ILD Collaborative

Project ECHO

Hypersensitivity Pneumonitis: Update on Diagnostic and Treatment Challenges

Robert Hallowell, MD

Disclosures

- Advisory board: Boehringer Ingelheim, Puretech, Arcellx
- Authorship Fees: UpToDate, Dynamed
- Paid consultation: Vicore, Merck
- PI on clinical trials: Boehringer Ingelheim, Vicore

70 y/o man with 9 months of malaise, dry cough, progressive dyspnea

- Worked in an office for 25 years
- No hobbies
- No farm exposure
- **No pets**
- **No birds in the home (ever)**
- **No bird exposure**
- **No down products in the home**
- No hot tub

The exposure history is critical but difficult to obtain

Standard HP panel was ***negative***

Symptoms improved after he retired

The exposure history is critical but difficult to obtain












Some causes of hypersensitivity pneumonitis

Mold
Farmer's Lung (moldy hay)
Tobacco Grower's Lung
Mushroom Worker's Lung
Potato Riddler's Lung
Paprika Slicer's Lung
Wine Maker's Lung
Cheese Washer's Lung
Coffee Worker's Lung
Tea Grower's Lung
Malt worker's Disease

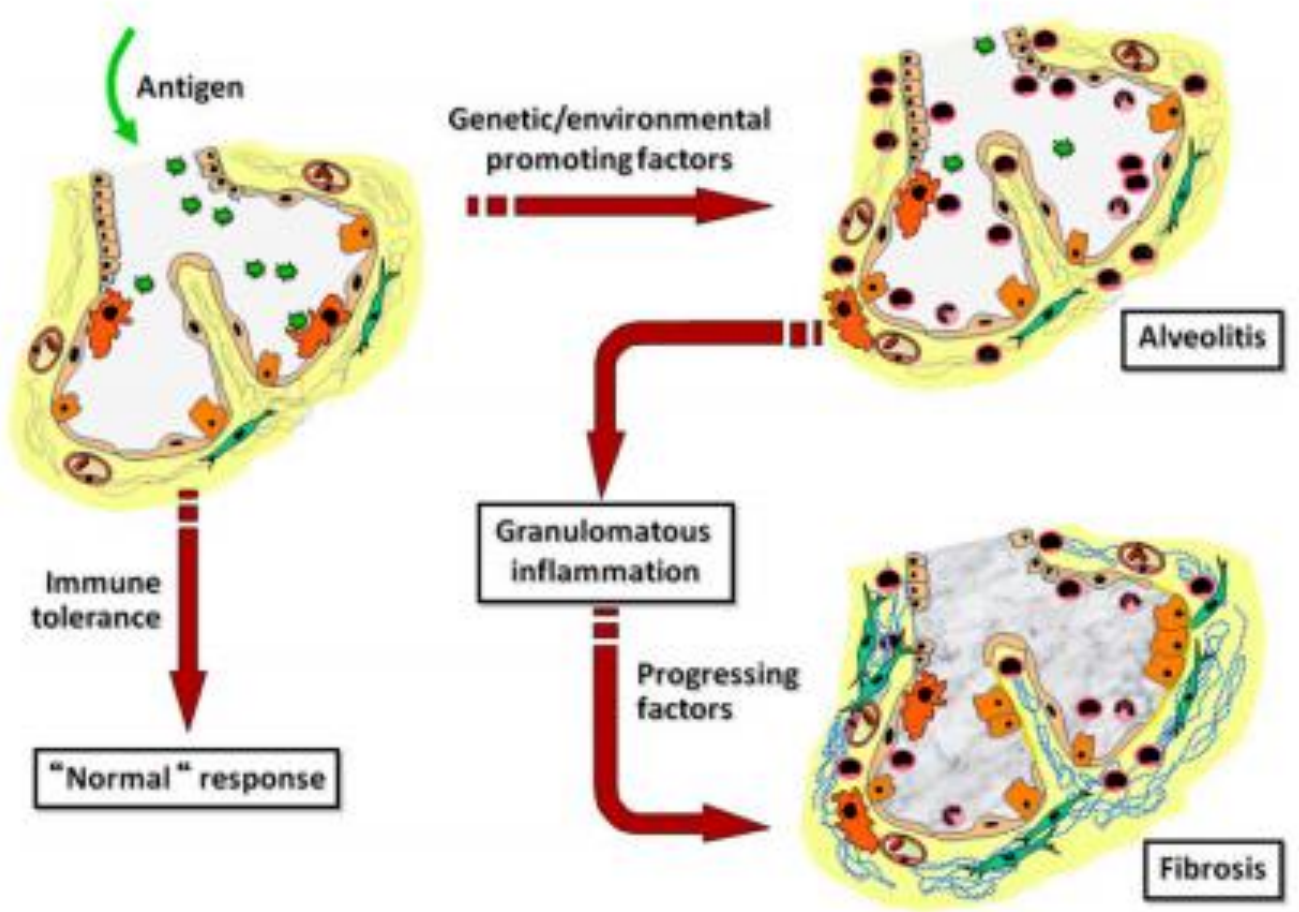
Bible Printer's Lung
Bagpipe Lung
Gardening/landscaping
Woodworker's lung

Mold or bacteria
Humidifier Fever
Hot Tub Lung
Lifeguard Lung
Shower Lung
Grain Measurer's Lung
Machinist Lung

Inorganic chemicals
Chemical Workers Lung
Detergent Worker's Lung
Vineyard Sprayer's Lung
Epoxy Resin Lung

Animal proteins
Bird Fancier's Lung
Pigeon Breeder's Lung
Furrier's Lung
Lab worker's Lung (rats, gerbils)
Bat Lung droppings
Fish Meal Worker's Lung
Mollusk Shell Lung
Oyster Shell Pneumonitis

The presumed pathogenesis of HP



Selman et al. *Am J Respir Crit Care Med* Vol 186, Iss. 4, pp 314–324, Aug 15, 2012

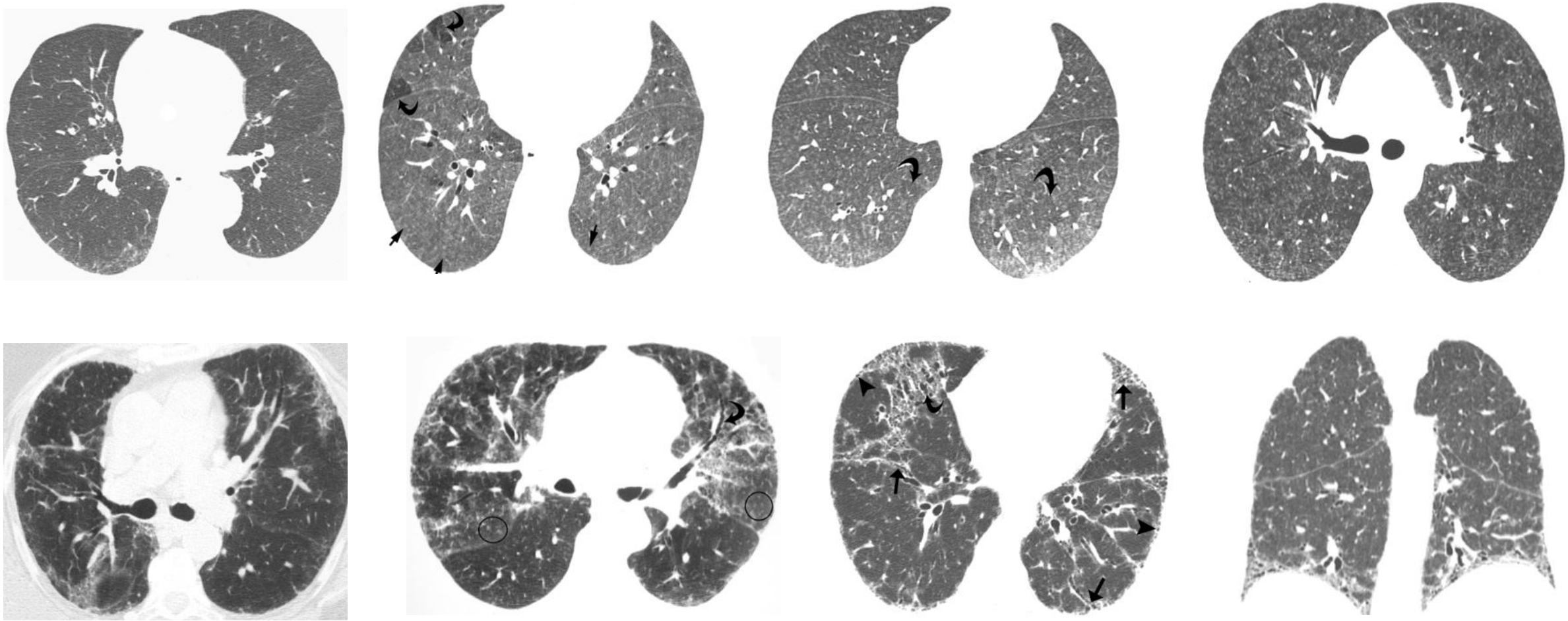
Down products alone can cause HP

Author	Total chronic HP patients, n	Down products as only known exposure, n (%)
Silva et al.	18	2 (11%)
Morell et al.	20*	10 (50%)
Tsutsui et al.	23	11 (48%)
Ishizuka et al.	28	11 (39%)
Morisset et al.	70	6 (8.6%)

