Imperial College London

Royal Brompton & Harefield NHS
NHS Foundation Trust

Hypersensitivity pneumonitis

Milan, Italy
2nd March 2019

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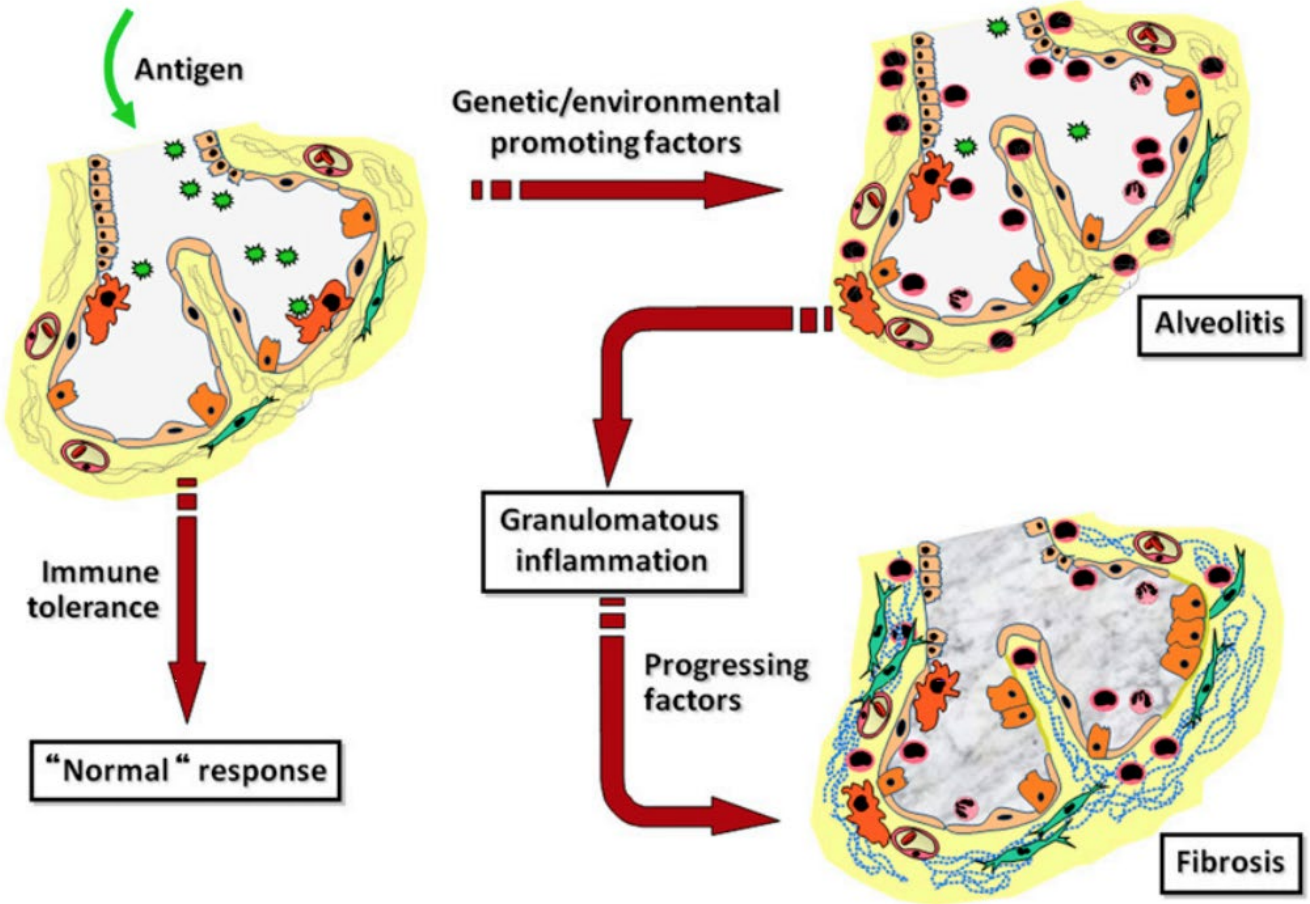
Declarations of interest

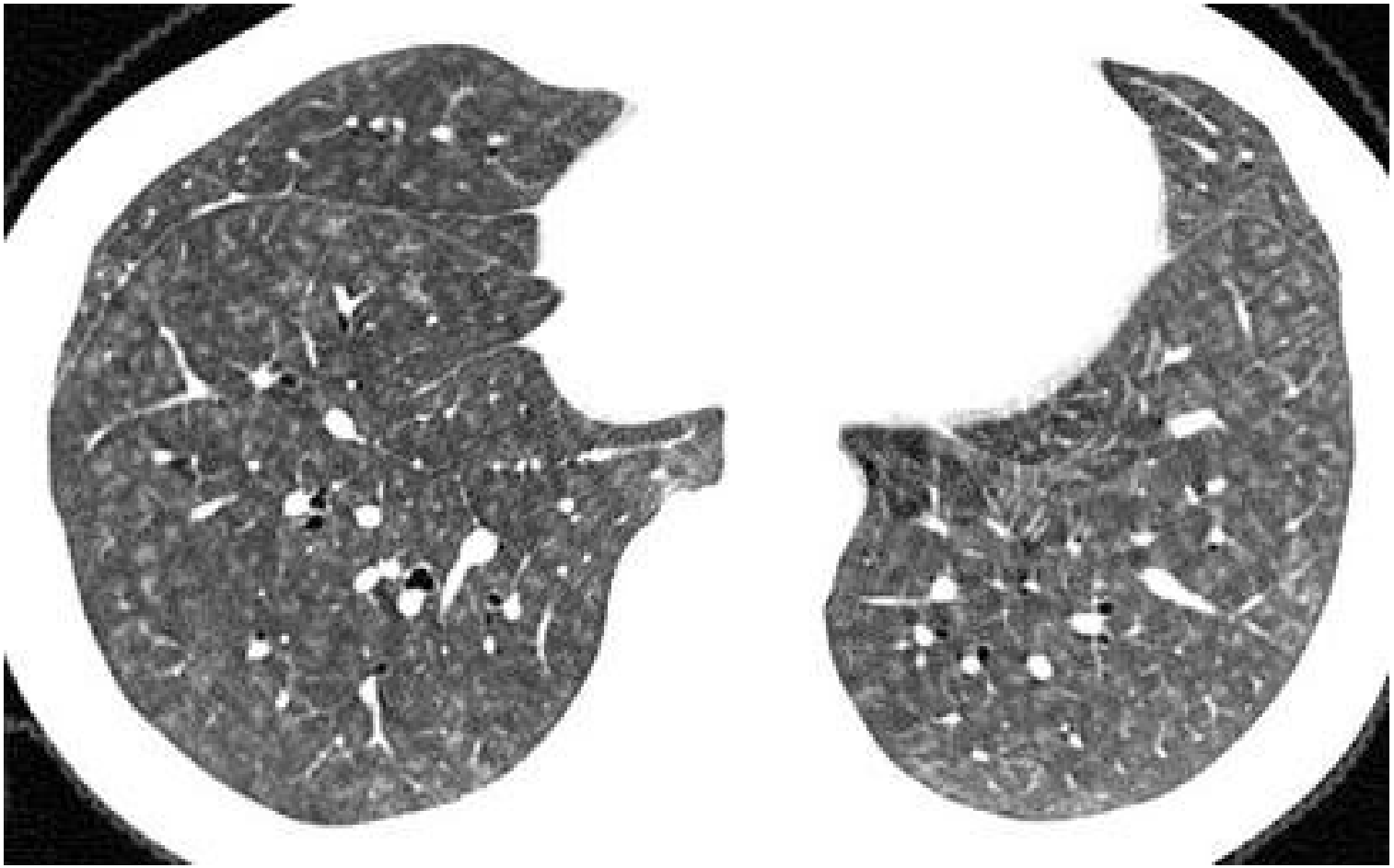
- Board membership/consultancy
  - GSK
  - Boehringer Ingelheim
  - UCB
  - Roche
  - Bayer
  - Biogen Idec
  - ProMetic
  - Apellis
  - Respivert
  - PatientsLikeMe
- Lecture Fees
  - UCB
  - AstraZeneca
  - Boehringer Ingelheim
  - Roche
  - Cipla
- Clinical Trials
  - Boehringer Ingelheim
  - Novartis
  - GSK
  - Gilead Sciences
  - Roche
  - InterMune
  - Galecto
  - Sanofi Aventis
- Grants
  - GSK
  - Novartis
  - UCB

Hypersensitivity pneumonitis - pathogenesis

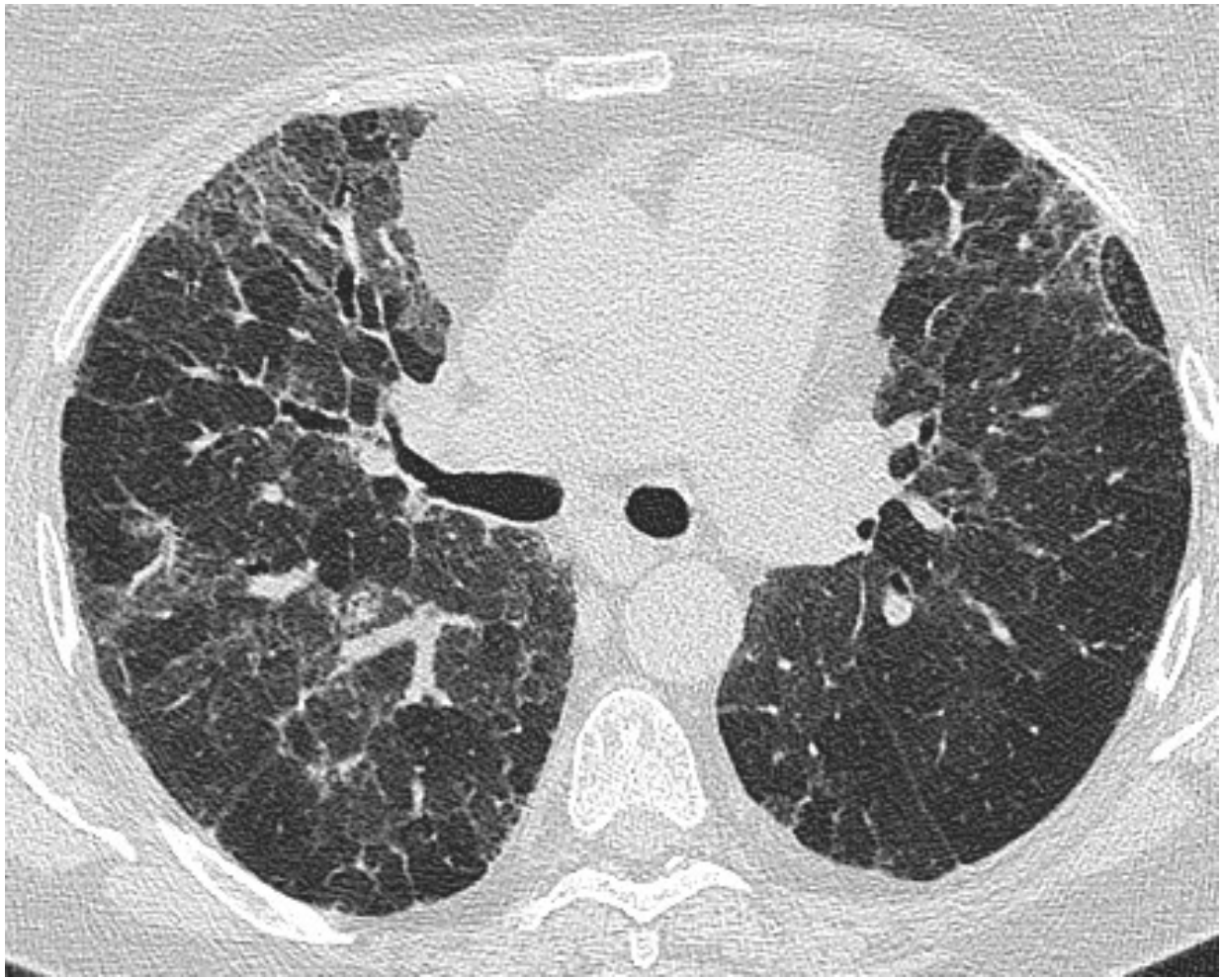


Selman et al AJRCCM 2012

Acute hypersensitivity pneumonitis



Chronic hypersensitivity pneumonitis



Assessment of suspected HP

- History
  - Exposure

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	*Saccharopolyspora 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 (i.e., bagasse)
Mushroom worker's lung	*T. sacchari*	Moldy mushroom compost
Enoki mushroom worker's lung (Japan)	*Penicillium citrinum*	Moldy mushroom compost
Suberosis	*Thermoactinomyces viridis, Aspergillus fumigatus, Penicillium frequentans, 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
Hardwood worker's lung	*Paecilomyces*	Kiln-dried wood
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	*Mycobacterium avium complex*	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, S. 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	*Mycobacterium immunogenum; Pseudomonas fluorescens*	Aerosolized metalworking fluid
Residential provoked pneumonitis Amebae	*Aureobasidium pullulans*	Residential exposure
Humidifier lung	*Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani, Bacillus* sp., others	Contaminated water from home humidifier, ultrasonic misting fountains
Shower curtain disease	*Phoma violacea*	Moldy shower curtain
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* (i.e., wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

