Fibrose pulmonaire idiopathique

Recommandations diagnostiques et thérapeutiques

Dominique Valeyre

Université Paris 13, Sorbonne-Paris-Cité

Assistance publique hôpitaux de Paris, site Avicenne, Bobigny

Centre constitutif CRMR « Maladies pulmonaires rares de l'adulte »

Filière Respifil

Paris, DU Maladies systémiques,7 Juille

Disclosure of interests

- Member of scientific advisory boards on IPF supported by Intermune, Roche and Bohringer-Ingelheim
- Past or present Member of steering committees or investigator in trials on IPF (Intermune; Bohringer-Ingelheim; Roche)
- Transportation and accomodation in academic meetings (ERS; ATS; CPLF) supported by Bohringer-Ingelheim; Roche
- Présentation « Nouveautés dans la sarcoïdose », Avancées de Pneumologie, journée supportée par Astra Zenecca

Aperçu

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- Introduction
- Diagnostic de FPI
  - Critères diagnostiques 2011
  - Limitations des critères diagnostiques actuels
  - DMD et classification comportementale
  - Evolution attendue des critères
  - Recommandations diagnostiques en pratique clinique
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  - Recommandations (2011, 2015, Recos françaises)
- Situations particulières
  - Formes familiales/génétiques
  - EA
  - Progression sous un antifibrosant
- Conclusion

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

AMERICAN THORACIC SOCIETY DOCUMENTS

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moisés Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)

American Thoracic Society Documents

An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. King, Jr., David A. Lynch, Andrew G. Nicholson, Christopher J. Ryerson, Jay H. Ryu, Moisés Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouros, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Dudden, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Johkoh, Dong Soon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and Dominique Valeyre; on behalf of the ATS/ERS Committee on Idiopathic Interstitial Pneumonias

Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study

Simon L F Walsh, Athol U Wells, Sujal R Desai, Venerino Poletti, Sara Piciucchi, Alessandra Dubini, Hilario Nunes, Dominique Valeyre, Pierre Y Brillet, Marianne Kambouchner, António Morais, José M Pereira, Conceição P Souto Moura, Jan C Grutters, Daniel A van den Heuvel, Hendrik W van Es, Matthijs F van Oosterhout, Cornelis A Seldenrijk, Elisabeth Bendstrup, Finn Rasmussen, Line B Madsen, Bibek Gooptu, Sabine Pomplun, Hiroyuki Taniguchi, Junya Fukuoka, Takeshi Johkoh, Andrew G Nicholson, Charlie Sayer, Lilian Edmunds, Joseph Jacob, Maria A Kokosi, Jeffrey L Myers, Kevin R Flaherty, David M Hansell

Introduction

- FPI 3èmePID par la plus fréquence (après sarcoïdose et PID-CTD) et et la plus sévère (médiane de survie 3-5 ans)
- Depuis 2000-2002, la FPI a été clairement différenciée de la fNSIP
- Depuis 2012, les traitements CS + IS s'avèrent délétères en cas de FPI alors qu'ils sont volontiers bénéfiques en cas de fNSIP
- Depuis 2014, 2 médicaments antifibrosants (pirfénidone et nintédanib) ont montré une efficacité en ralentissant de moitié le déclin fonctionnel en cas de FPI, avec un effet probable sur la mortalité (PFD) et sur l'incidence des EA (nintedanib)
- Il est devenu indispensable d'avoir un diagnostic sûr et le plus précoce possible de FPI

Diagnostic Criteria

The diagnosis of IPF requires the following:

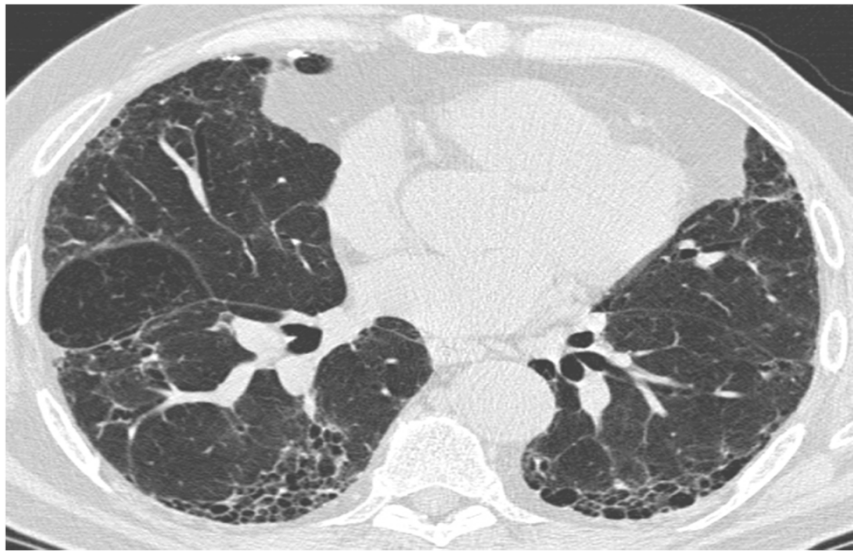
1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (*see* Table 4).
3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy (*see* Tables 5 and 6).

Raghu AJRCCM 2011

BLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Featu
ubpleural, basal predominance eticular abnormality oneycombing with or without traction ronchiectasis bsence of features listed as inconsistent with IP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lob

efinition of abbreviation: UIP = usual interstitial pneumonia.



Courtesy Pr Michel Brauner

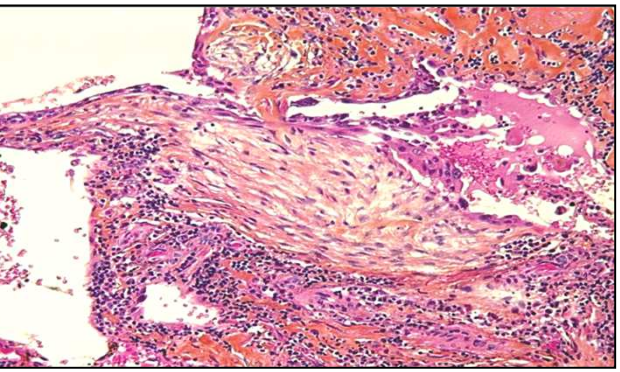
Raghu AJRCCM 2011

5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

ern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Crite
ce of marked fibrosis/ ctural distortion, ± combing in a hinantly subpleural/ otal distribution ce of patchy ment of lung hyma by fibrosis ce of fibroblast foci e of features a diagnosis suggesting rnate diagnosis urth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP PATTERN column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membran • Organizing pneur • Granulomas† • Marked interstitia inflammatory cell infiltrate away fro honeycombing • Predominant airw centered changes • Other features suggestive of an alternate diagnosi

ion of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.
be associated with acute exacerbation of idiopathic pumonary fibrosis.
olated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherw

cenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present i
ch areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using