*Initially diagnosed with IPF; others in cohort have no other known antigen exposure

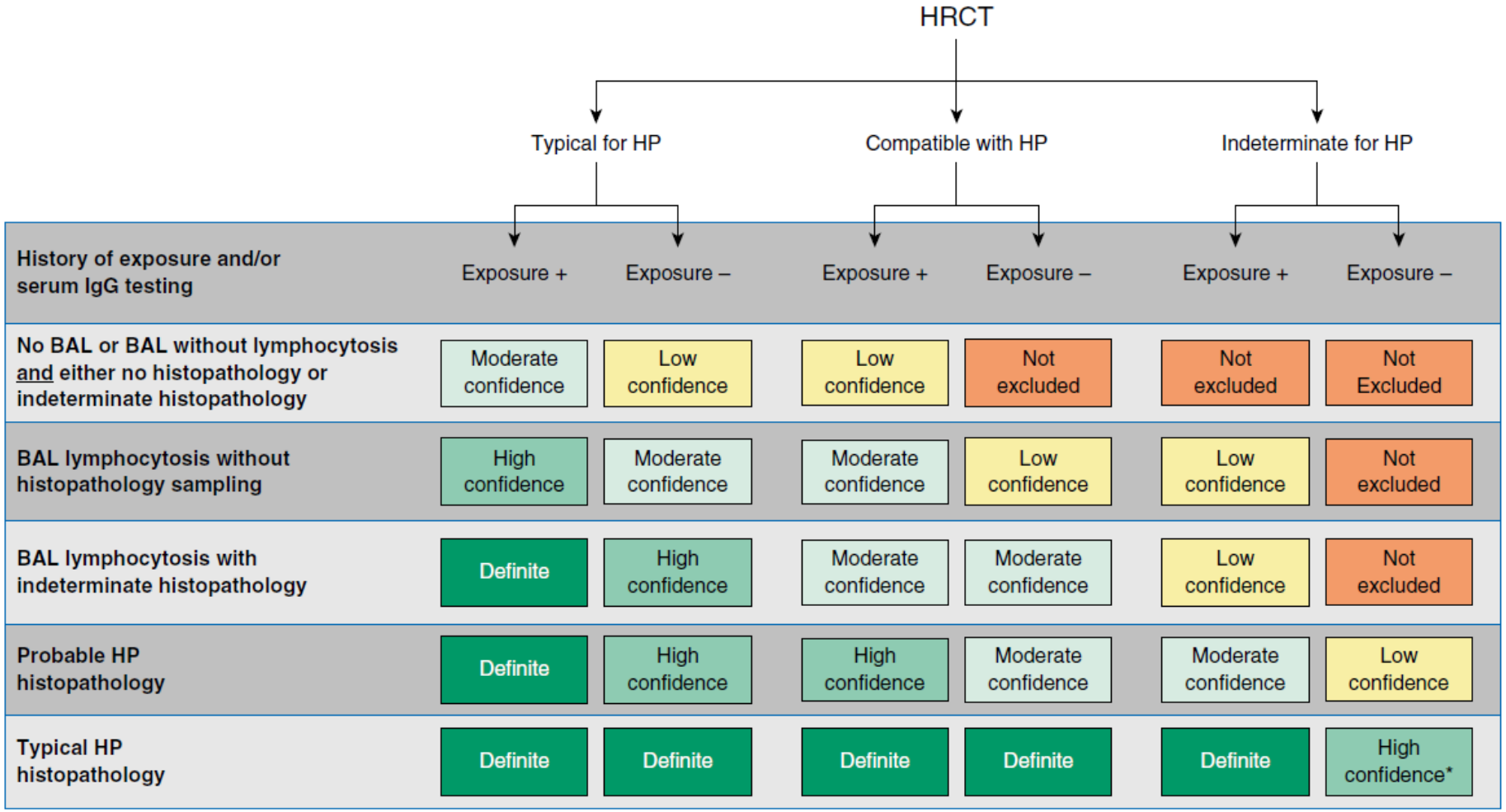
Silva et al. Radiology: Volume 246: Number 1—January 2008
Morell et al. Lancet Respir Med 2013; 1: 685–94
Tsutsui et al. Ann Am Thorac Soc Vol 12, No 7, pp 1013–1021, Jul 2015
Ishizuka et al. Ann Am Thorac Soc Vol 12, No 2, pp 167–173, Feb 2015
Morisset et al. CHEST 2017; 151(3):619-625