Selman et al AJRCCM 2012

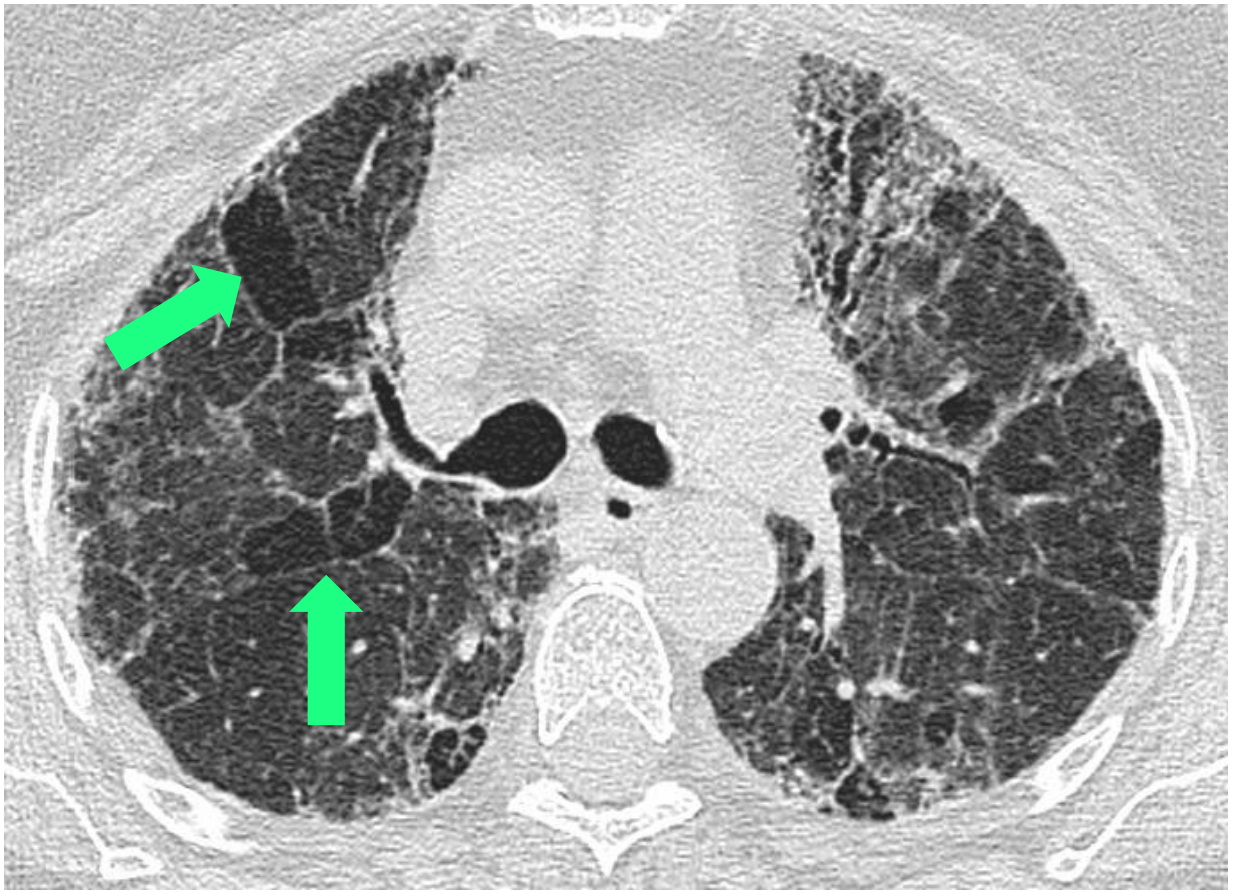
Assessment of suspected HP

- History
  - Exposure
  - But 60% lack clear exposure
- Examination
  - “Squawks” on auscultation
- Imaging
  - Acute – centrilobular nodules, ground glass +/- gas trapping
  - Chronic – fibrosis, mosaicism, bronchocentric distribution

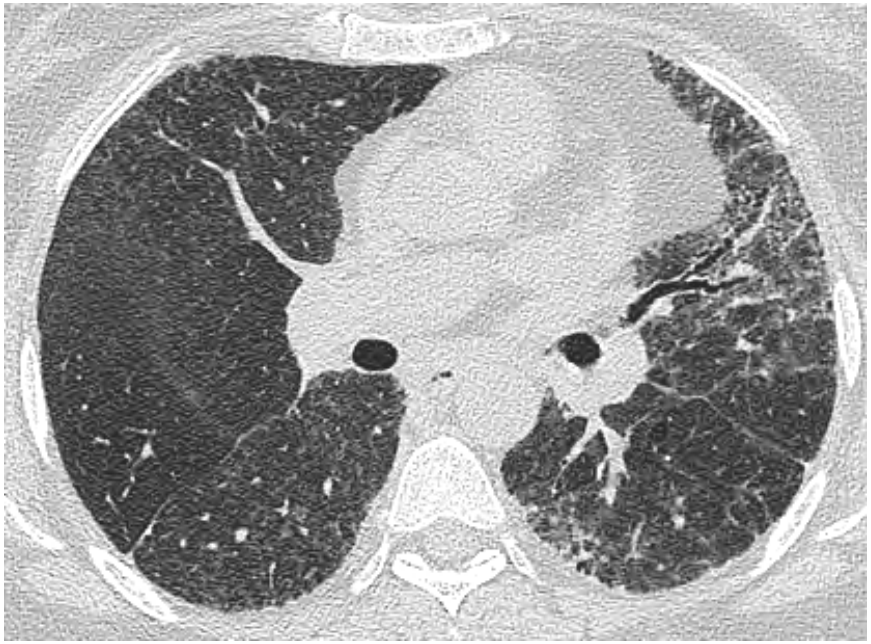
HRCT pointers to chronic hypersensitivity pneumonitis

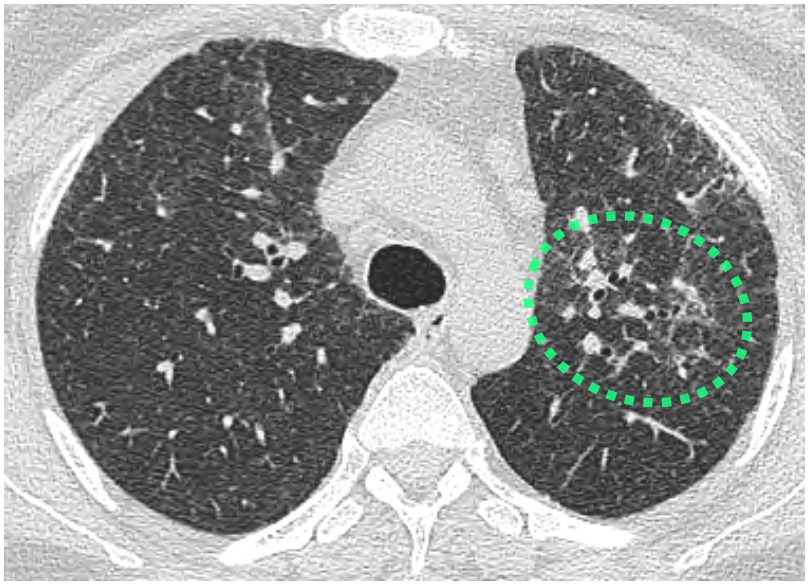
- Lobules of decreased attenuation ***in spared (non-fibrotic) lung***
- Unusual distribution of fibrosis, particularly ***vague bronchocentricity in upper lobes***
- Coexistent subacute changes - indistinct relatively low attenuation centrilobular nodules ***(rare)***

Lobules of decreased attenuation in spared lung

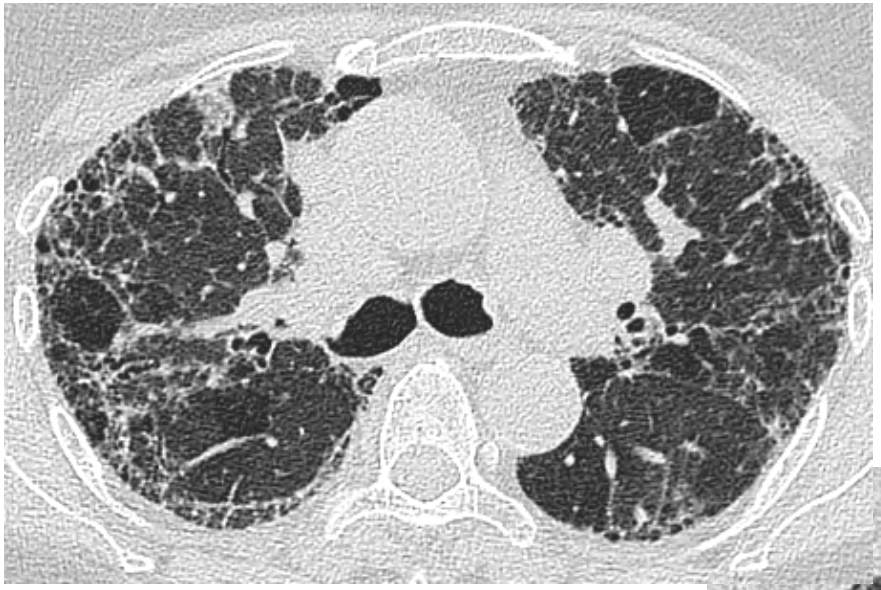


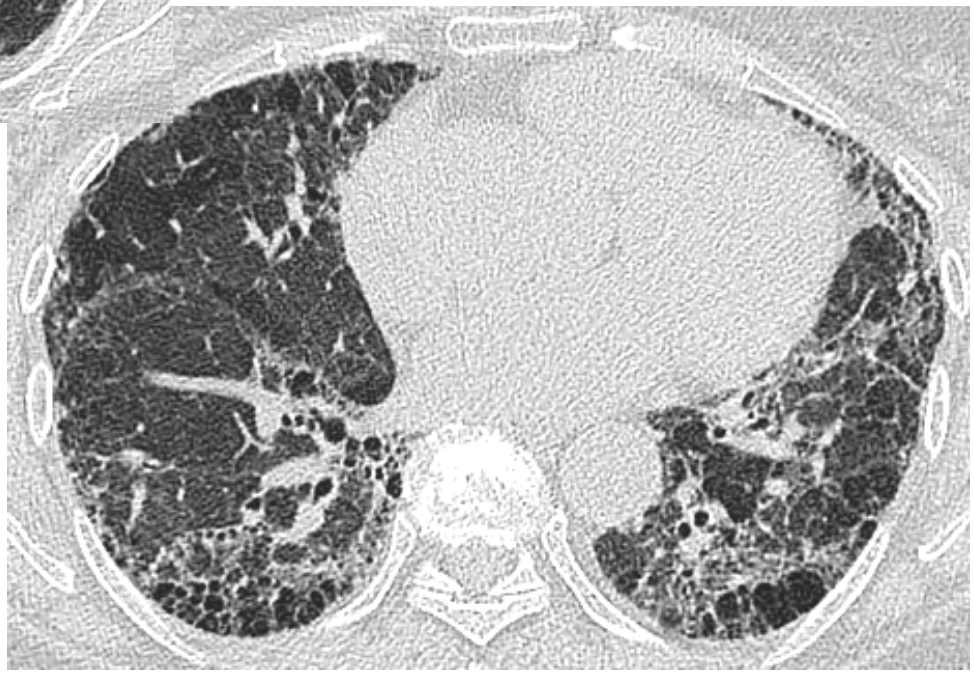
Unusual distribution of fibrosis, particularly vague bronchocentricity in upper lobes





Chronic hypersensitivity with UIP features





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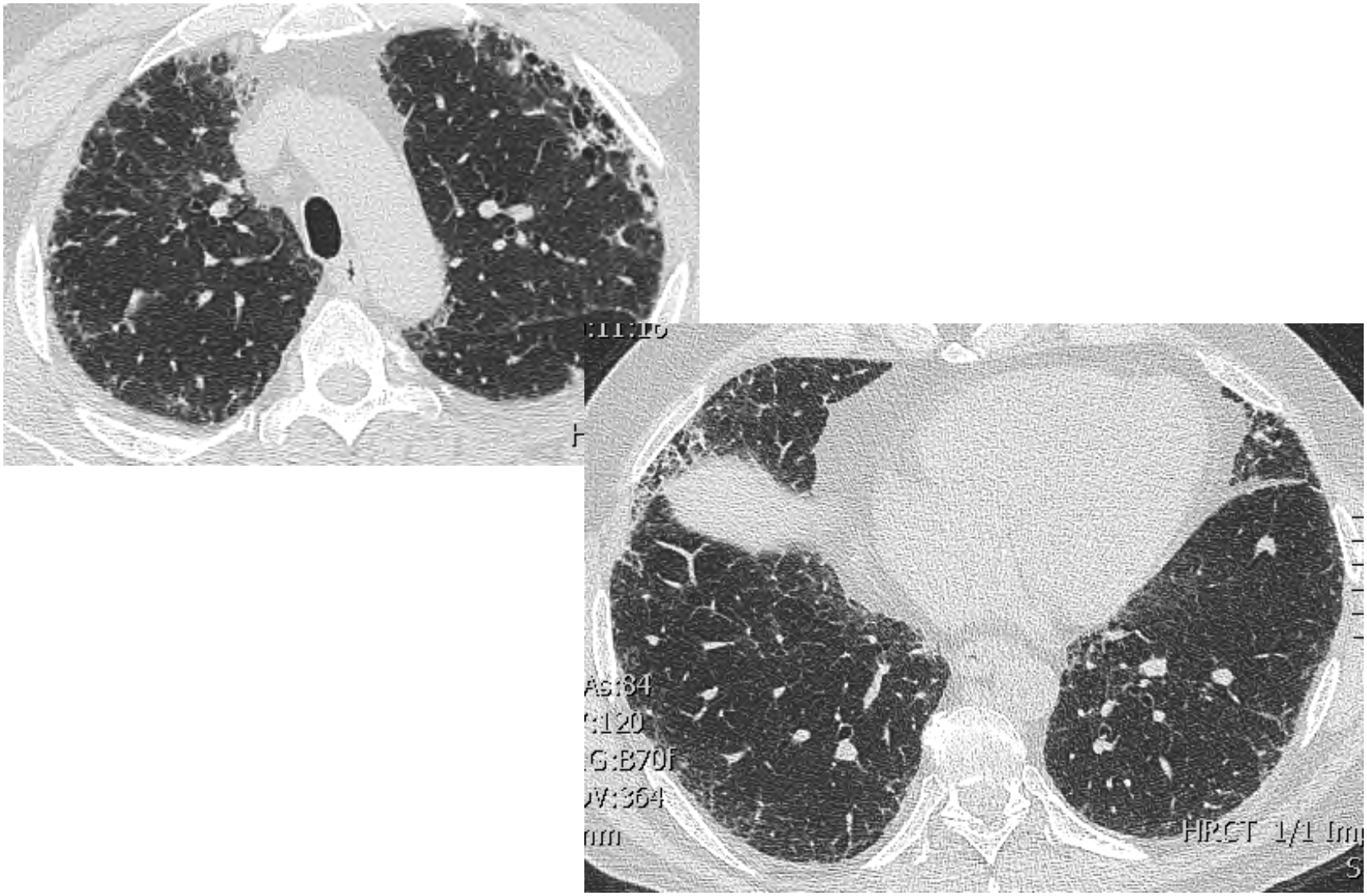
  - Acute – centrilobular nodules, ground glass +/- gas trapping
  - Chronic – fibrosis, mosaicism, bronchocentric distribution
- Bronchoscopy
  - Lymphocytes >?20%
- Biopsy
  - Airway centred granulomata, chronic cellular bronchiolitis, chronic interstitial inflammatory cell infiltrate
- Blood testing
  - Specific circulating antibodies