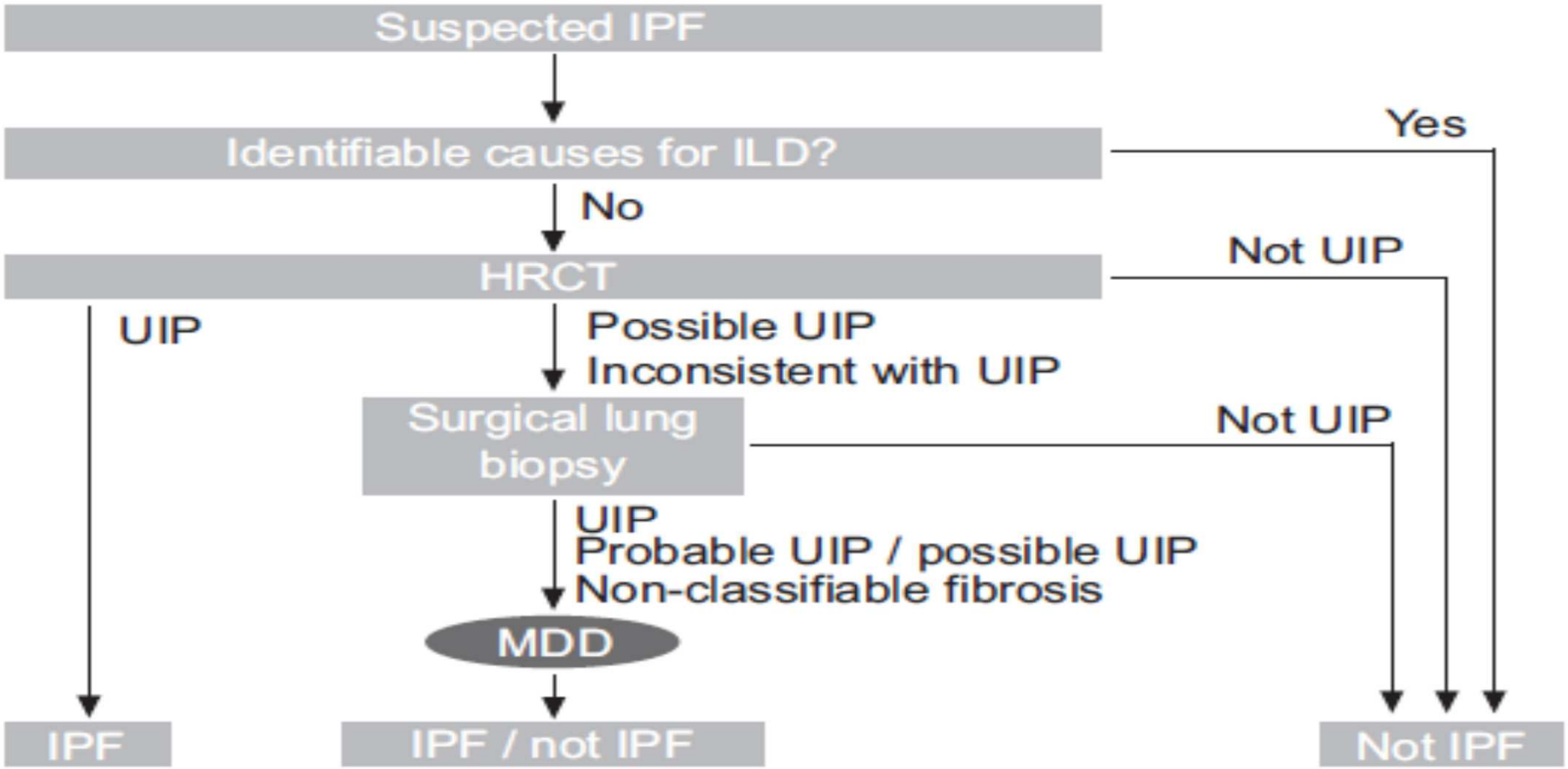
Courtesy Dr Marianne Kambouchner

Raghu AJRCCM 2011

6. COMBINATION OF HIGH-RESOLUTION COMPUTED TOMOGRAPHY AND SURGICAL LUNG BIOPSY FOR THE OSIS OF IPF (REQUIRES MULTIDISCIPLINARY DISCUSSION)

ttern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis o
	UIP **Probable UIP** **Possible UIP** **Nonclassifiable fibrosis‡**	**YES**
	Not UIP	No
UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP Nonclassifiable fibrosis	Probabl
	Not UIP	No
ent with UIP	UIP	Possible
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

Raghu AJRCCM 2011



Raghu AJRCCM 2011 revised by AU Wells ERR 2013

Limites

- 50% des FPI non diagnostiquées si application stricte
- RM en TDM → Kappa interobservateur modeste

Multidisciplinary diagnosis in Avicenne hospital

Registration of cases by one of us (Y Uzunhan) since a short laps of time

Weekly meeting on ILD

Discussion of ~20 selected cases/week at presentation or follow up

- from our team (~500 new ILD/yr, ~ 80 new IIP/yr)
- files from other centres
- Diagnosis considered; probabilities; behavioural diagnosis; decision for surgery; therapeutic decision; inclusions in studies

People present

- Pneumologists (often all present): H Nunes, Y Uzunhan, D Bouvry, O Freynet, D Sadoun, B Duchemann, F Jeny, D Valeyre + pneumologists from other universitary or general hospitals; from Paris area or others
- Radiologists: (at least one) PY Brillet or M Brauner or D Piver
- Pathologists: JF Bernaudin or M Kambouchner