Characteristic CT findings in HP



Silva et al. *AJR* 2007; 188:334–344

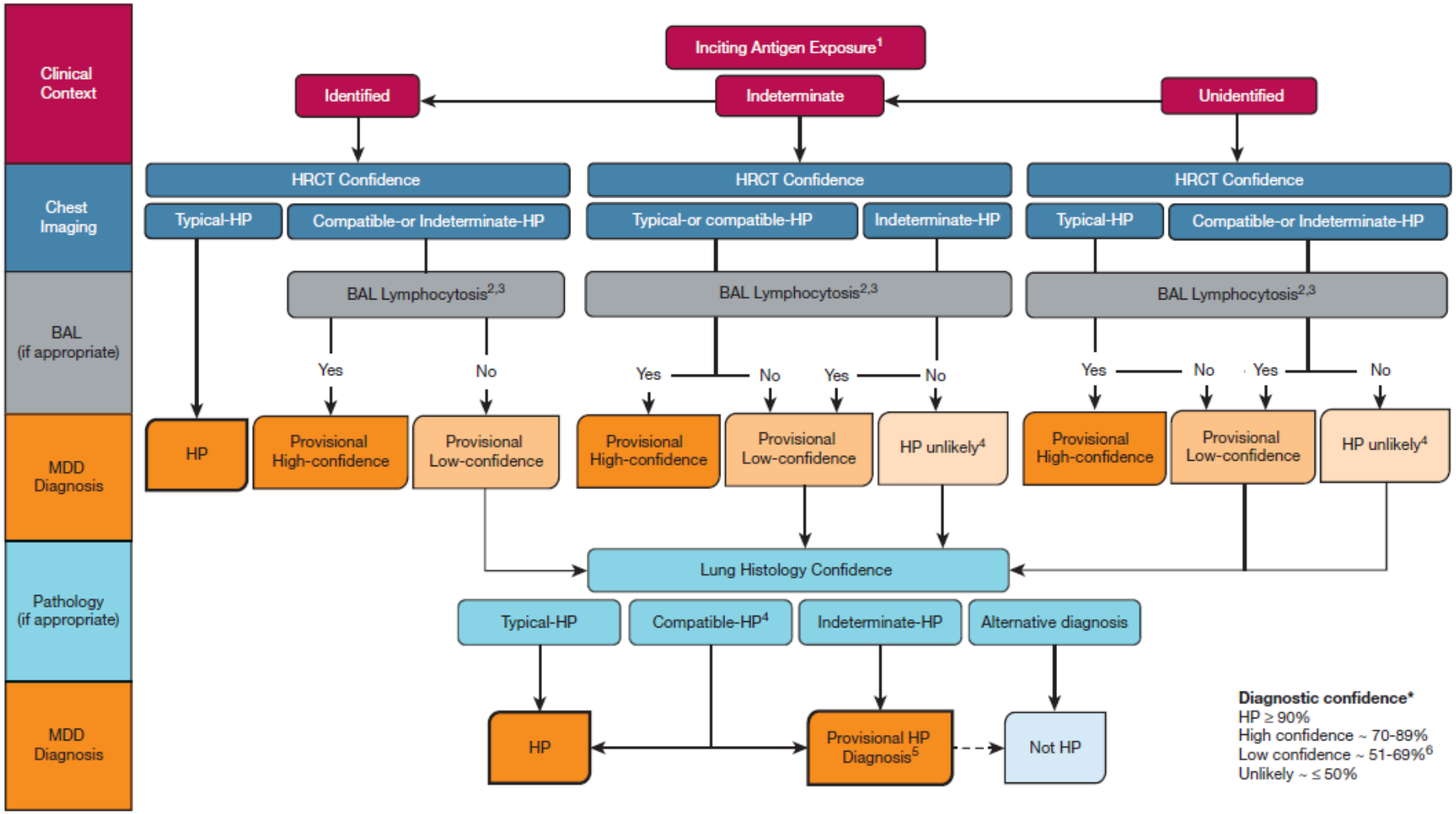
Diagnostic algorithm--ATS



History of exposure and/or serum IgG testing	Typical for HP: Exposure +	Typical for HP: Exposure –	Compatible with HP: Exposure +	Compatible with HP: Exposure –	Indeterminate for HP: Exposure +	Indeterminate for HP: Exposure –
No BAL or BAL without lymphocytosis and either no histopathology or indeterminate histopathology	Moderate confidence	Low confidence	Low confidence	Not excluded	Not excluded	Not Excluded
BAL lymphocytosis without histopathology sampling	High confidence	Moderate confidence	Moderate confidence	Low confidence	Low confidence	Not excluded
BAL lymphocytosis with indeterminate histopathology	Definite	High confidence	Moderate confidence	Moderate confidence	Low confidence	Not excluded
Probable HP histopathology	Definite	High confidence	High confidence	Moderate confidence	Moderate confidence	Low confidence
Typical HP histopathology	Definite	Definite	Definite	Definite	Definite	High confidence*