Case History

- 55 year old practising primary care physician
- 6 months mild exertional dyspnoea
- No exposures
- Lifelong non-smoker
- No clubbing
- Occasional bibasal crepitations

	Pred LL	Pred UI	Test1	% Pred	S.R.
Date			01/06/11		
FEV 1	2.76	4.43	2.98	82.9	-1.21
FVC	3.55	5.55	3.77	82.9	-1.28
TLCOSB	7.89	12.53	6.54	64.0	-2.59
TLCOc	7.89	12.53	6.25	61.3	-2.79
VA	6.64	6.64	4.66	70.1	
KCO	1.02	1.90	1.40	96.1	-0.21
KCOc	1.02	1.90	1.34	92.0	-0.43

HRCT



Broncho-alveolar lavage

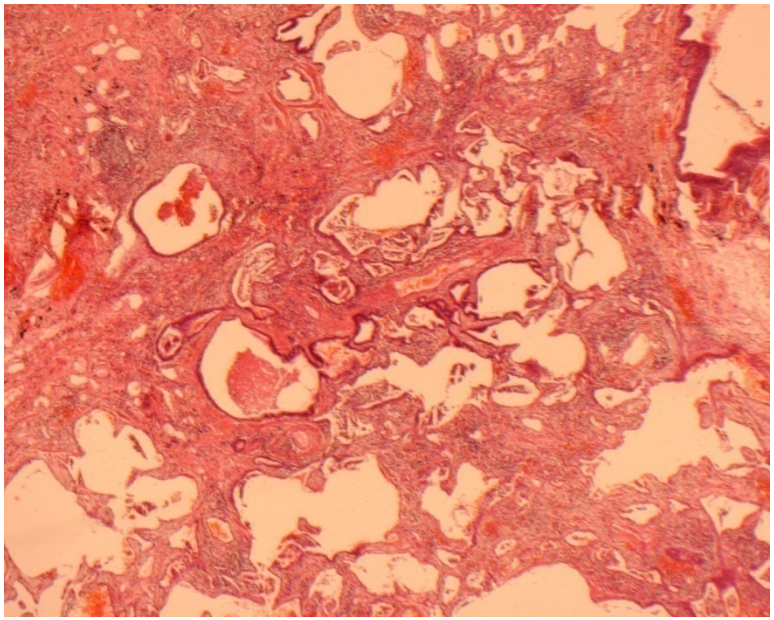
BRONCHOALVEOLAR LAVAGE REPORT

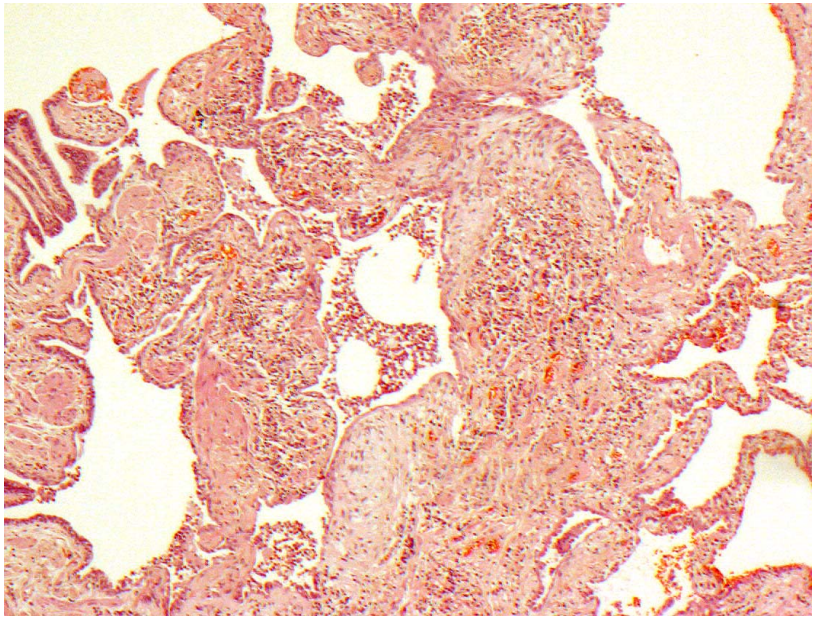
Volume in:	-	**Volume out:**	-
Volume Received:	98ml	**Total Cell Conc.**	0.221 $x10^6$/ml
Total Cells counted	**300**	**Cell Viability %**	**78**
	Cells Counted	**%**	**Normal Range**
Macrophages	150	50	>80%
Lymphocytes	112	37.3	≤14%
Neutrophils	18	6	≤ 4%
Eosinophils	15	5	≤ 3%
Mast Cells	1	0.3	≤ 0.5%
Ciliated Epithelial Cells	2	0.7	
Squamous Epithelial Cells	2	0.7	
Others	0	0	
Debris/Mucus	+		
RBC	++		
Inclusion Bodies	-		
Pigmented Macrophages	-		

Comments: Lymphocytosis. Mild Neutrophilia. Mild Eosinophilia

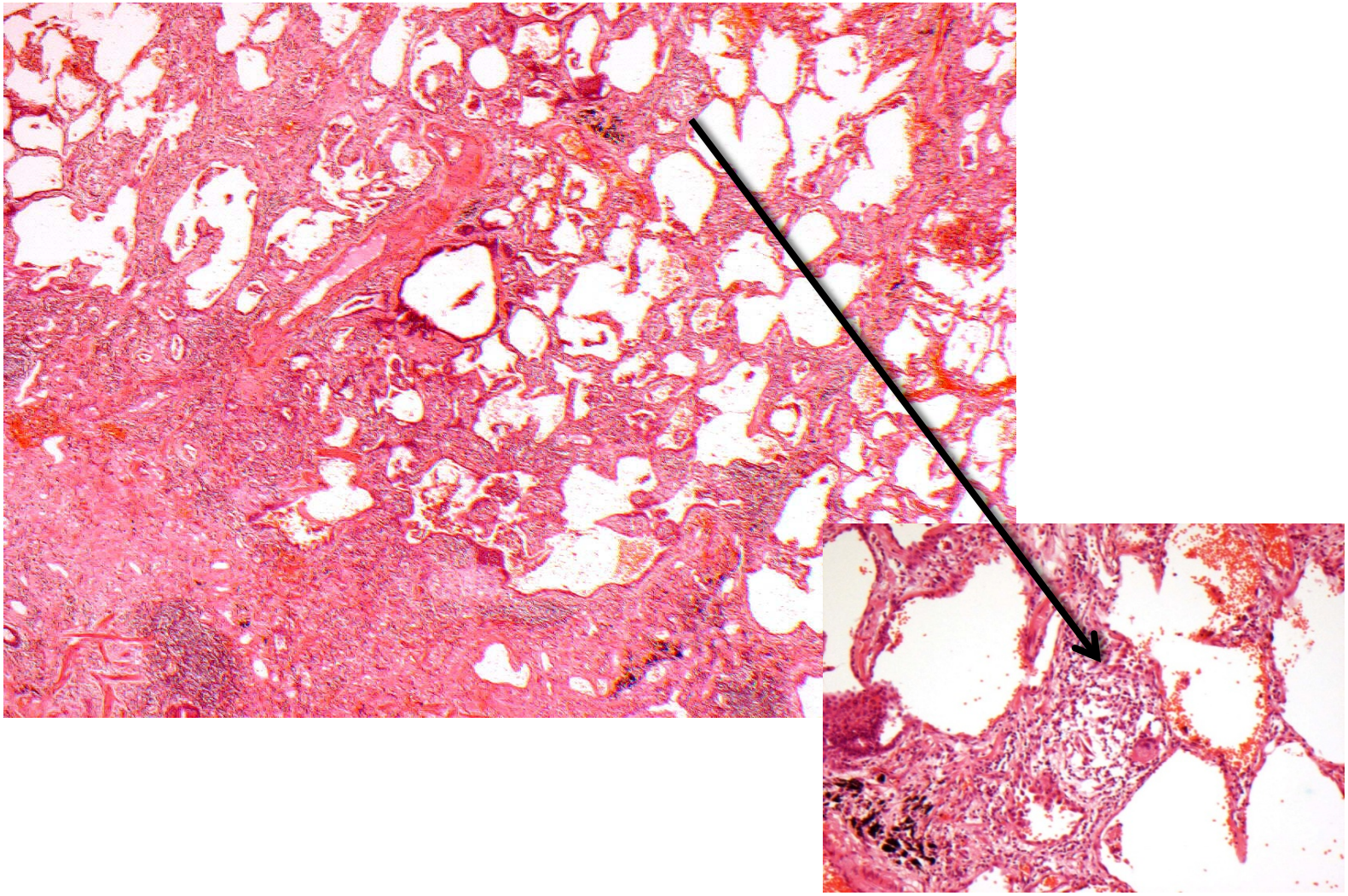
Lymphocytosis

Surgical Lung Biopsy





Surgical Lung Biopsy

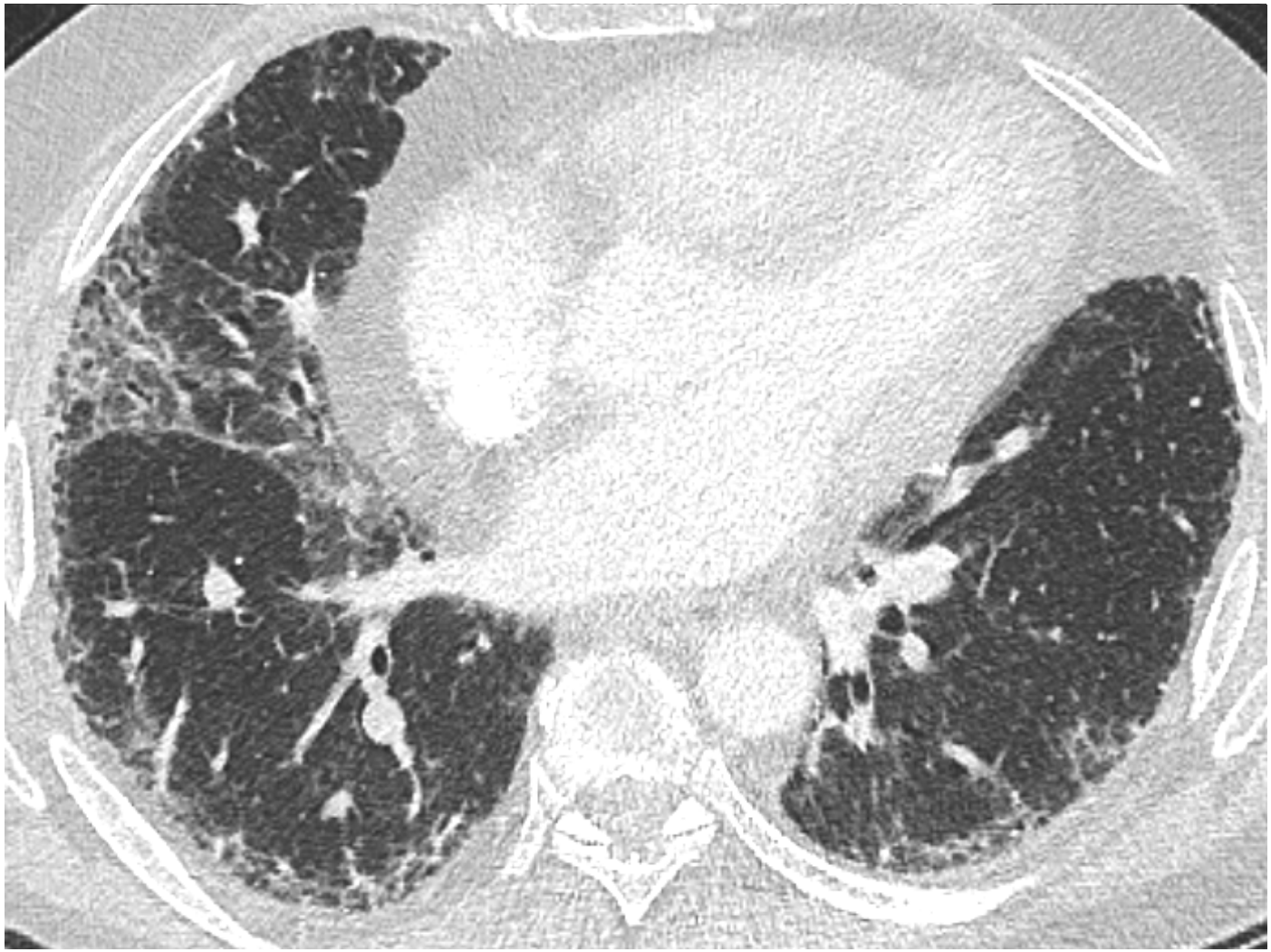


Follow up

- MDT diagnosis – probable fibrotic hypersensitivity pneumonitis

Follow up

- Diagnosis – probable fibrotic hypersensitivity pneumonitis
- Treated with intravenous methylprednisolone followed by prednisolone 10 mg daily, azathioprine 150 mg daily and NAC
- After 12 months, worsening breathlessness and 14% decline in FVC



Follow up

- Diagnosis – probable fibrotic hypersensitivity pneumonitis
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- Repeat bronchoscopy – 28% lymphocytes

Follow up

- Diagnosis – probable fibrotic hypersensitivity pneumonitis
- Treated with intravenous methylprednisolone followed by prednisolone 10 mg daily, azathioprine 150 mg daily and NAC
- After 12 months, worsening breathlessness and 14% decline in FVC
- Repeat bronchoscopy – 28% lymphocytes
- Treatment changed to intravenous cyclophosphamide 600 mg/m^2 body surface area every 4 weeks for 6 doses.

