which of the following?

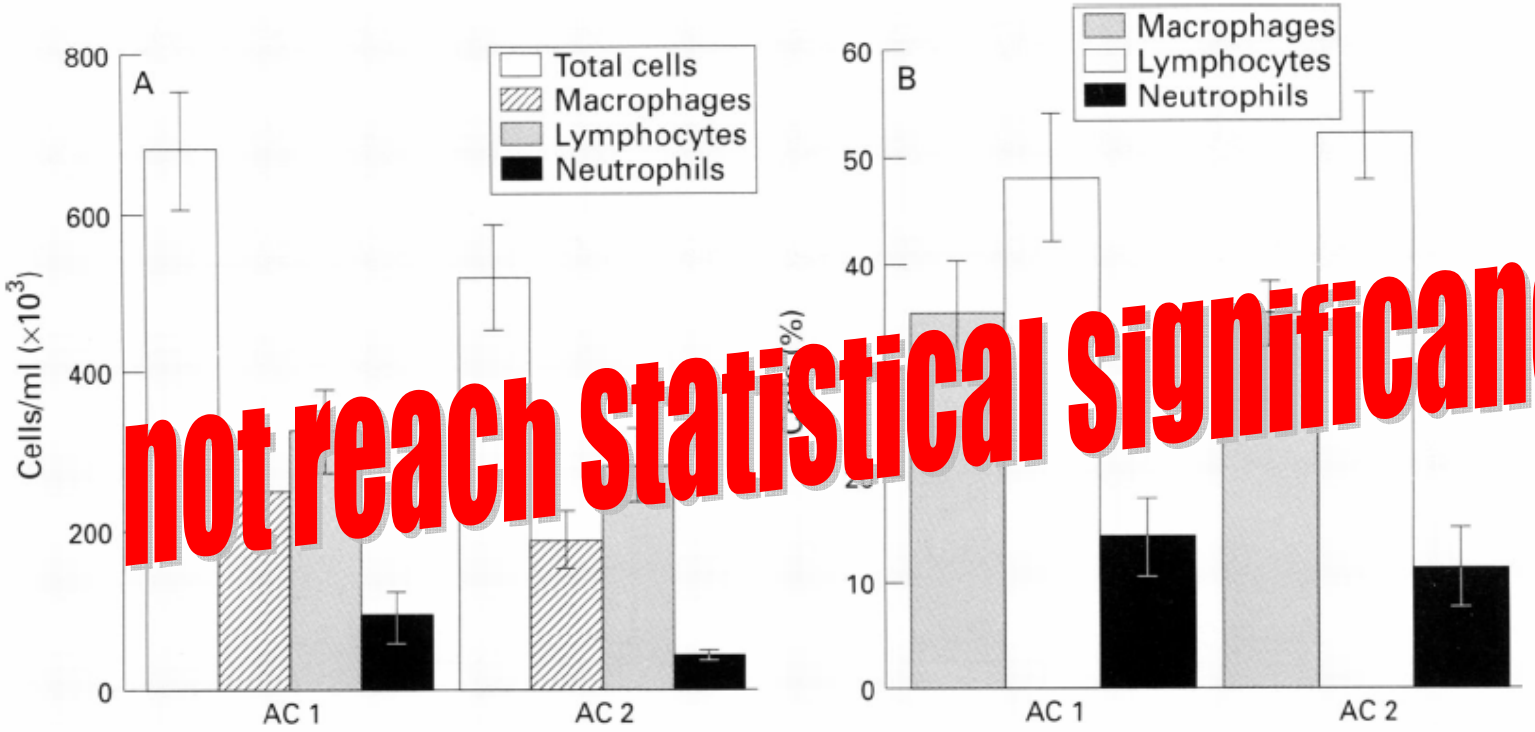
A. Medications
B. Insect proteins
C. Avian proteins
D. Rodent urinary proteins

conclusion

- Difficult to determine prevalence and incidence
- Classification
- Diagnosis
- Characteristic imaging and pathology
- Pathophysiology
- Immunology
- Treatment

Thank you for your attention!

1.126



not reach statistical significance

Figure 3 Pre-treatment (AC1) and post-treatment (AC2) values of BAL fluid cell counts for the eight patients with farmer's lung who had two evaluations expressed as (A) the number of cells per ml BAL fluid recovered and (B) as a percentage of the total cells. Although the number of cells decreased in five subjects the difference for the group did not reach statistical significance.

Thorax 1996;**51**:1210–1215

Effect of contact avoidance or treatment with oral prednisolone on bronchoalveolar lavage surfactant protein A levels in subjects with farmer's lung.