Raghu et al. *Am J Respir Crit Care Med* Vol 202, Iss 3, pp e36–e69, Aug 1, 2020

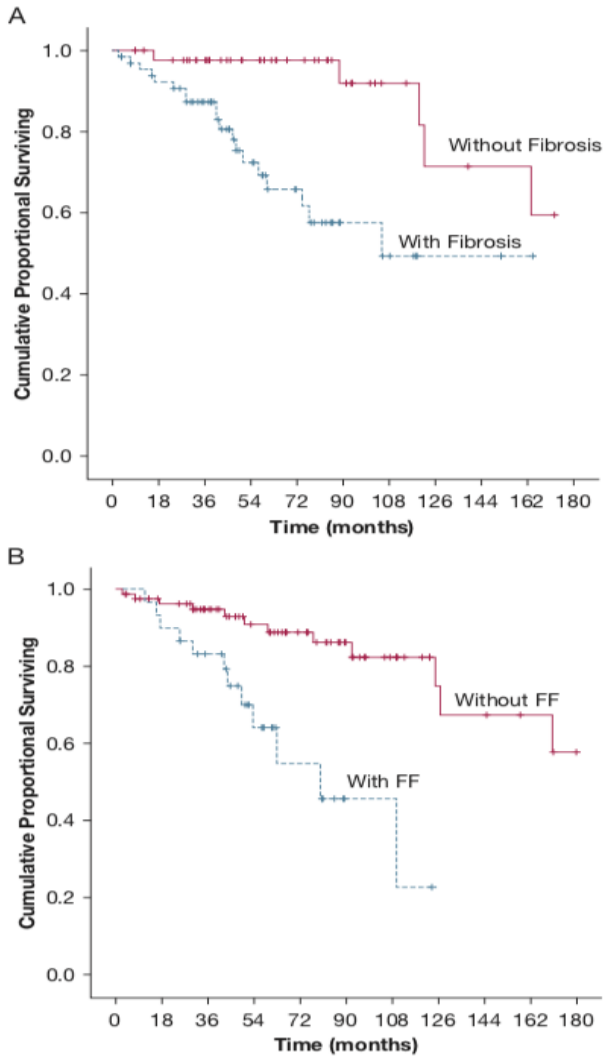
Diagnostic algorithm--ACCP

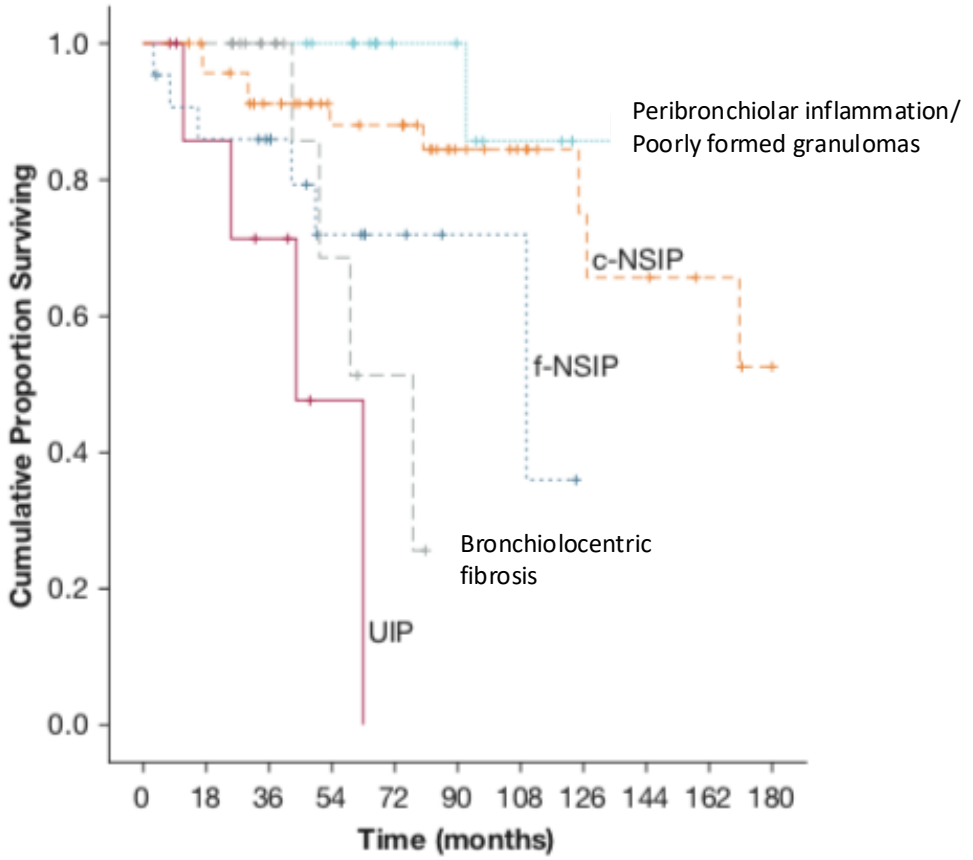


Fernandez Perez et al. CHEST 2021; 160(2):e97-e156

Pathology determines outcomes in chronic HP

119 patients with cHP and pathology



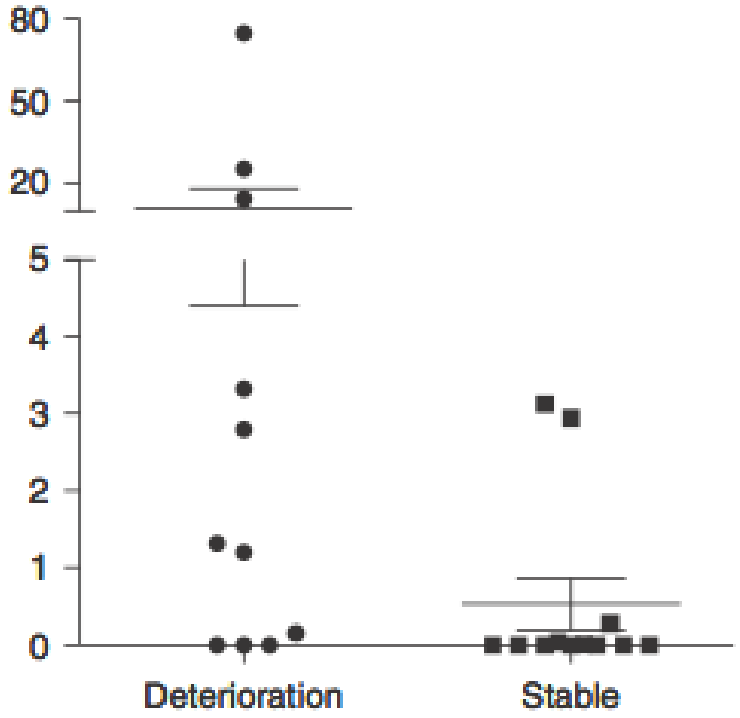


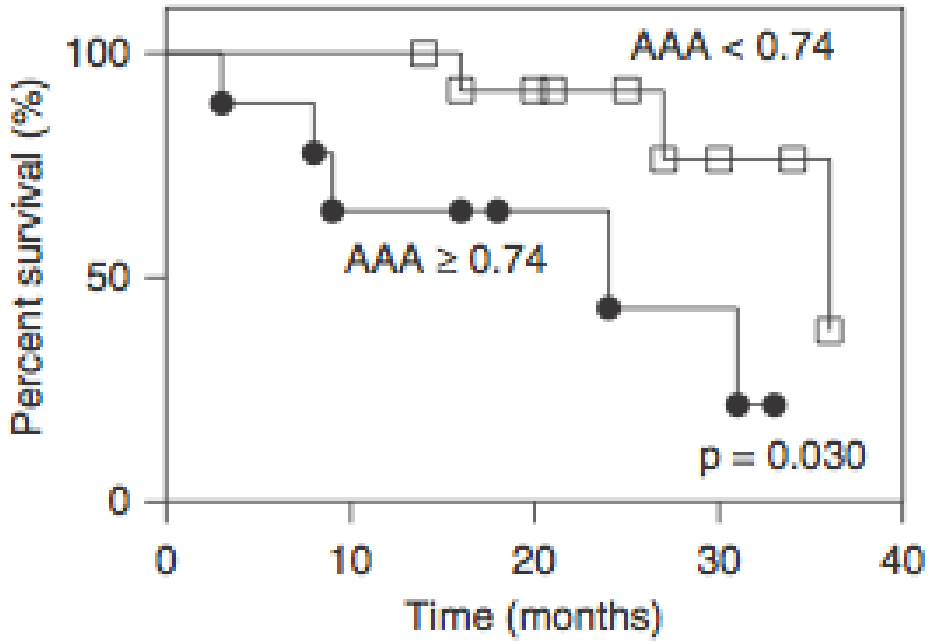
Wang et al. *CHEST* 2017; 152(3):502-509

Antigen avoidance is first-line therapy

23 patients with Bird Fancier's Lung (mostly down comforters)

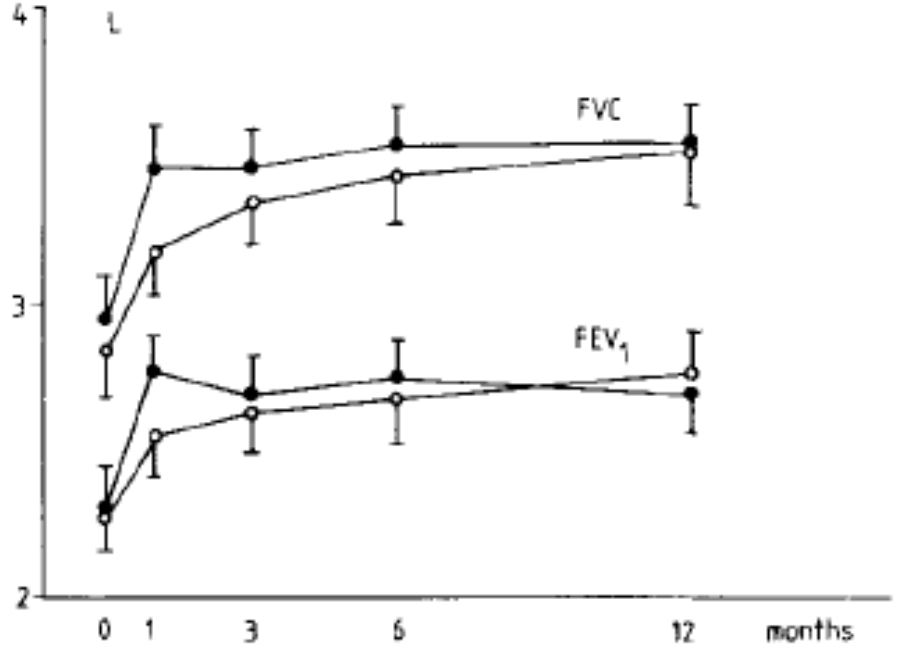
Antigen
[ ]
μg/1g dust

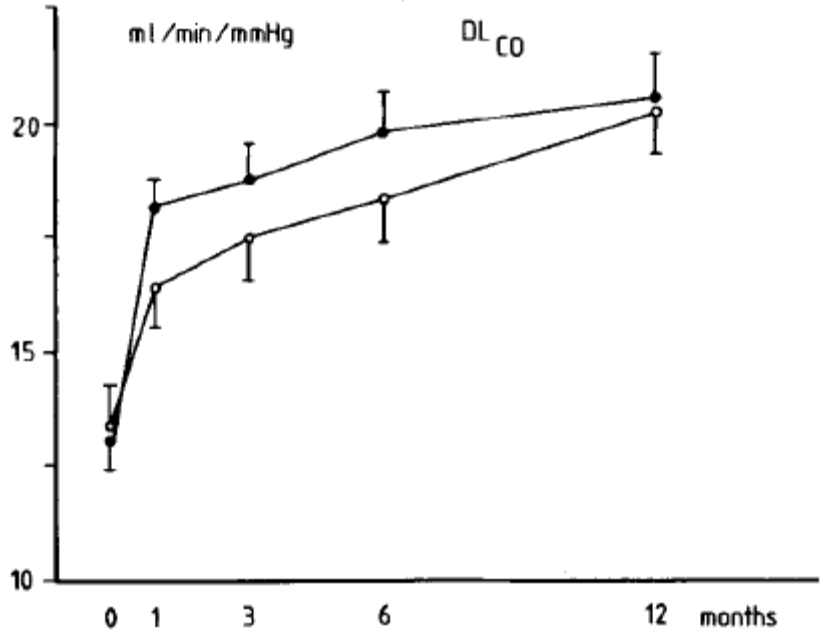




The impact of steroids on acute HP

- 36 patients with acute Farmer's Lung in a randomized, double-blind, placebo trial
  --20 received prednisolone (40 mg tapered over 8 weeks); 16 received placebo





Kokkarinen et al. *Am Rev Respir Dis* 1992; 145:3-5.