Follow up lung function

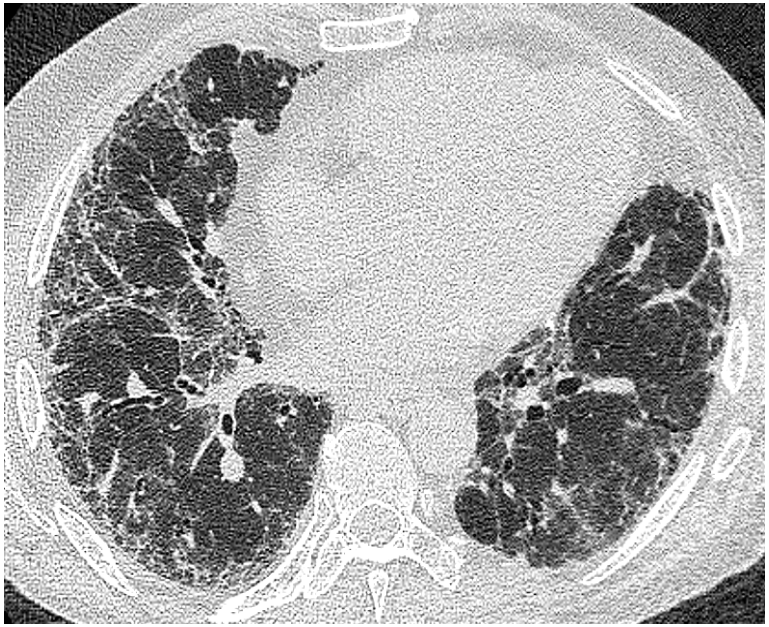
Pred + Aza started ↓ **Cytoxan started** ↓

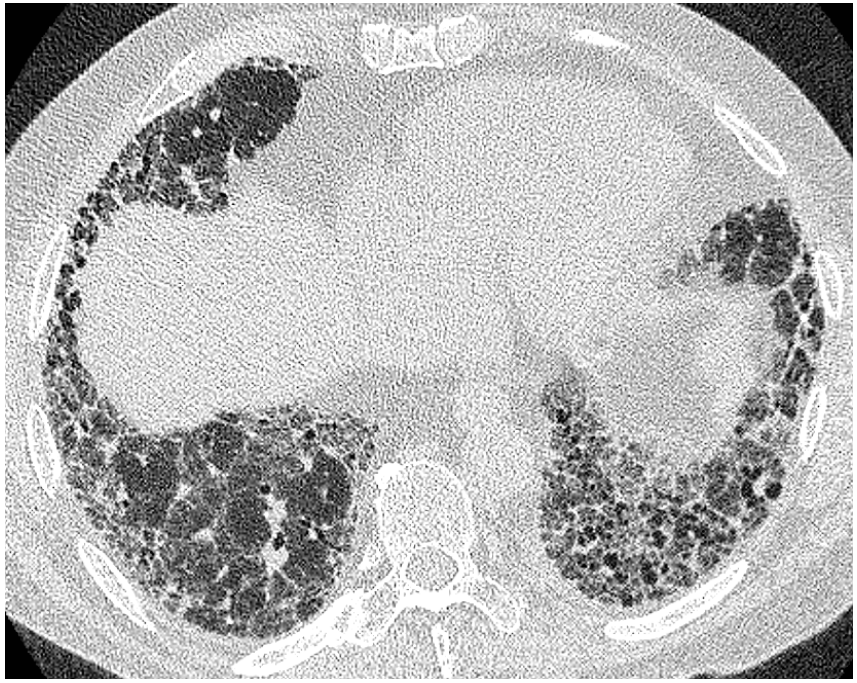
Date	Pred LI	Pred UI	**Test 1** 01/06/11	**Test 2** 17/01/12	**Test 3** 10/07/12	**Test 4** 23/04/13	**Test 5** 22/04/14	**% Pred**
FEV_1	2.79	4.46	2.98	2.85	2.80	2.50	2.41	66.6
FVC	3.61	5.61	3.77	3.59	3.44	3.08	2.95	64.1

Follow up

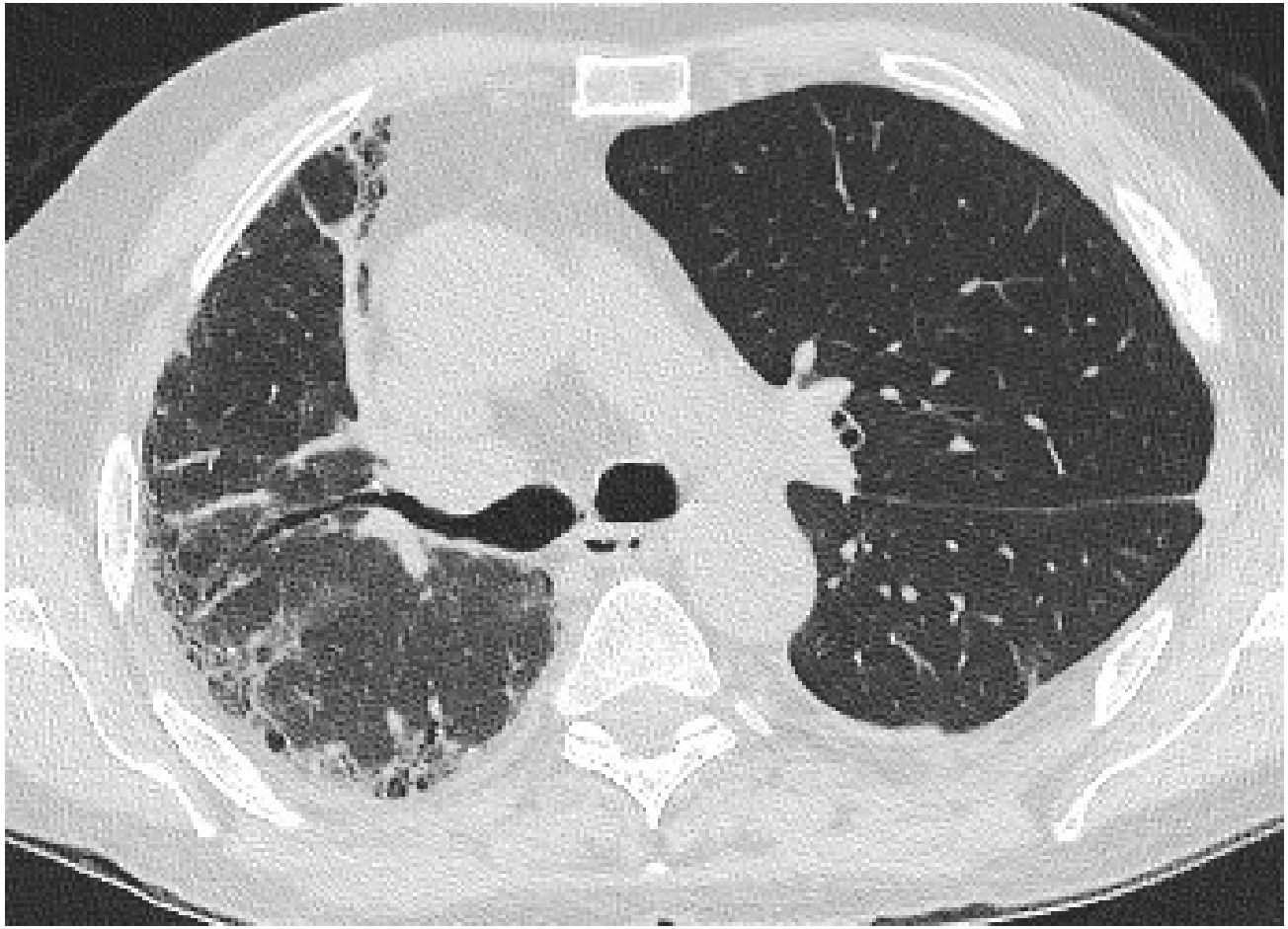
- Further MDT discussion. Revised diagnosis to probable IPF based on longitudinal disease behaviour
- Treatment started with pirfenidone 801 mg t.i.d.
- Gradual decline in lung function – Dlco 22% predicted
- As of January 2016 on active transplant waiting list