Suspected IPF diagnosis distribution in Avicenne hospital ILD meeting

Study of 30 last cases for which IPF could be considered

16/30 (47%) → definite or probable IPF (with CT or CT + pathology)

12/30 (40%) → possible UIP at CT but no surgery (for age or comorbdity)

4/30 (13%) → inconsistent UIP CT pattern, surgery not possible, no evident alternative diagnosis

With IPF guidelines:

→ Almost as many « possible UIP pattern » in older patients (high prevalence of IPF) as in patients with definite IPF pattern

→ Half IPF diagnosis are missed

2nd case record

Male 70, smoker, no risk factor, no systemic disease, with CT UIP pattern

Screened in an E-rare academic study based on BAL biological research

Screen failure face to >30% BAL lymphocytes

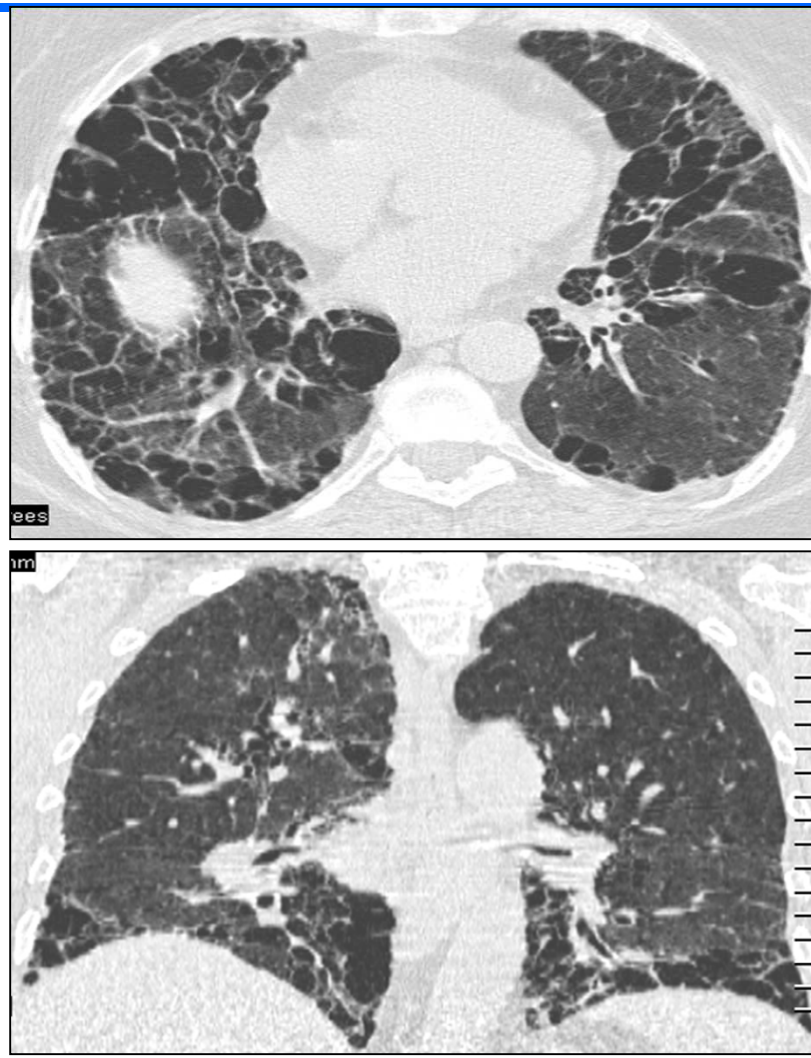
Investigation for alternative hypothesis

Evidence of typical granulomas on multiple bronchial biopsies

No modification in next 2 yrs

Conclusions

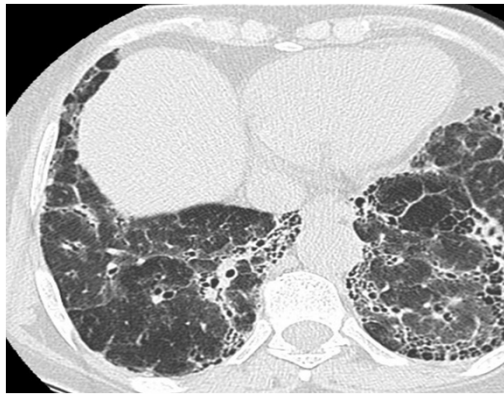
- IPF guidelines: typical UIP eligible for anti IPF therapy
- versus « end-stage advanced pulmonary sarcoidosis »* (often a burnt out process without progression)