Steroids may be beneficial in cHP

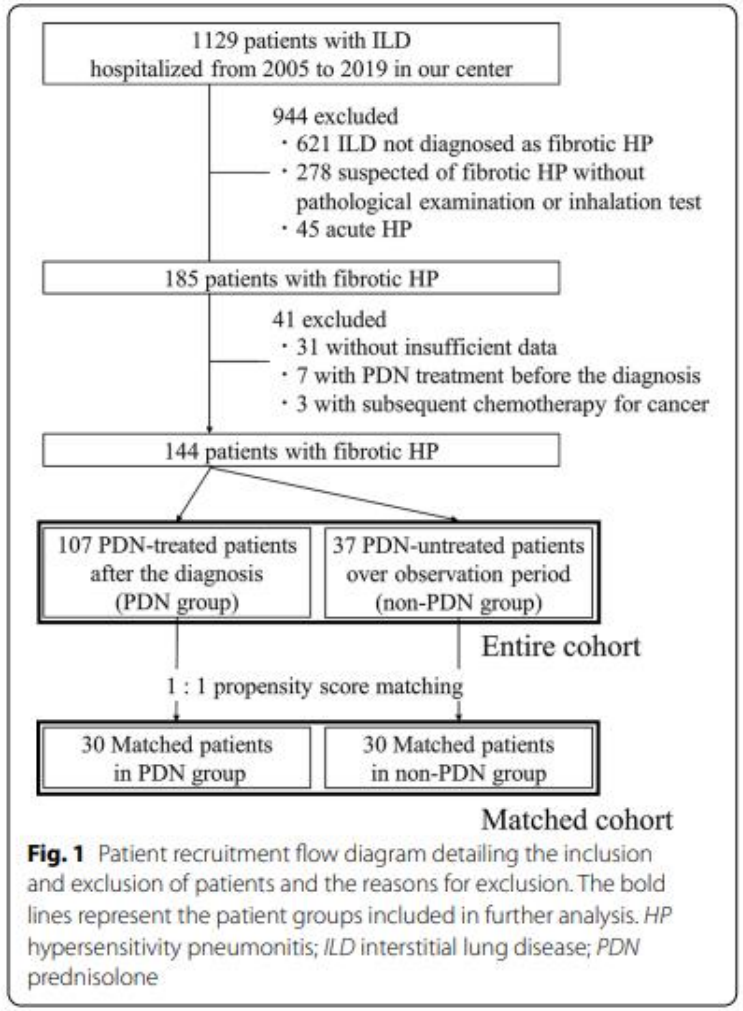


Fig. 1 Patient recruitment flow diagram detailing the inclusion and exclusion of patients and the reasons for exclusion. The bold lines represent the patient groups included in further analysis. *HP* hypersensitivity pneumonitis; *ILD* interstitial lung disease; *PDN* prednisolone

Baseline characteristics:

Antifibrotics

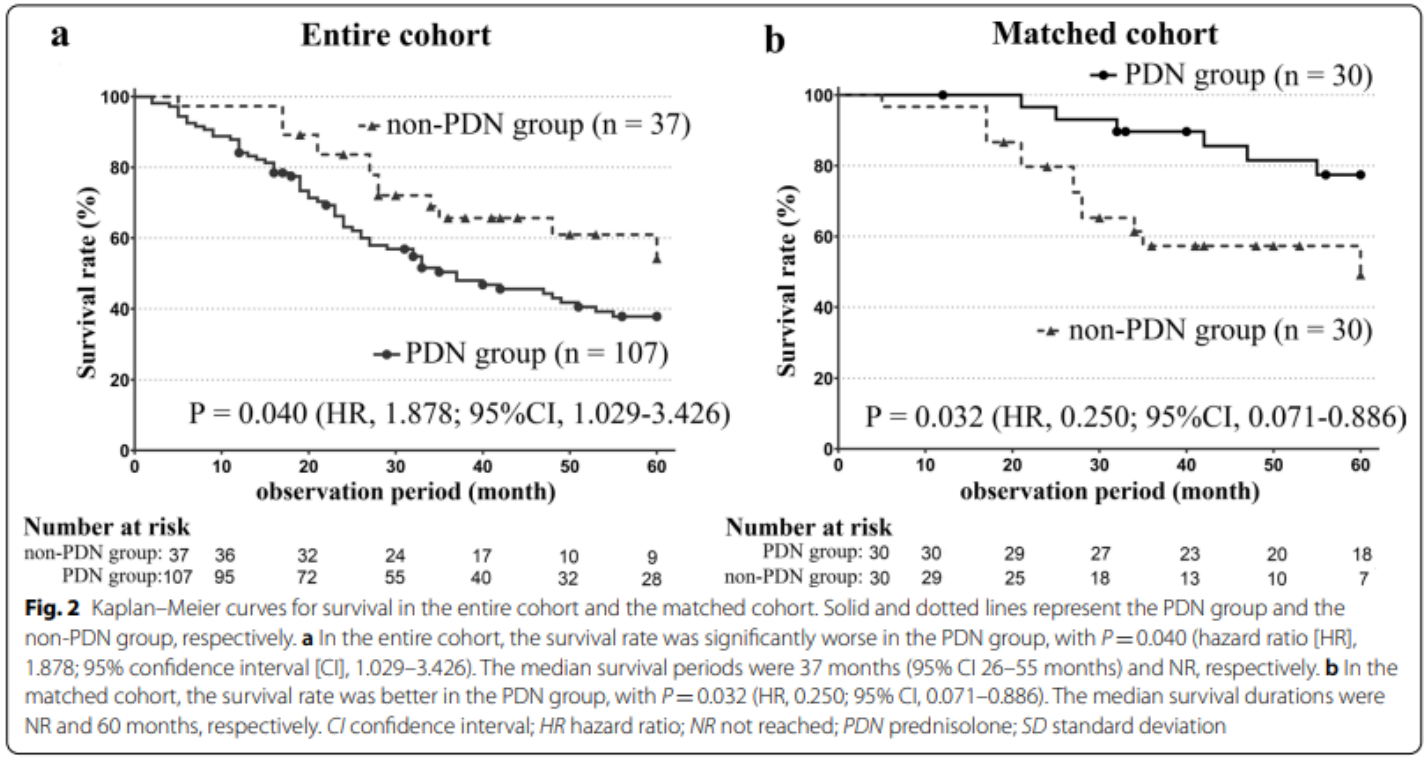
13% pred group; 22% non-pred group (NS)

Immunosuppression

46% in the pred group (mostly CsA, TAC)

0% in the non-pred group

Steroids may be beneficial in cHP



Number at risk

non-PDN group:	37	36	32	24	17	10	9
PDN group:	107	95	72	55	40	32	28

Number at risk

PDN group:	30	30	29	27	23	20	18
non-PDN group:	30	29	25	18	13	10	7

Fig. 2 Kaplan–Meier curves for survival in the entire cohort and the matched cohort. Solid and dotted lines represent the PDN group and the non-PDN group, respectively. **a** In the entire cohort, the survival rate was significantly worse in the PDN group, with $P = 0.040$ (hazard ratio [HR], 1.878; 95% confidence interval [CI], 1.029–3.426). The median survival periods were 37 months (95% CI 26–55 months) and NR, respectively. **b** In the matched cohort, the survival rate was better in the PDN group, with $P = 0.032$ (HR, 0.250; 95% CI, 0.071–0.886). The median survival durations were NR and 60 months, respectively. *CI* confidence interval; *HR* hazard ratio; *NR* not reached; *PDN* prednisolone; *SD* standard deviation

For the *Entire* cohort:

PDN group was sicker at baseline

- FVC 58% vs 71% (p<0.001)
- DLCO 45% vs 56% (p=0.005)

PDN group had more fibrosis

- Traction bronchiectasis 93% vs 78% (P=0.03)
- Honeycombing 58% vs 38% (p=0.055)

For the Matched cohort:

Most patients did not have extensive fibrosis

Propensity score based on the following: Age, sex, smoking history, %FVC, %FEV1, presence of honeycombing, traction bronchiectasis and mosaic attenuation on CT