January 2016

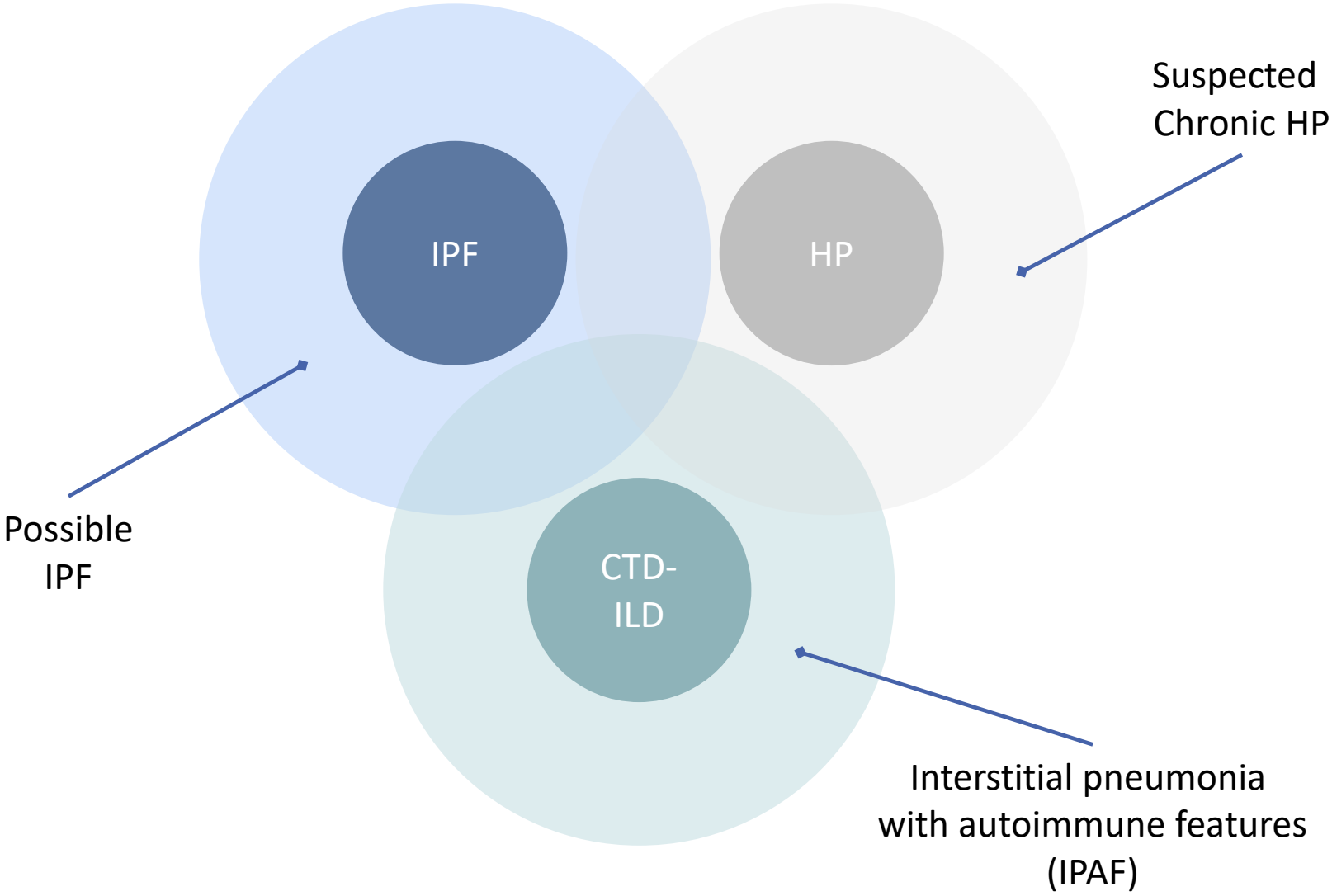




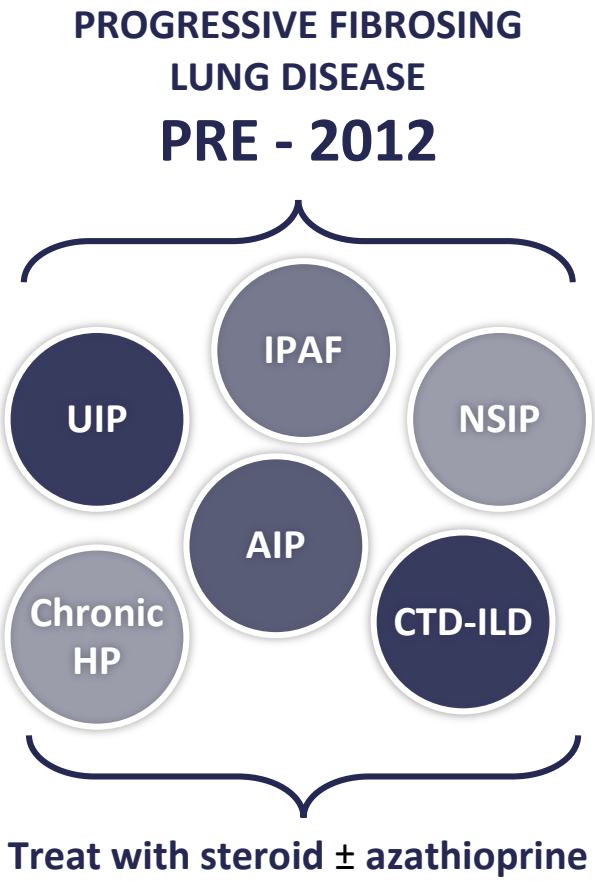
June 2016



Fibrotic ILD re-visualised



Post-2012: A new era in diagnosing and treating pulmonary fibrosis



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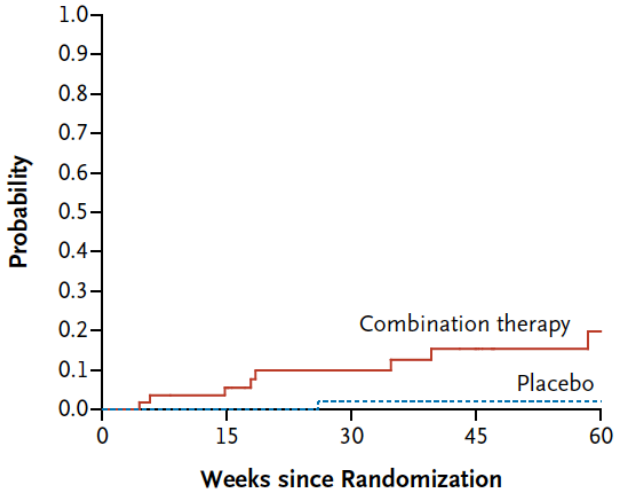
ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

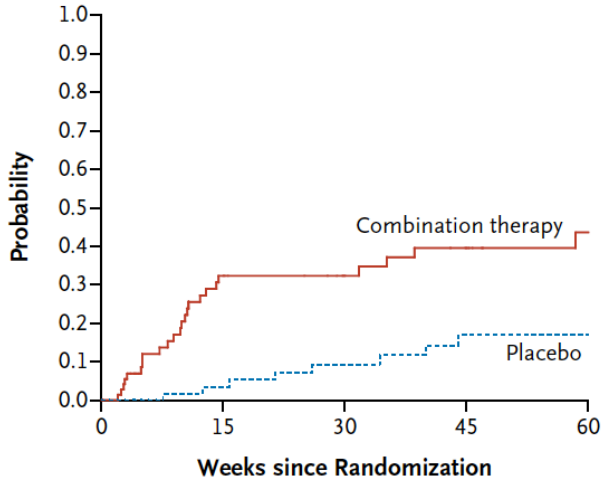
The Idiopathic Pulmonary Fibrosis Clinical Research Network*

Time to Death



No. at Risk					
Combination therapy	77	50	34	29	14
Placebo	78	57	44	31	17

Time to Death or Hospitalization



No. at Risk					
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

A new era for IPF

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This Week at NEJM.org | May 29, 2014

Listen to the Weekly Audio Summary

ORIGINAL ARTICLES

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

L. Richeldi and Others | N Engl J Med 2014;370:2071-2082 | Published Online May 18, 2014

CME Comments

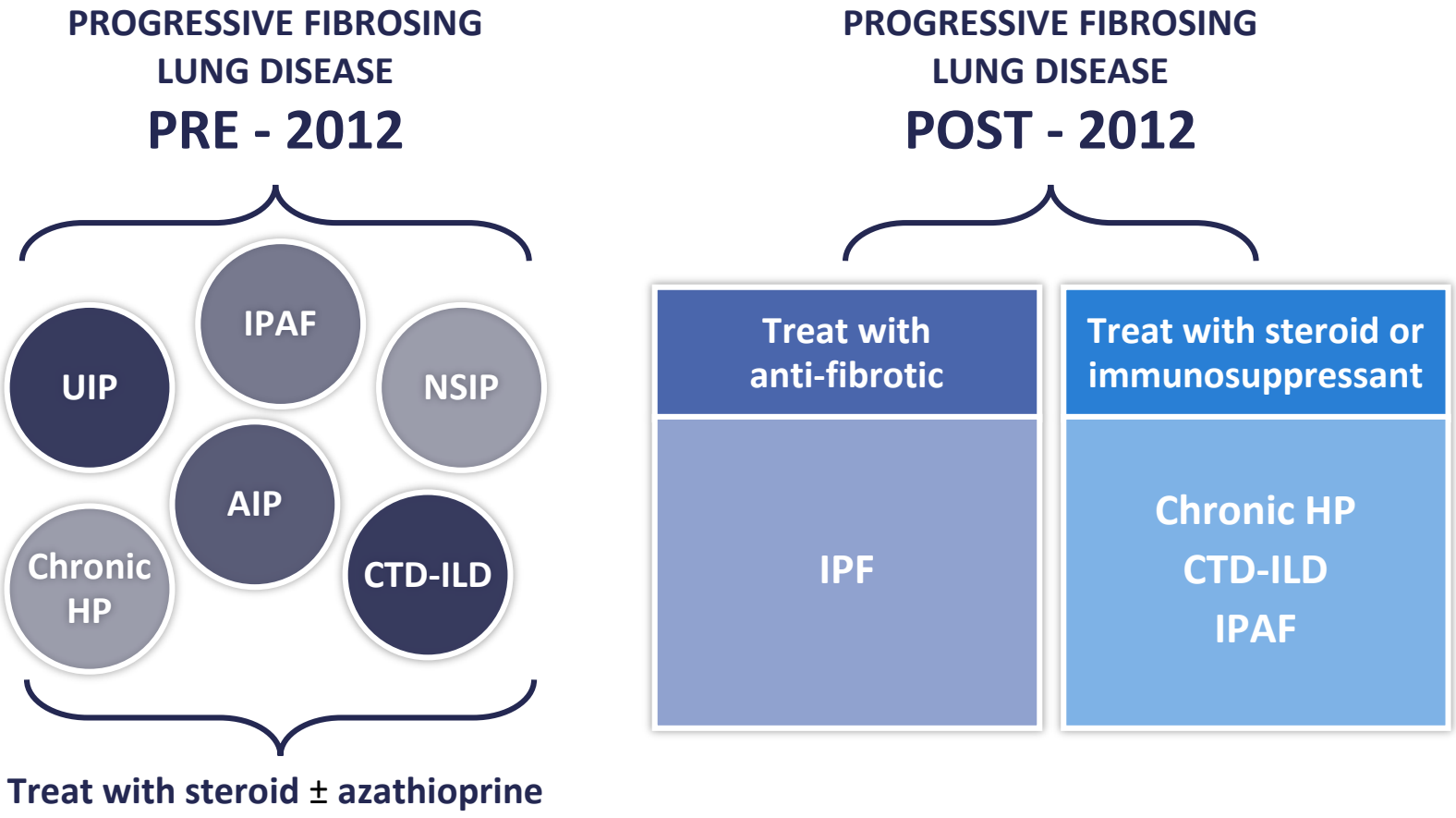
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

T.E. King, Jr., and Others | N Engl J Med 2014;370:2083-2092 | Published Online May 18, 2014

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network | N Engl J Med 2014;370:2093-2101 | Published Online May 18, 2014

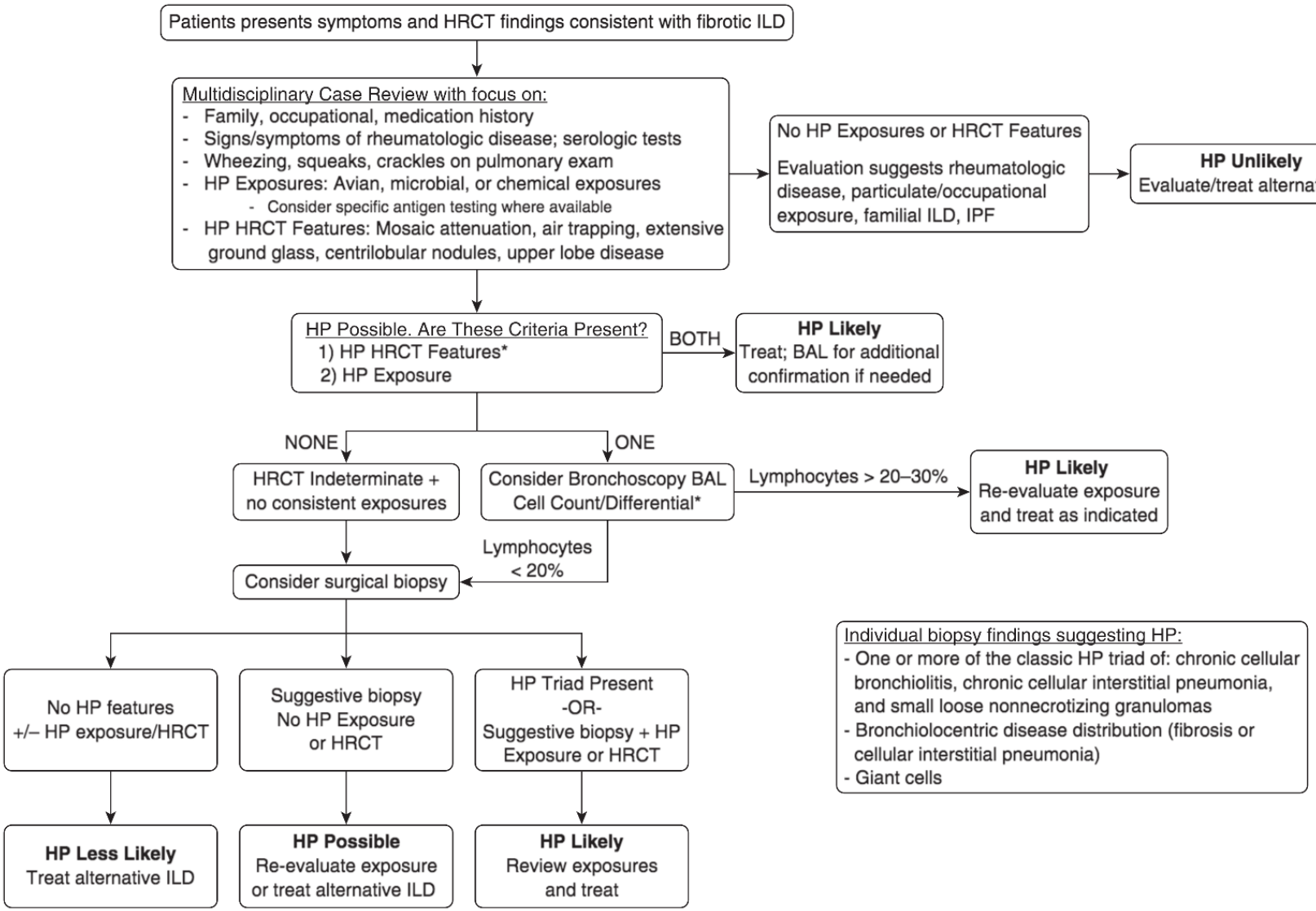
Post-2012: A new era in diagnosing and treating pulmonary fibrosis



Defining chronic HP

Diagnostic Confidence for Hypersensitivity Pneumonitis
Definite
1. Probable/Definite histopathologic likelihood with, a. Antigenic history, OR b. Definite HRCT likelihood, OR b. Probable HRCT likelihood and Lymphocytosis 2. Probable/Definite HRCT likelihood, Lymphocytosis & Antigenic history (absent biopsy)
Highly Probable
1. Probable/Definite HRCT likelihood with, a. Antigenic history (absent histopathology), OR b. Lymphocytosis (absent histopathology), OR c. Possible histopathologic likelihood with lymphocytosis or antigenic history, OR, d. Probable histopathologic likelihood 2. Probable/Definite histopathologic likelihood with Lymphocytosis and possible HRCT likelihood
Probable
1. Lymphocytosis & Antigenic history with a possible HRCT likelihood (with at least possible histopathologic likelihood) 2. Lymphocytosis or Antigenic history with a possible histopathologic & HRCT likelihood 3. Lone probable/definite histopathologic likelihood (with at least possible HRCT likelihood) 4. Lone probable/definite HRCT likelihood (with at least possible histopathologic likelihood) 5. Possible histopathologic likelihood with lymphocytosis or Antigenic history (with at least possible HRCT likelihood)