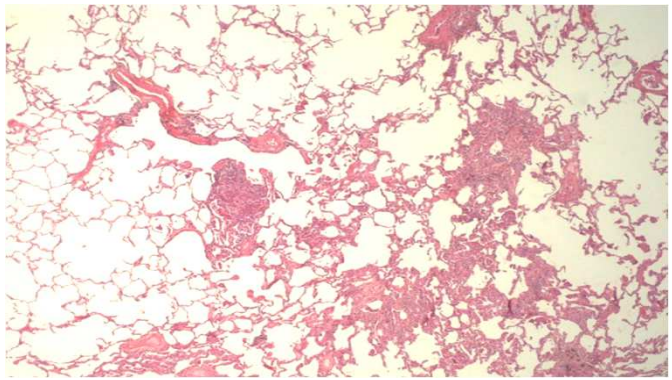


Absehra AJR 2000, Xu Am J Surg Pathol 2013, Shigemitsu ERJ 2010; Tachibana Intern Med2012; Stock Thorax 2013

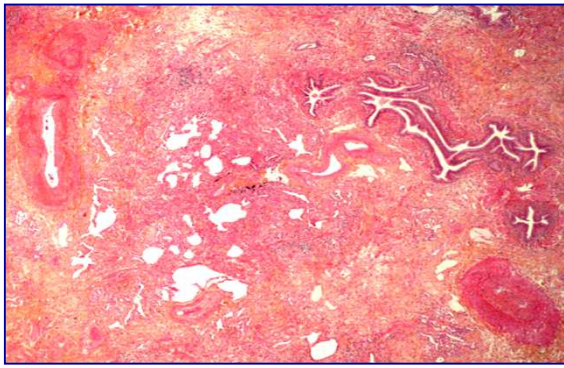
3rd case record

e, 6, ex-smoker
significant exposure
precipitins including against moistures
: 15% lymphocytes, CD4/8=1
gical biopsy: PH-UIP