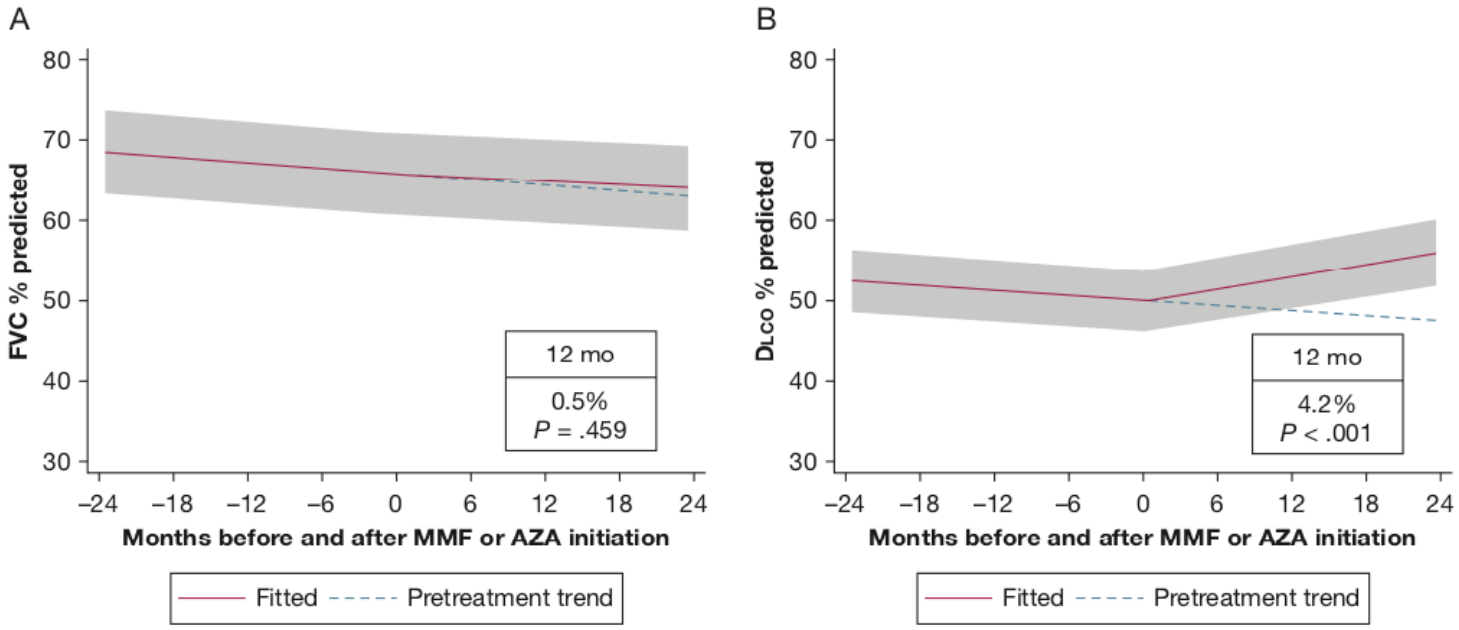
Steroid-sparing agents may be beneficial

Retrospective evaluation of 70 patients with chronic HP

51 received MMF

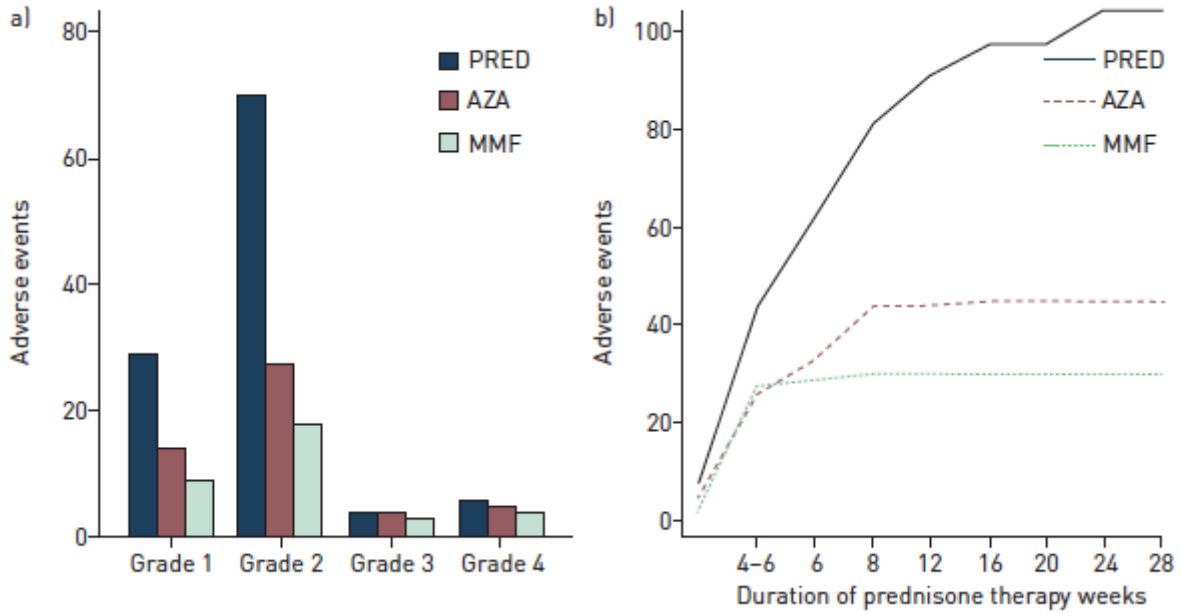
19 received AZA

(84% were receiving concurrent prednisone)



FVC 10% improvement in 13% of patients
DLCO 10% improvement in 20% of patients
Ave prednisone (mg/d) 12.3 → 3.75

Steroid-sparing agents are better tolerated than steroids in HP



- 131 chronic HP patients
- 71% received immunosuppression

- Same outcome: prednisone/AZA/MMF

- Treatment related AEs (vs prednisone):
  - 54% less w/ AZA
  - 66% less w/ MMF

Rituximab for chronic HP

Retrospective study of 20 cHP patients progressing despite antigen avoidance

FVC trend

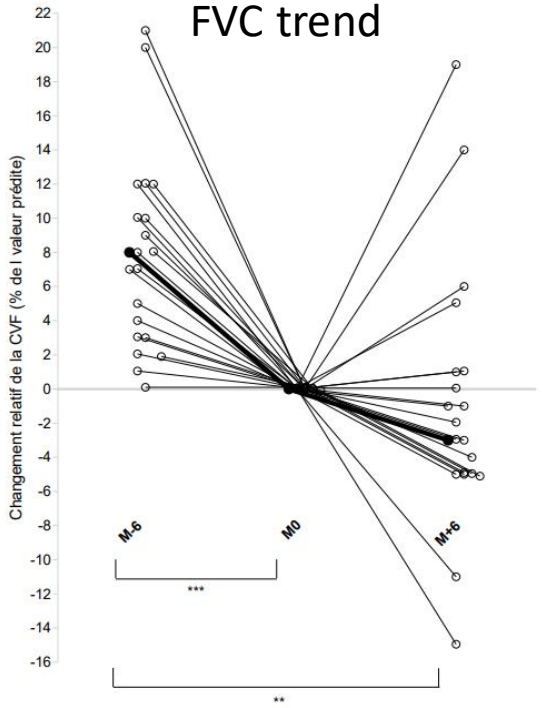


*Figure 1: relative change in FVC (% of predicted value), 6 months before and after the introduction of rituximab (n = 20The median value is represented by the bold line. ** and ***: p <0.01 and <0.001, respectively.*

DLCO trend

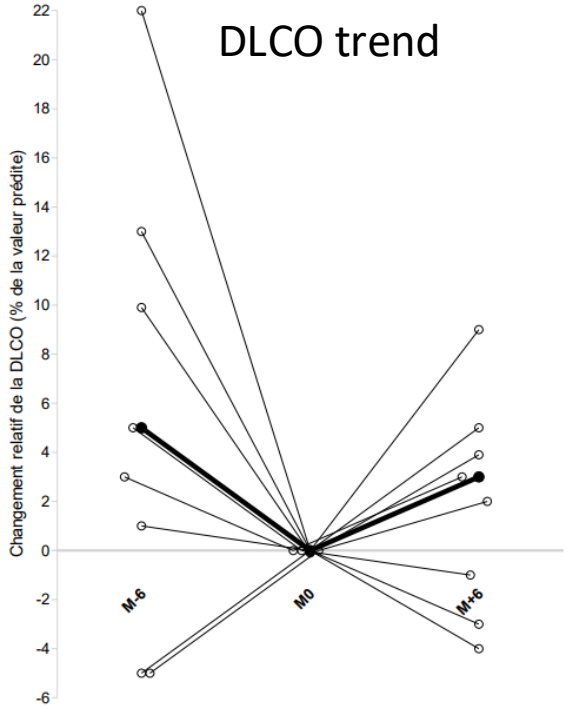


Figure 2: relative change in DLCO (% of predicted value) in 8 patients (for whom a DLCO value was available at the initiation of rituximab), 6 months before and after the introduction of rituximab. The median value is represented by the bold line.