Salisbury et al AJRCCM 2017



Salisbury et al AJRCCM 2017

Identification of Diagnostic Criteria for Chronic Hypersensitivity Pneumonitis

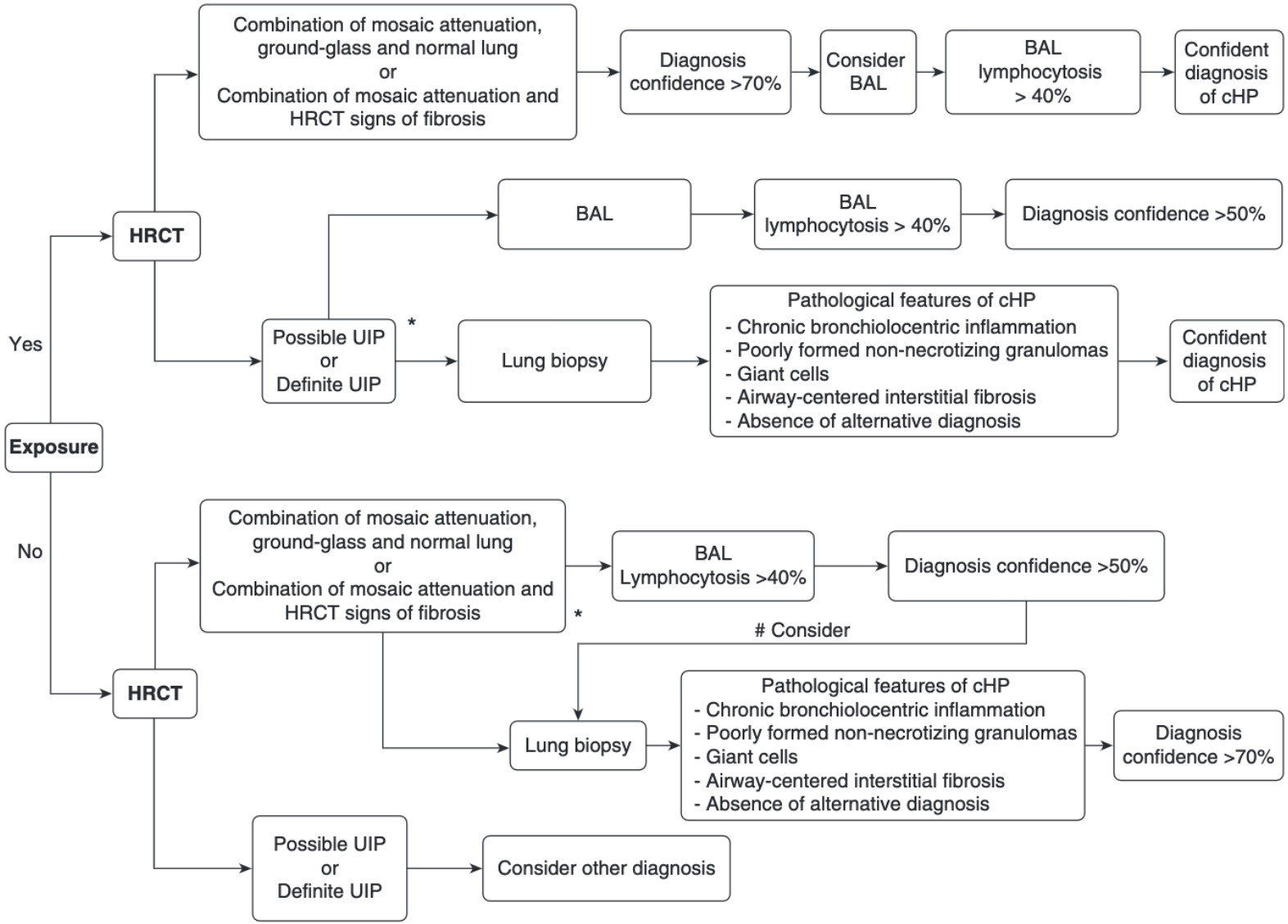
An International Modified Delphi Survey

Julie Morisset[1], Kerri A. Johannson[2], Kirk D. Jones[3], Paul J. Wolters[4], Harold R. Collard[4], Simon L. F. Walsh[5], Brett Ley[4], and the HP Delphi Collaborators

[1]Département de Médecine, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; [2]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [3]Department of Pathology and [4]Department of Medicine, University of California, San Francisco, San Francisco, California; and [5]Department of Radiology, King's College, Hospital National Health Service Foundation Trust, London, United Kingdom

Characteristics	Expert Interview (*n* = *11*)	Modified Delphi (*n* = *45*)
Response rate, *n*/total (%)	11/15 (73. 3)	45/53 (84.9)
Female, *n* (%)	4 (36.4)	14 (31.1)
Country, *n* (%)		
Australia	—	3 (6.7)
Belgium	—	1 (2.2)
Brazil	—	1 (2.2)
Canada	1 (9.1)	5 (11.1)
France	—	1 (2.2)
Germany	1 (9.1)	4 (8.9)
Greece	—	1 (2.2)
Italy	1 (9.1)	5 (11.1)
Japan	—	1 (2.2)
Mexico	1 (9.1)	1 (2.2)
The Netherlands	1 (9.1)	1 (2.2)
Spain	—	1 (2.2)
United Kingdom	—	3 (6.7)
United States	6 (54.5)	17 (37.8)
Years in clinical practice, median (IQR)	16 (13–21)	20 (10–25)
% of clinical time dedicated to ILD, median (IQR)	75 (50–90)	61 (40–82)

Definition of abbreviations: ILD = interstitial lung disease; IQR = interquartile range.



Morrisett et al AJRCCM 2018

TREATING CHRONIC HYPERSENSITIVITY PNEUMONITIS

Remove the antigen…

Corticosteroids

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

JOUKO I. KOKKARINEN, HANNU O. TUKIAINEN, and ERKKI O. TERHO

AM REV RESPIR DIS 1992; 145:3–5

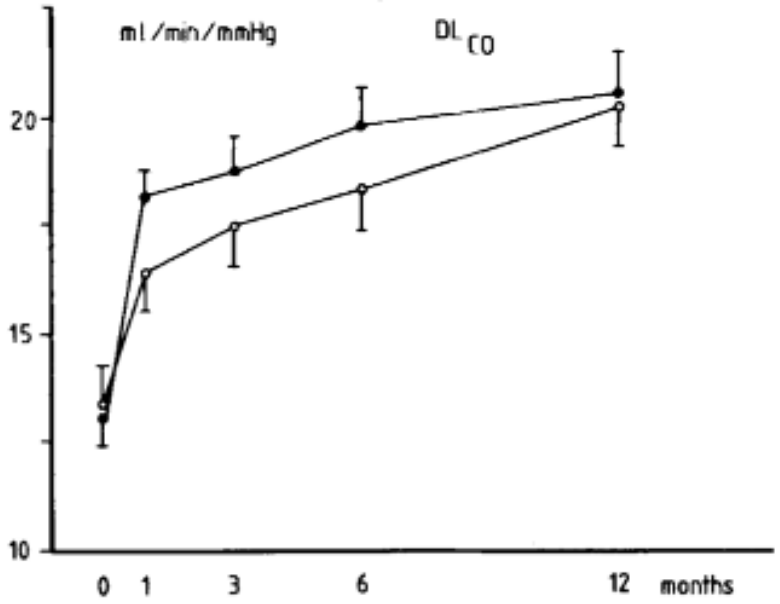


Fig. 2. D_{LCO} (mean and SEM) during the first year of follow-up in the corticosteroid and placebo groups. Difference between the treatment groups at the 1-month follow-up was significant ($p = 0.03$). Closed circles = prednisolone ($n = 17$); open circles = placebo ($n = 13$).

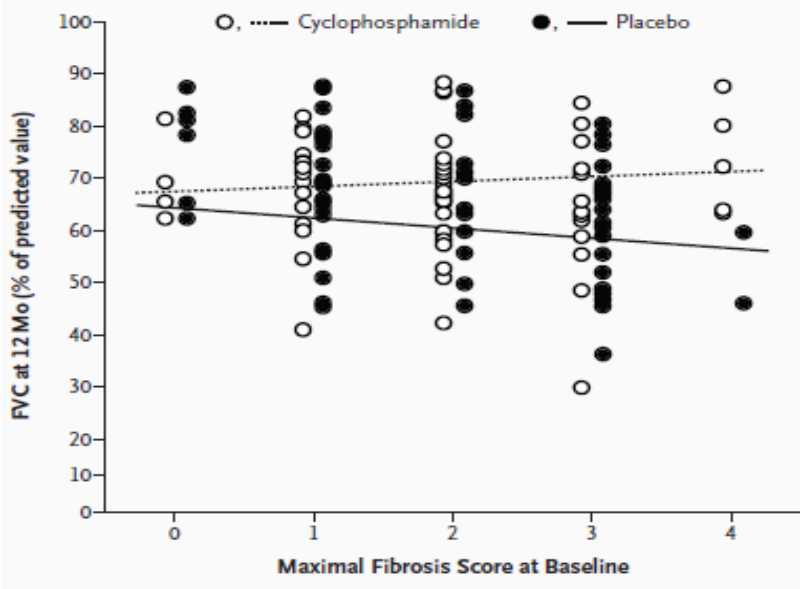
Cyclophosphamide

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cyclophosphamide versus Placebo in Scleroderma Lung Disease

Donald P. Tashkin, M.D., Robert Elashoff, Ph.D., Philip J. Clements, M.D., M.P.H., Jonathan Goldin, M.D., Ph.D., Michael D. Roth, M.D., Daniel E. Furst, M.D., Edgar Arriola, Pharm.D., Richard Silver, M.D., Charlie Strange, M.D., Marcy Bolster, M.D., James R. Seibold, M.D., David J. Riley, M.D., Vivien M. Hsu, M.D., John Varga, M.D., Dean E. Schraufnagel, M.D., Arthur Theodore, M.D., Robert Simms, M.D., Robert Wise, M.D., Fredrick Wigley, M.D., Barbara White, M.D., Virginia Steen, M.D., Charles Read, M.D., Maureen Mayes, M.D., Ed Parsley, D.O., Kamal Mubarak, M.D., M. Kari Connolly, M.D., Jeffrey Golden, M.D., Mitchell Olman, M.D., Barri Fessler, M.D., Naomi Rothfield, M.D., and Mark Metersky, M.D., for the Scleroderma Lung Study Research Group*



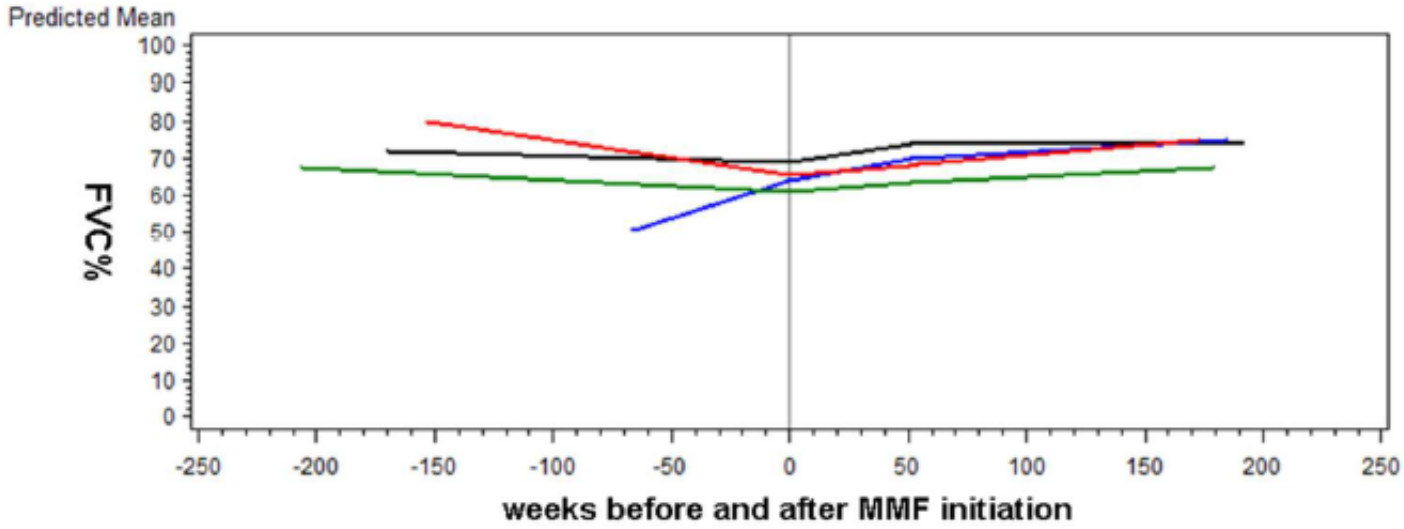
Tashkin NEJM 2006

Brompton cyclophosphamide experience

Disease	Number of patients		Mortality within one year of first dose		Mean FVC change % following cyclophosphamide		%TLCO change following cyclophosphamide	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Scleroderma	21	12	0%	0%	-0.43%	-1.37%	-0.17%	4.61%
Mixed connective tissue disease	0	4	NA	0%	NA	2.88%	NA	2.02%
Idiopathic myositides including antisynthetase	8	9	0%	0%	7.22%	11.46%	-0.94%	11.25%
Unclassfiable connective tissue disease	32	15	0%	5%	-0.81	5.98%	-6.45%	0.26%
Chronic hypersensitivity pneumonitis	15	26	26%	19%	-8.90%	-1.24%	5.83%	-5.66%
Unclassifiable interstitial lung disease	8	15	38%	26%	0.97%	2.00%	-6.28%	-2.73%