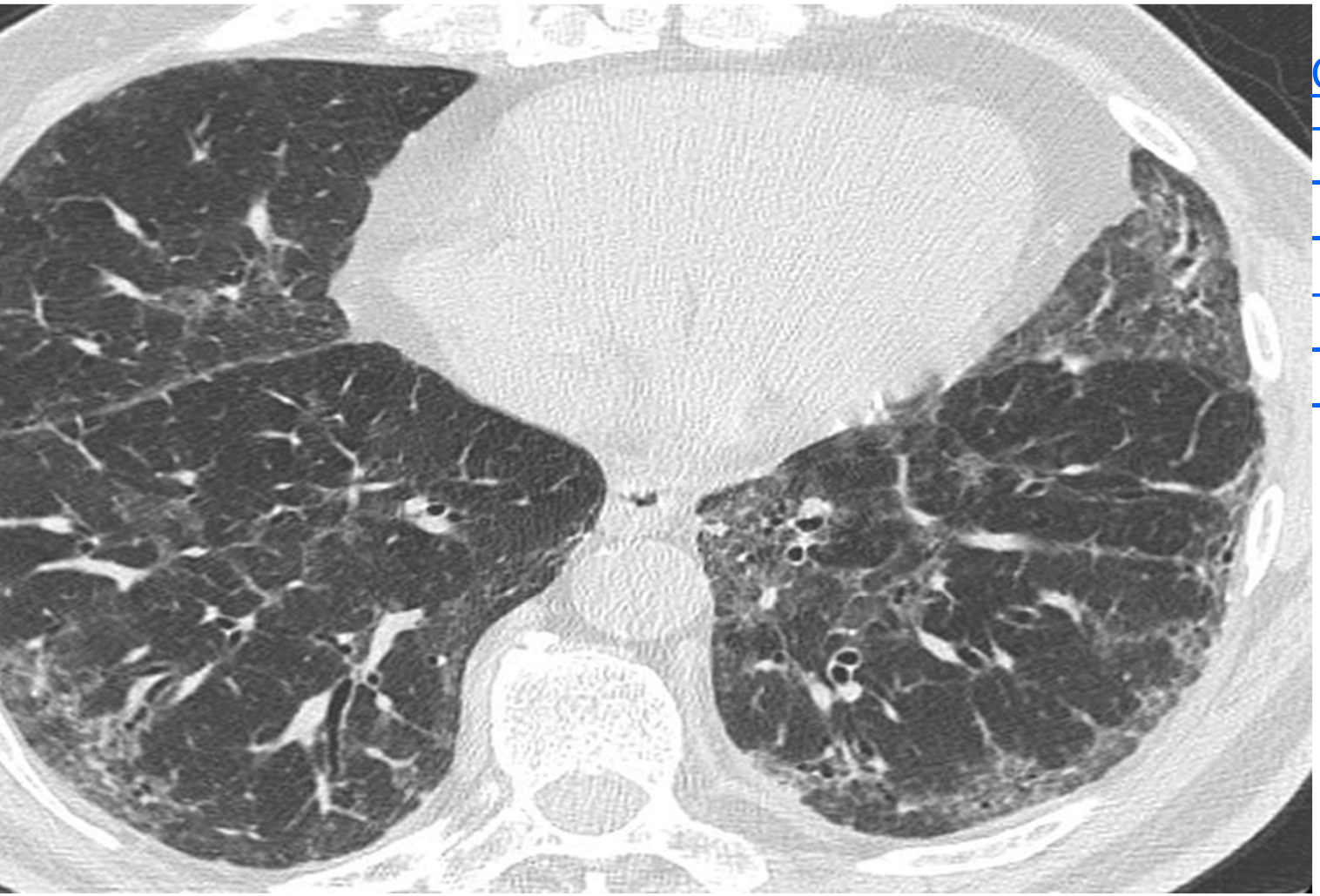
Courtesy:
M Kabouchner



gnosis
delines diagnosis: definite IPF
D: fibrosing HP of unknown origin

nments:
en as severe as IPF
rogressive, anti IPF drugs???

n case record



Clinical context

-Fortuitous discovery

- Male, 75, ex smoker
- no exposure
- no systemic disease
- FVC=80%; DLCO=70%
- Progression 12 mo later