Steroid trend

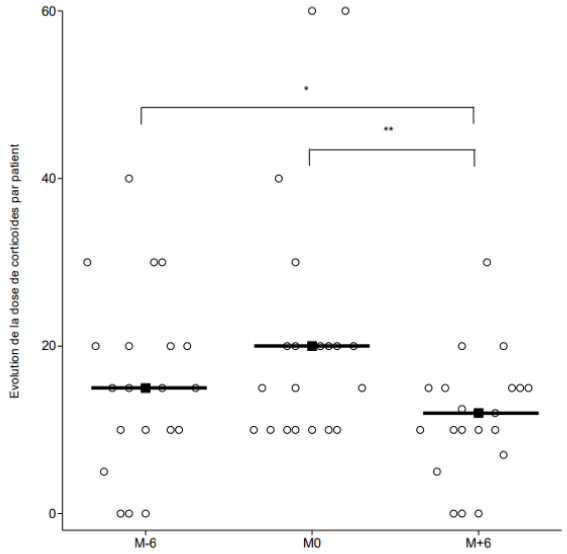
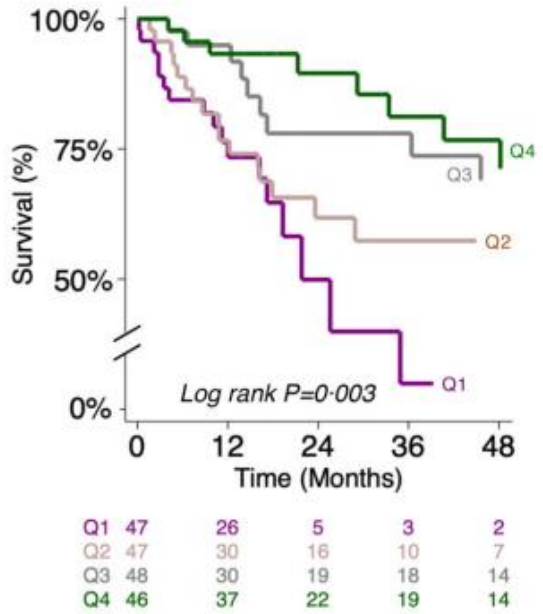


*Figure 3: Difference in the dose of corticosteroids 6 months before and after the introduction of rituximab (n = 20). The median values are represented by the bold lines. * and **: p <0.05 and <0.01 respectively.*

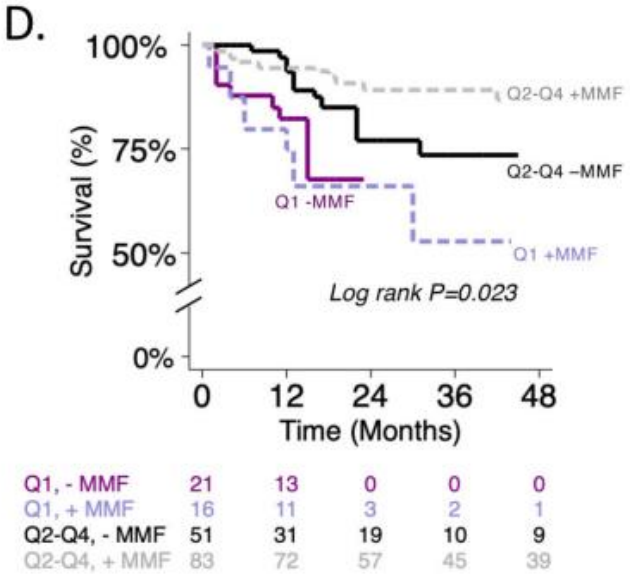
Ferreira et al. *Respiratory Medicine*, Elsevier, 2020, 172, pp.106146

Telomere length impacts treatment outcomes in chronic HP

B.

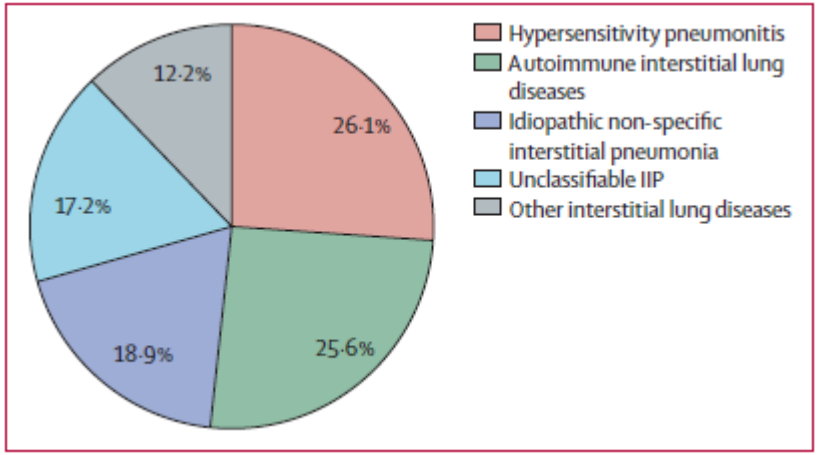


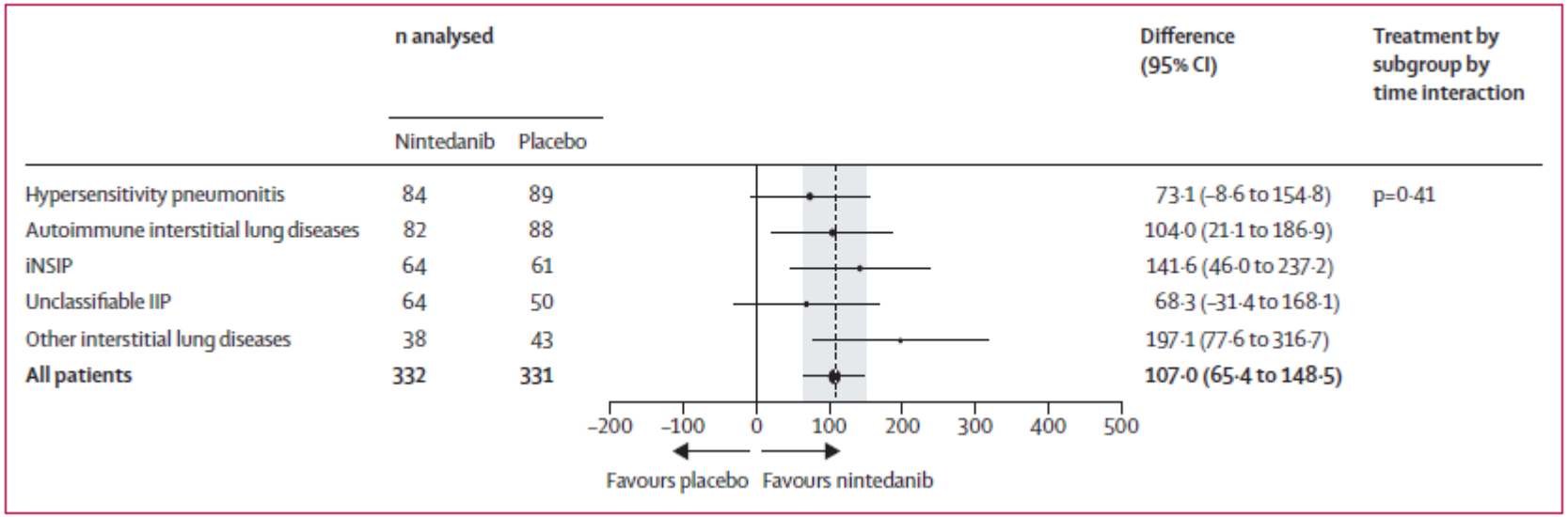
D.