Saunders P et al ATS 2017

Mycophenolate mofetil



Red line=RA, Black line=SSc, Blue line=PM/DM, Green line=lung dominant-CTD

Fischer et al J Rheumatol 2013

CHEST

Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis

Julie Morisset, MD; Kerri A. Johannson, MD; Eric Vittinghoff, PhD; Carlos Aravena, MD; Brett M. Elicker, MD; Kirk D. Jones, MD; Charlene D. Fell, MD; Helene Manganas, MD; Bruno-Pierre Dubé, MD; Paul J. Wolters, MD; Harold R. Collard, MD, FCCP; Christopher J. Ryerson, MD; and Brett Ley, MD

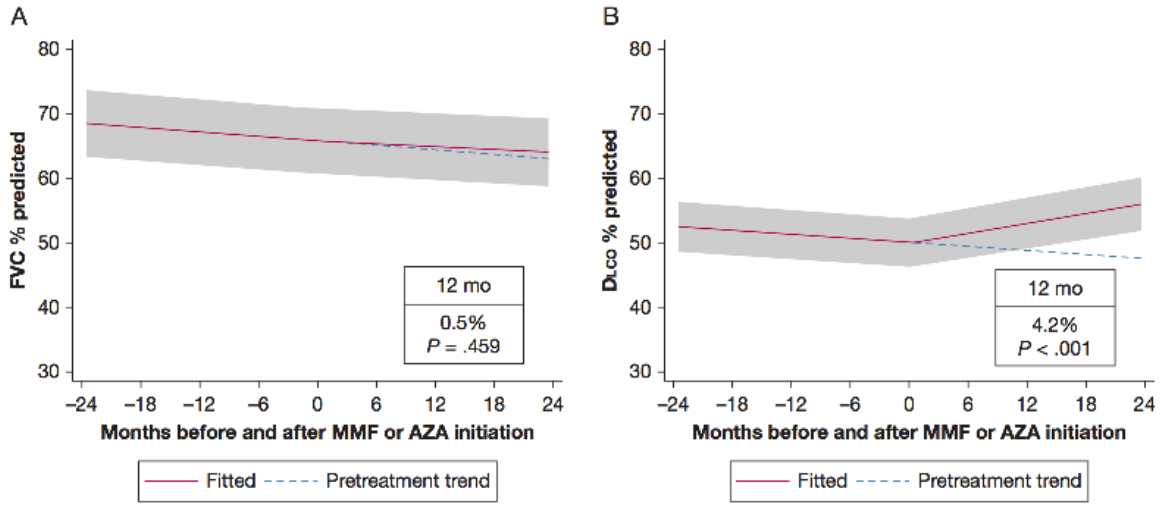
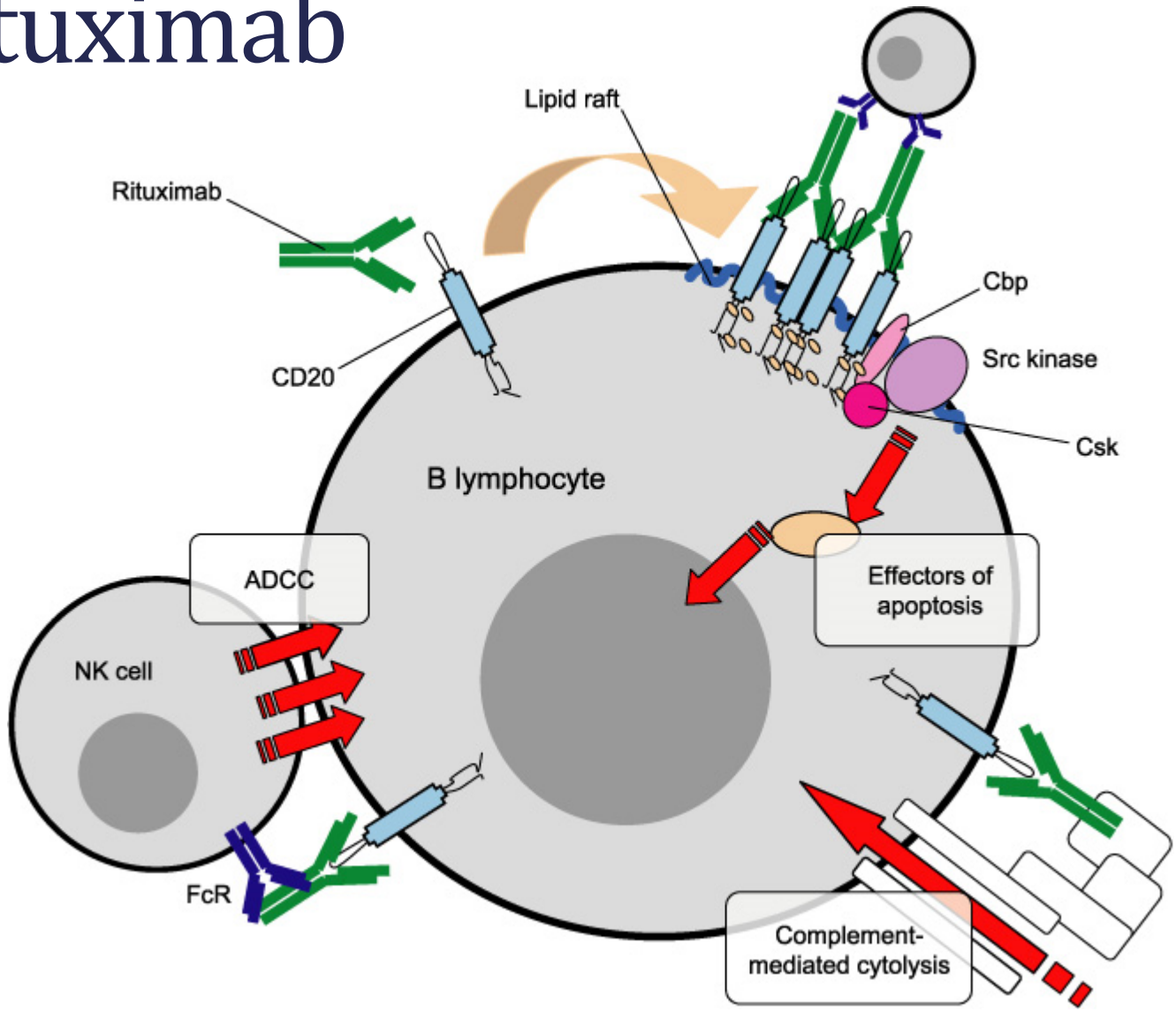


Figure 2 – *Mixed-effects model estimates for FVC % predicted and DLCO % predicted before and after initiation of mycophenolate or azathioprine. The gray shading indicates the 95% CI. DLCO = diffusion capacity of the lung for carbon monoxide. See Figure 1 legend for expansion of other abbreviations.*

Rituximab


Lipid raft
Rituximab
CD20
Cbp
Src kinase
Csk
B lymphocyte
ADCC
NK cell
FcR
Effectors of apoptosis
Complement-mediated cytolysis

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Rituximab in severe, treatment-refractory interstitial lung disease

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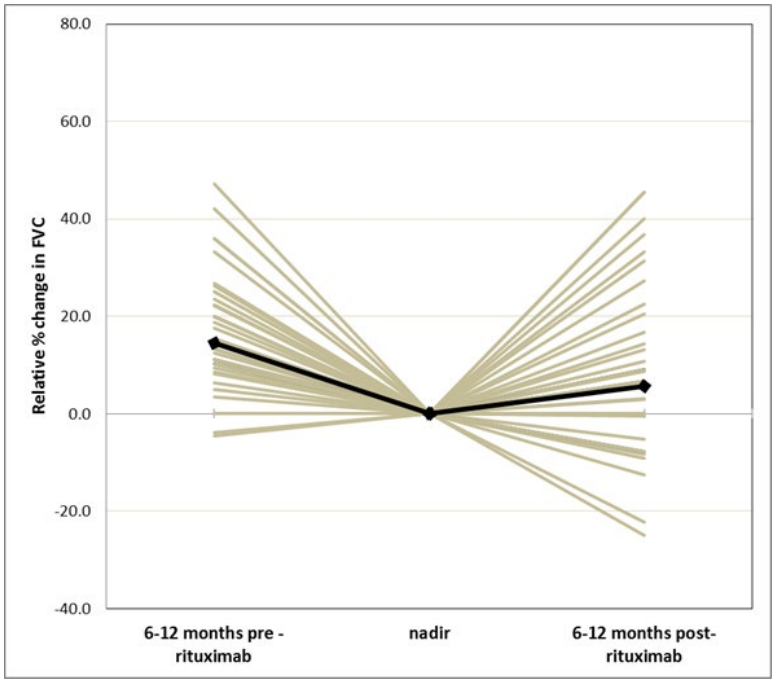
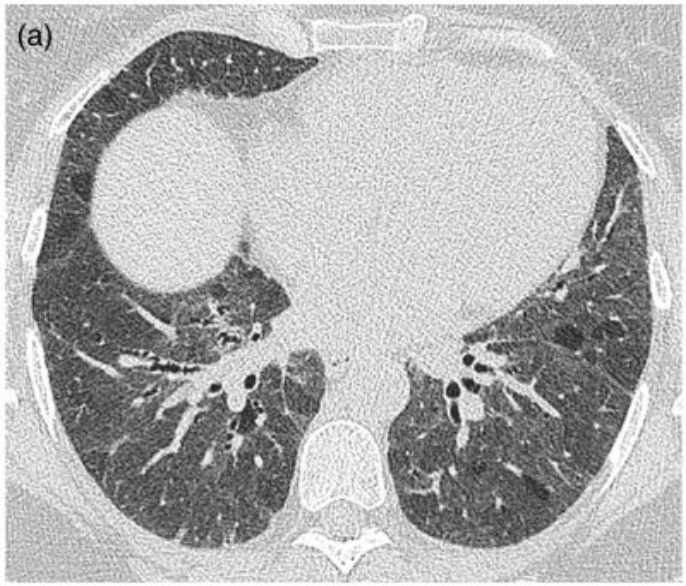
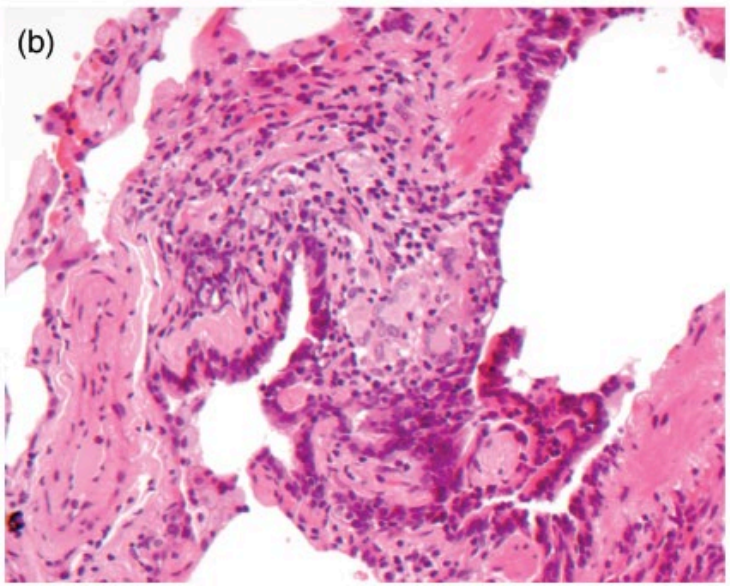
[1]*Royal Brompton Hospital,* [4]*St Mary's Hospital, London, UK,* [2]*Princess Alexandra Hospital, Brisbane, Queensland, Australia, and* [3]*Department of Pneumonology, Carlo Poma Hospital, Mantua, Italy*

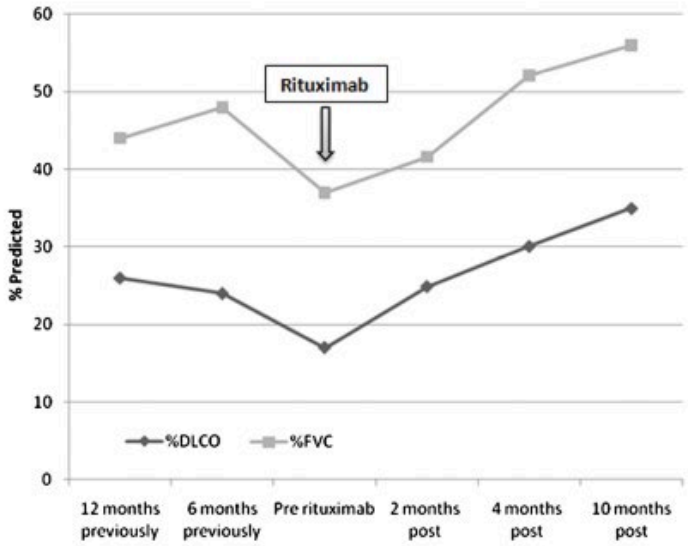


n = 50
Age 52.5 (± 10.9)
Female (33)
ILD diagnosis
CTD-ILD (33)
– Idiopathic inflammatory myopathy (10)
– Systemic sclerosis (8)
– Undifferentiated connective tissue disease (9)
– Mixed connective tissue disease (2)
– Rheumatoid arthritis (2)
– Systemic lupus erythematosus (1)
– Sjogren's (1)
Hypersensitivity pneumonitis (6)
Other ILDs
– Drug-induced (3)
– Vasculitis (2)
– Desquamative interstitial pneumonia (non-smokers) (2)
– Cryptogenic organising pneumonia (1)
– Smoking related (1)
– Acute interstitial pneumonia (1)
– Unclassifiable (1)
Pulmonary function tests†
DL_{CO} % 24.5 (11.4–67.0)
FEV_1 % 49.0 (24.7–92.0)
FVC % 44.0 (24.0–99.0)
$PaO_{2\ kPa}$ 8.3 (5.1–10.8)