Table 1 *s percentage predicted in the asymptomatic farmers (AS) a*

Lung fu	*fore treatment*	*AC after treatment (n=8)*
FEV_1	)(6.26)	
FVC		
FEV_1/F		
TLCO		70.25(7.23)

FEV_1 = city; TLCO = lung carbon monoxide transfer factor.

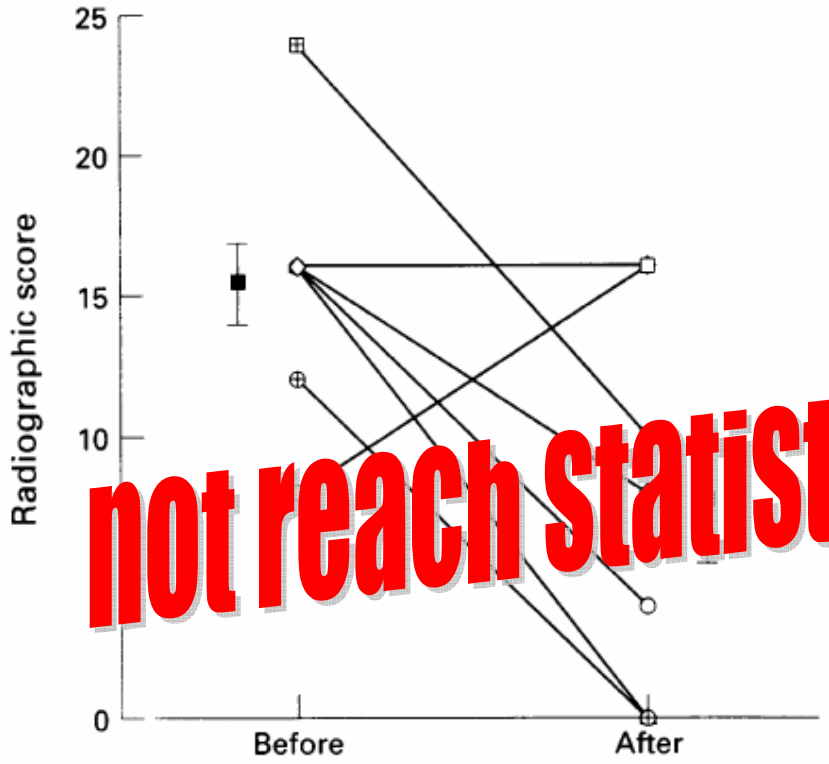


Figure 1 *Individual radiographic score before and after one month of treatment for seven of the eight subjects with acute farmer's lung who were studied twice. Although the score decreased (improved) in five subjects the difference did not reach statistical significance.*

not reach statistical significance

1.126

Thorax 1996;**51**:1210–1215

Causes and Presenting Features in 85 Consecutive Patients With Hypersensitivity Pneumonitis

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)

*Two patients did not have pulmonary function data available from the time of presentation.

Mayo Clin Proc. 2007;82(7):812-816

1: J Allergy Clin Immunol. 1991 May;87(5):1002-9.

Difference in the phenotypes of bronchoalveolar lavage lymphocytes in patients with summer-type hypersensitivity pneumonitis, farmer's lung, ventilation pneumonitis, and bird fancier's lung: report of a nationwide epidemiologic study in Japan.

Ando M, Konishi K, Yoneda R, Tamura M.

First Department of Internal Medicine, Kumamoto University Medical School, Japan.

We performed a nationwide epidemiologic study of hypersensitivity pneumonitis (HP) in Japan by questionnaire and found that 835 cases of HP were recognized during the 1980s; 74.4% were summer-type HP, 8.1% farmer's lung, 4.3% ventilation pneumonitis, 4.1% bird fancier's lung, 2.3% other types, such as chemical worker's lung, and 6.8% of unknown causative agent. It was found that the CD4/CD8 ratios of bronchoalveolar lavage (BAL) lymphocytes were significantly different with the type of disease. The ratio was 0.6 +/- 0.1 (mean +/- SEM) in summer-type HP (N = 271), 4.4 +/- 0.7 in farmer's lung (N = 22), 1.6 +/- 0.3 in ventilation pneumonitis (N = 19), and 2.0 +/- 0.5 in bird fancier's lung (N = 19). In farmer's lung, the CD4/CD8 ratio in smokers was 6.2 +/- 1.9 (N = 6) in contrast with 3.4 +/- 0.7 for nonsmokers (N = 16) (p less than 0.05). It has been generally considered that the phenotypes of BAL lymphocytes in patients with HP are predominately CD8 cells. Our present results, however, indicate that the phenotypes of BAL lymphocytes vary with the type of HP, probably depending on factors such as causative agent, smoking, or staging of the disease.

PMID: 1902851 [PubMed - indexed for MEDLINE]