- 189 patients with HP
- Stratified by leukocyte telomere length

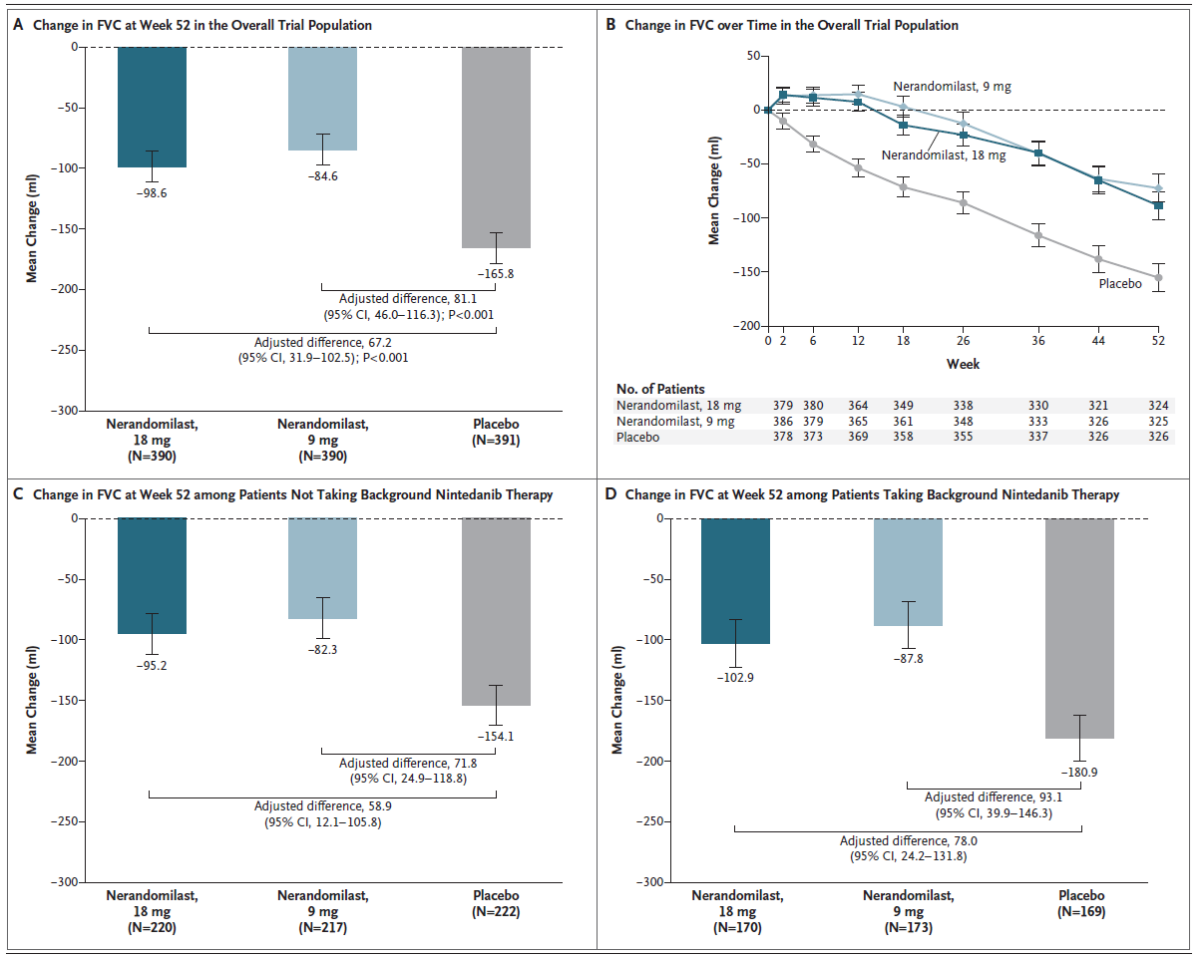
Nintedanib has been used to treat fibrotic HP (INBUILD trial)





Wells et al. *Lancet Respir Med* 2020

The FIBRONEER study (Nerandomilast) included HP patients



ILD diagnoses

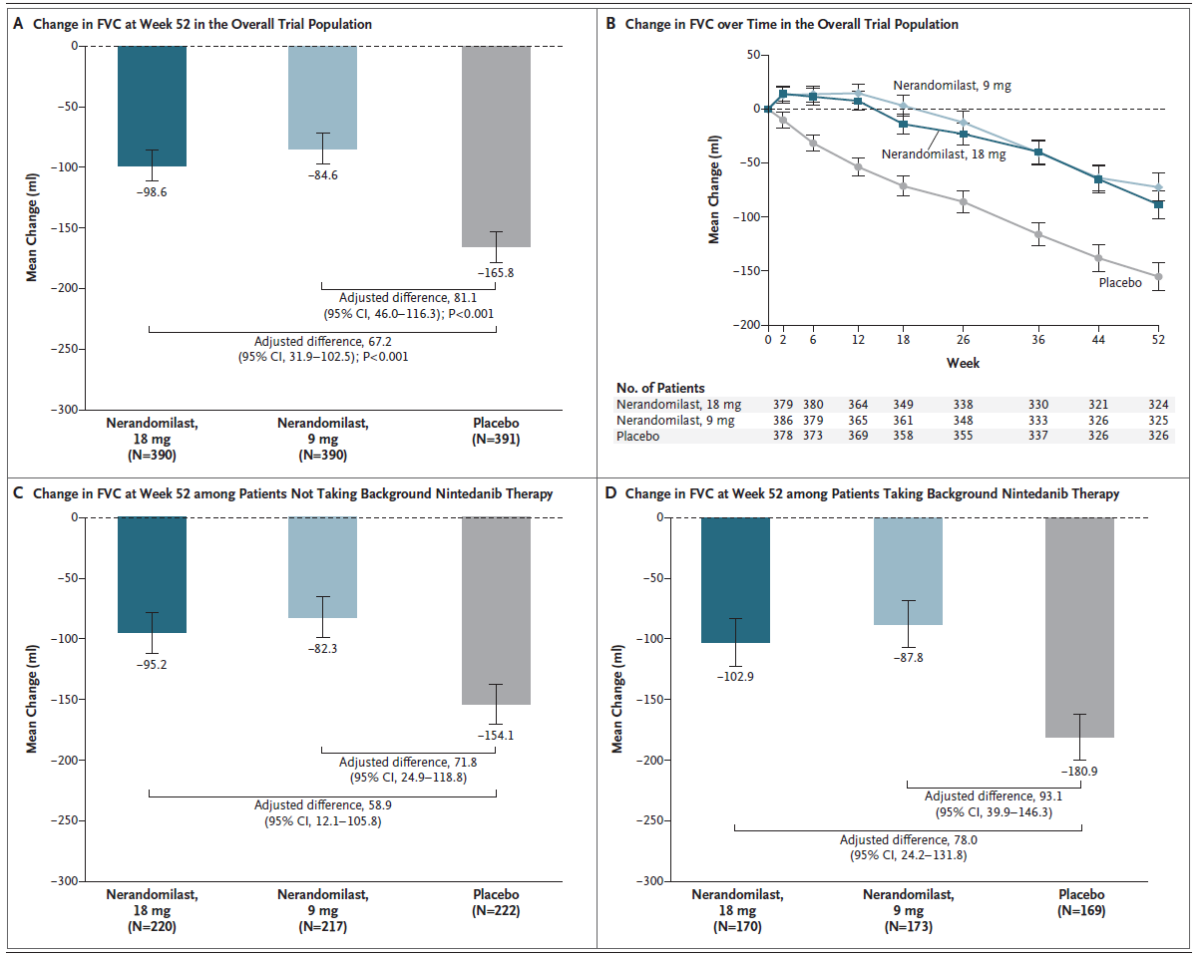
Table S1. ILD diagnoses as per the categories in the case report form*

	Placebo (N = 392)	Nerandomilast 9 mg twice daily (N = 393)	Nerandomilast 18 mg twice daily (N = 391)
Hypersensitivity pneumonitis	77 (19.6)	83 (21.1)	73 (18.7)
Unclassifiable idiopathic interstitial pneumonia	82 (20.9)	76 (19.3)	73 (18.7)
Idiopathic non-specific interstitial pneumonia	73 (18.6)	73 (18.6)	82 (21.0)
Rheumatoid arthritis-associated ILD	32 (8.2)	45 (11.5)	41 (10.5)
Systemic sclerosis-associated ILD	23 (5.9)	25 (6.4)	27 (6.9)
Mixed connective tissue disease-associated ILD	12 (3.1)	16 (4.1)	19 (4.9)
Exposure-related ILD	12 (3.1)	11 (2.8)	9 (2.3)
Sarcoidosis-ILD	8 (2.0)	6 (1.5)	3 (0.8)
Other fibrosing ILDs	73 (18.6)	58 (14.8)	64 (16.4)

*Data are no. (%).

Maher et al. *N Engl J Med*. 2025 Jun 12;392(22):2203-14.

The FIBRONEER study (Nerandomilast) did not include myositis or ANCA patients



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International Pillow Fight Day
04/03/2027 (Saturday)

(Masks recommended)

Summary

- HP can be challenging to diagnose, and the presentation is not always “classic”
- *When identifiable*, avoidance of the implicated organic antigen is critical
- The use of immunosuppression may improve outcomes for select patients with an inflammatory component of disease
- Antifibrotic therapy may play a role in patients with progressively fibrotic disease