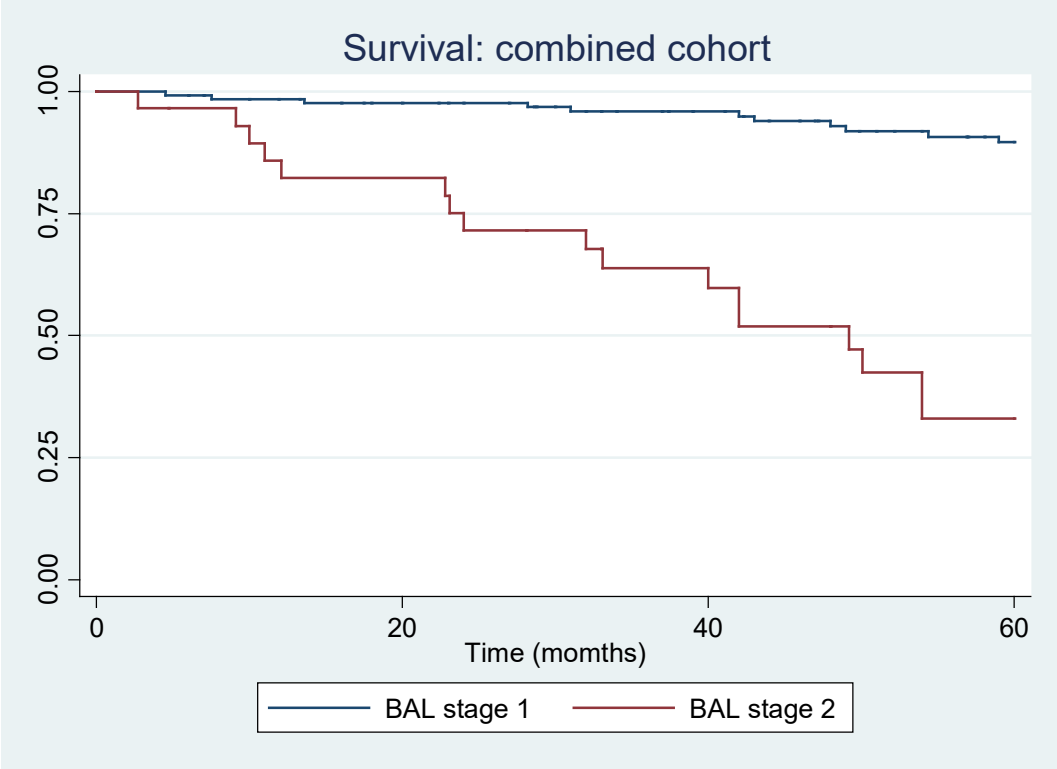
(c)



Lota et al Thorax 2013

Deciding whom to treat

BAL Lymphocytes > 20% but neutrophils < 10%



Wells au et al (unpublished)

Anti-fibrotic therapy?

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Home > Study Record Detail

Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD) (PF-ILD)

This study is currently recruiting participants.

See ▶ **Contacts and Locations**

Verified June 2017 by Boehringer Ingelheim

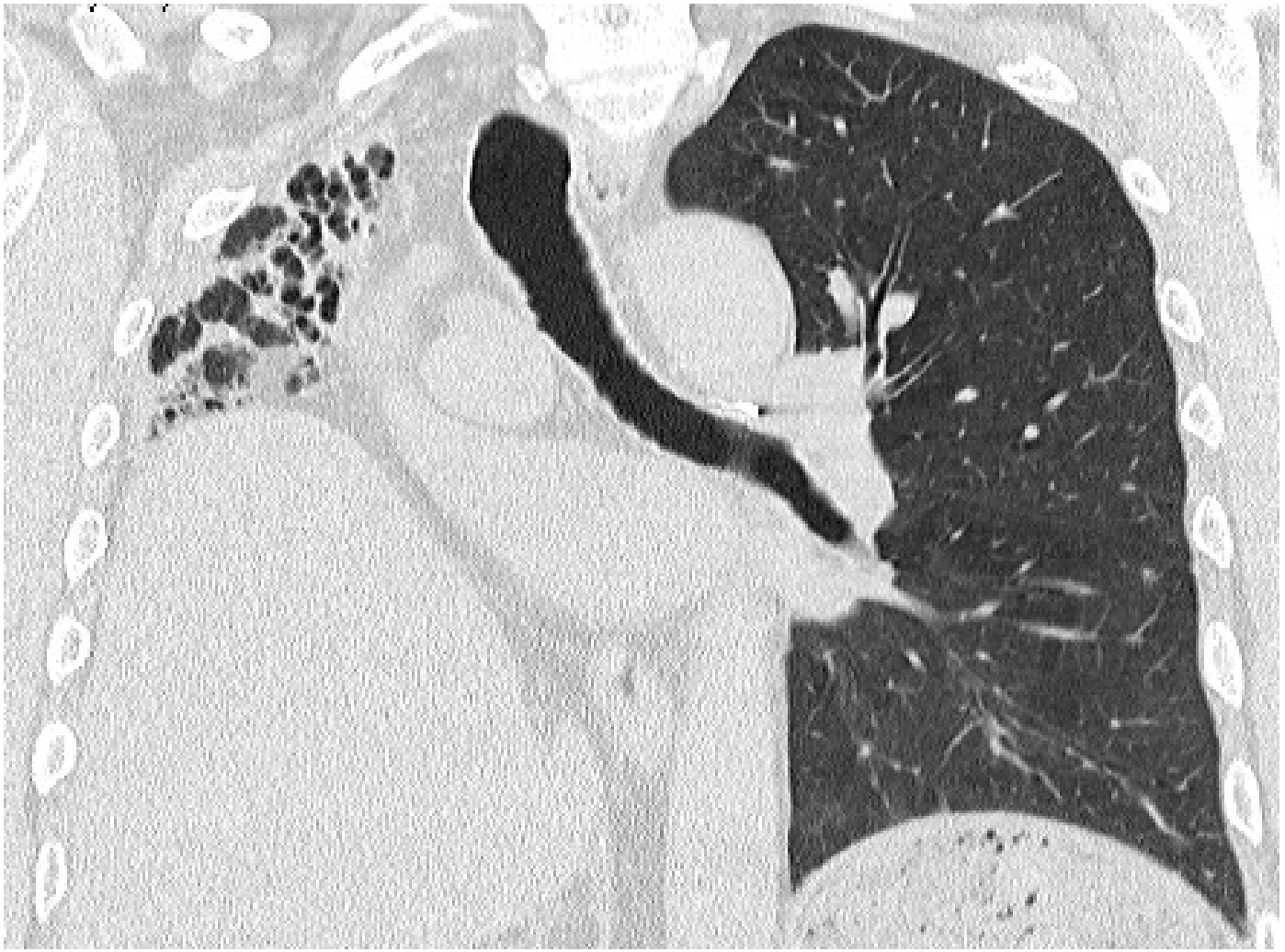
Sponsor:
Boehringer Ingelheim

Information provided by (Responsible Party):
Boehringer Ingelheim

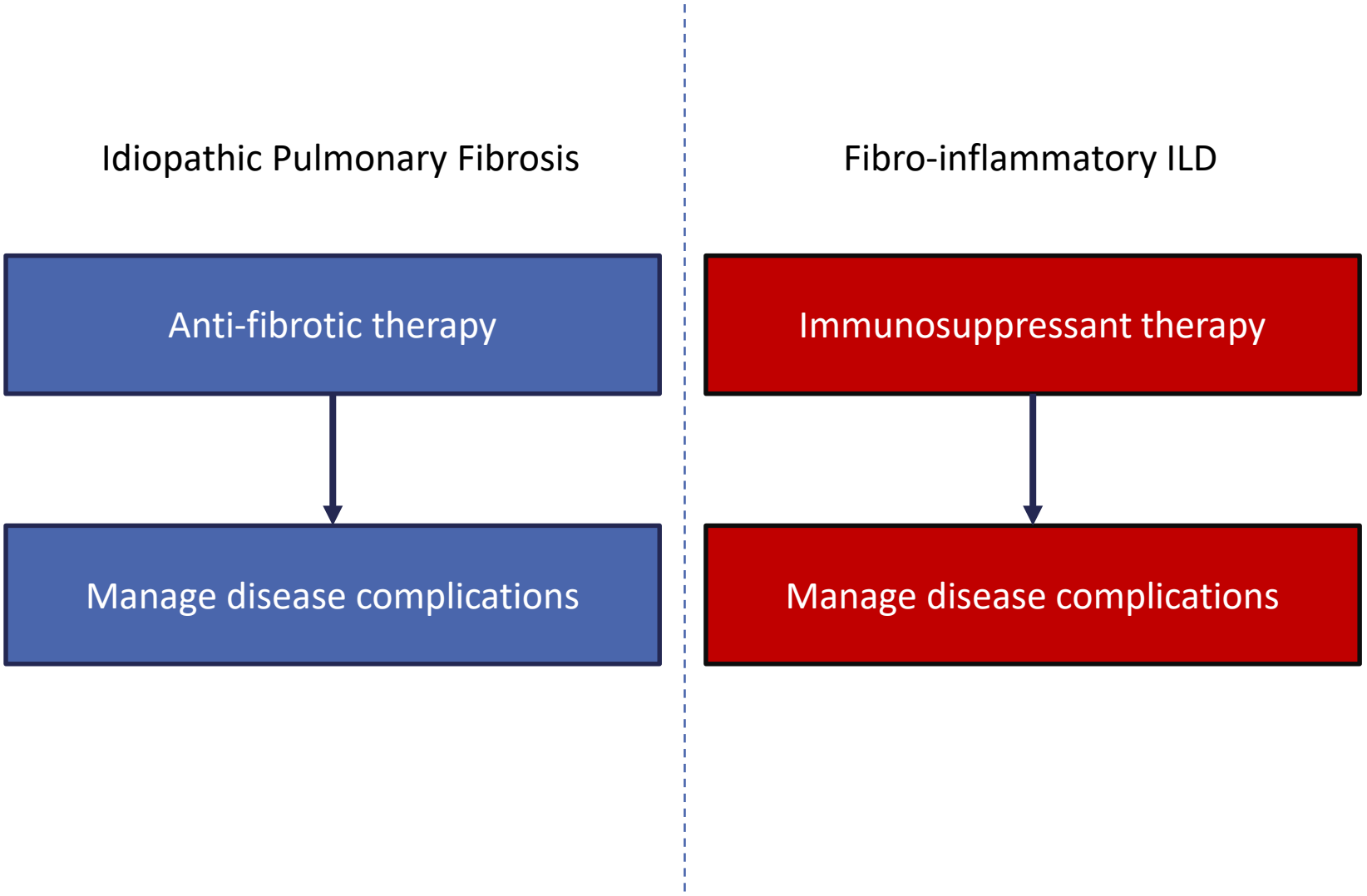
ClinicalTrials.gov Identifier:
NCT02999178

First received: December 19, 2016
Last updated: June 26, 2017
Last verified: June 2017
History of Changes

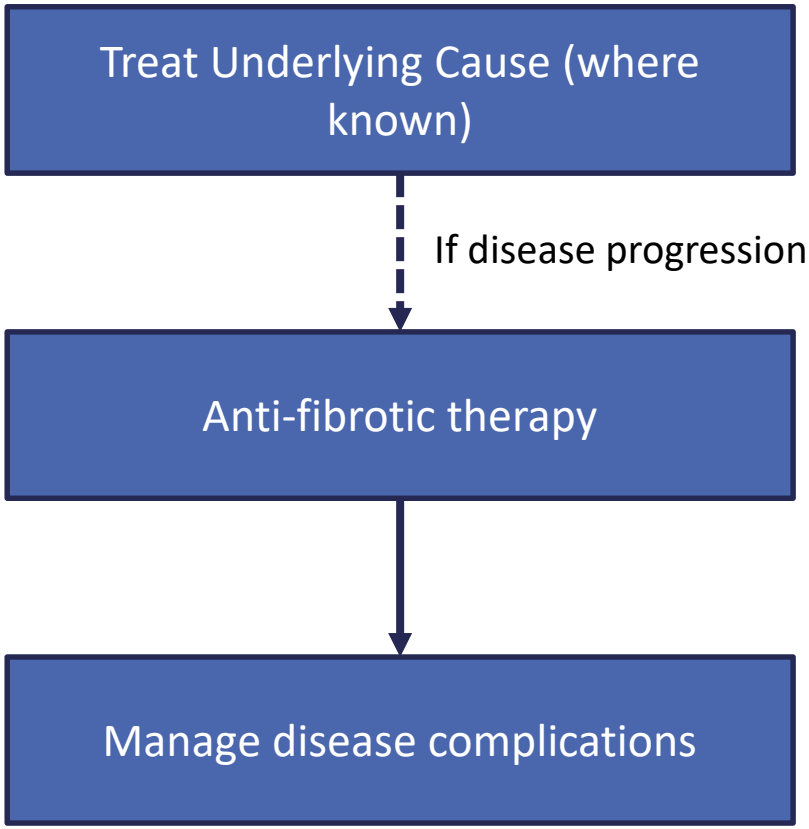
Transplant



Current treatment paradigm



The future treatment of fibrotic ILD?



Summary

- Chronic hypersensitivity pneumonitis is frequently challenging to diagnose
- A proportion of cases overlap with IPF in terms of disease behaviour and outcome
- Absence of lymphocytosis predicts a poorer outcome and response to treatment
- Best therapy remains to be defined but is likely to be corticosteroids +/- immunosuppressant therapy
- The outcome of trials with anti-fibrotic drugs are awaited

Questions?