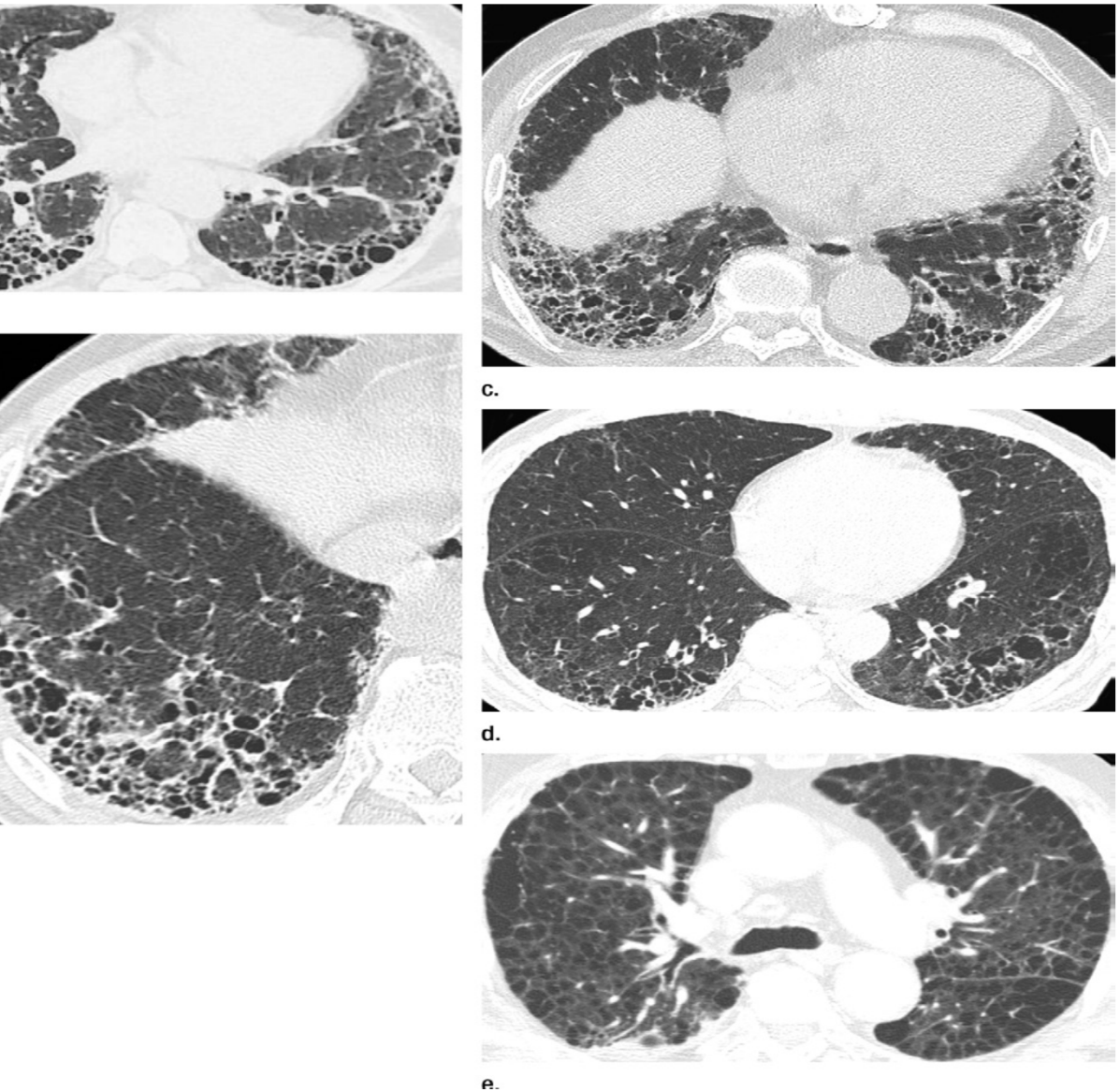
Diagnosis:

- possible IPF (guidelines)*
- why not definite IPF?

Therapeutic decision:

- No anti IPF therapy
- vs anti IPF therapy

hu AJRCCM 2011; Fell AJRCCM 2010***



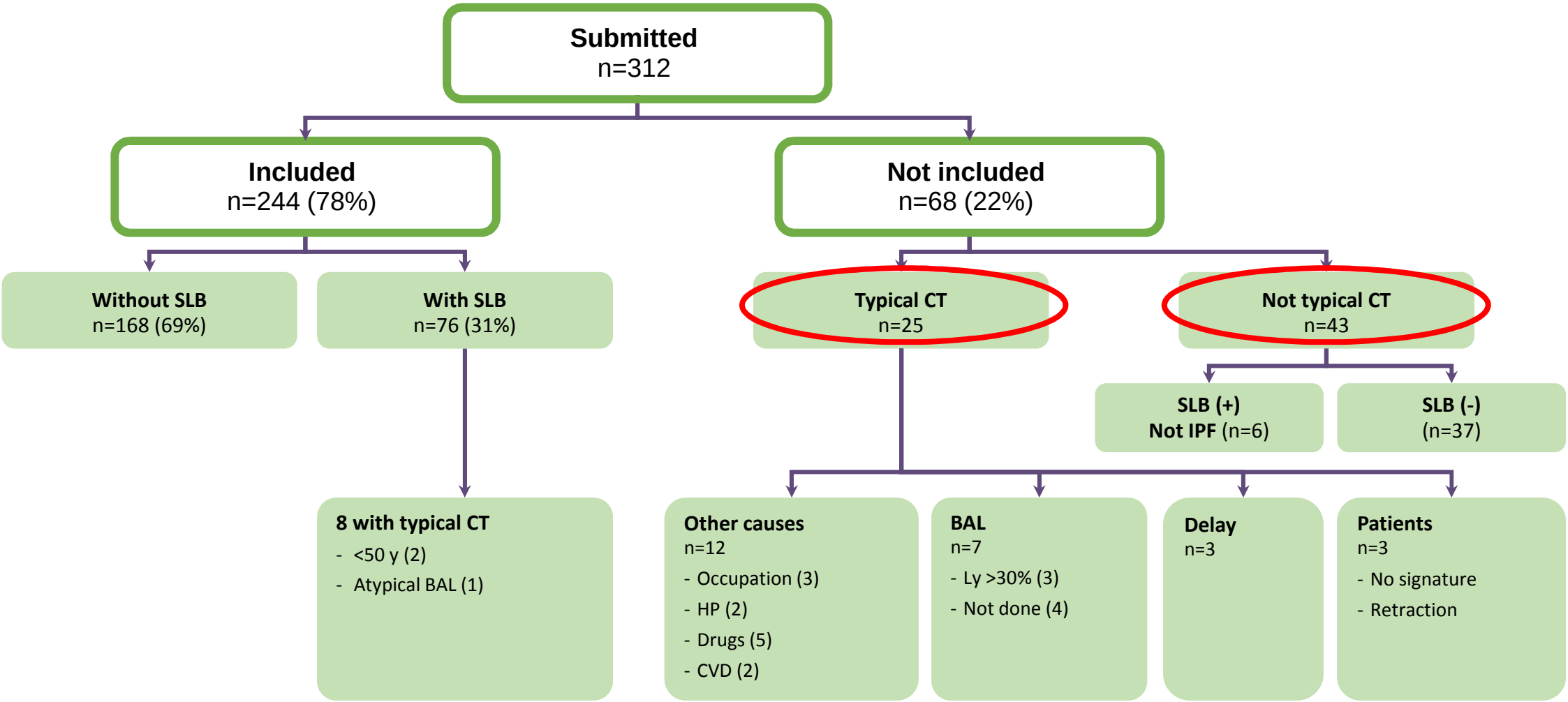
Watadani T. ***Radiology:*** Volume 266: Number 3-
March 2013

Thin-section CT images of representative reference standard cases of honeycombing. (a) Score of 5: Clustered
relatively thick walls in the subpleural regions. This image was scored as a 5 by 39 (91%) of 43 observers in reading
(b) Score of 4: Clustered cysts in both subpleural and peribronchovascular distribution. This image was scored as
(58%) of 43 reading sessions. (c) Score of 3: Traction bronchiectasis and small areas of honeycomblike multicystic
ilateral subpleural regions. (d) Score of 2: Clustered thin-walled cysts apart from the chest wall suggest complicated
ma, but CT images in the upper lungs were unavailable. This image was scored as a 3 in 27 (63%) of 43 reading
(e) Score of 1: This image was scored as a 1 by 41 (95%) 43 observers in reading sessions.

What we learned from the COFI study: review by a central panel of multi-center diagnosis in a nation-wide study (1)

- Prospective French cohort of IPF patients
- Centralized review of diagnosis every month by a panel
  - Pneumologists: Dominique Valeyre, Hilario Nunes (always), Dominique Israel-Biet, Raphael Borie, Bruno Crestani, Marie Wislez (most often), and any available participant (always >8)
  - Radiologist: Michel Brauner
  - Pathologist: Marianne Kambouchner

COFI – Inclusions



Perspectives pour améliorer le Dc de FPI

- DMD de bonne qualité, successives (évolution)
- Prise en compte de l'âge: Fell (AJRCCM 2010; Martinez Lancet RM 2017); attention aux infos post hoc d'essais
- « classification comportementale » (Travis AJRCCM 2013)
- Bien connaître principaux Dc différentiels:
  - CHP
  - fNSIP
  - Asbestose
  - Phase pré-CTD connectivites révélées par UIP
- Evolution attendue des critères TDM
  - Dc sans RM?; bronchiectasis distales (meilleur kappa?)

HELANCETRM-D-16-00035R3
2213-2600(16)30033-9
mbargo: May 11, 2016—23:30 (BST)
unded by NIHR, Green OA to be made free from November 11, 2016 [23:30] BST

Articles
FT
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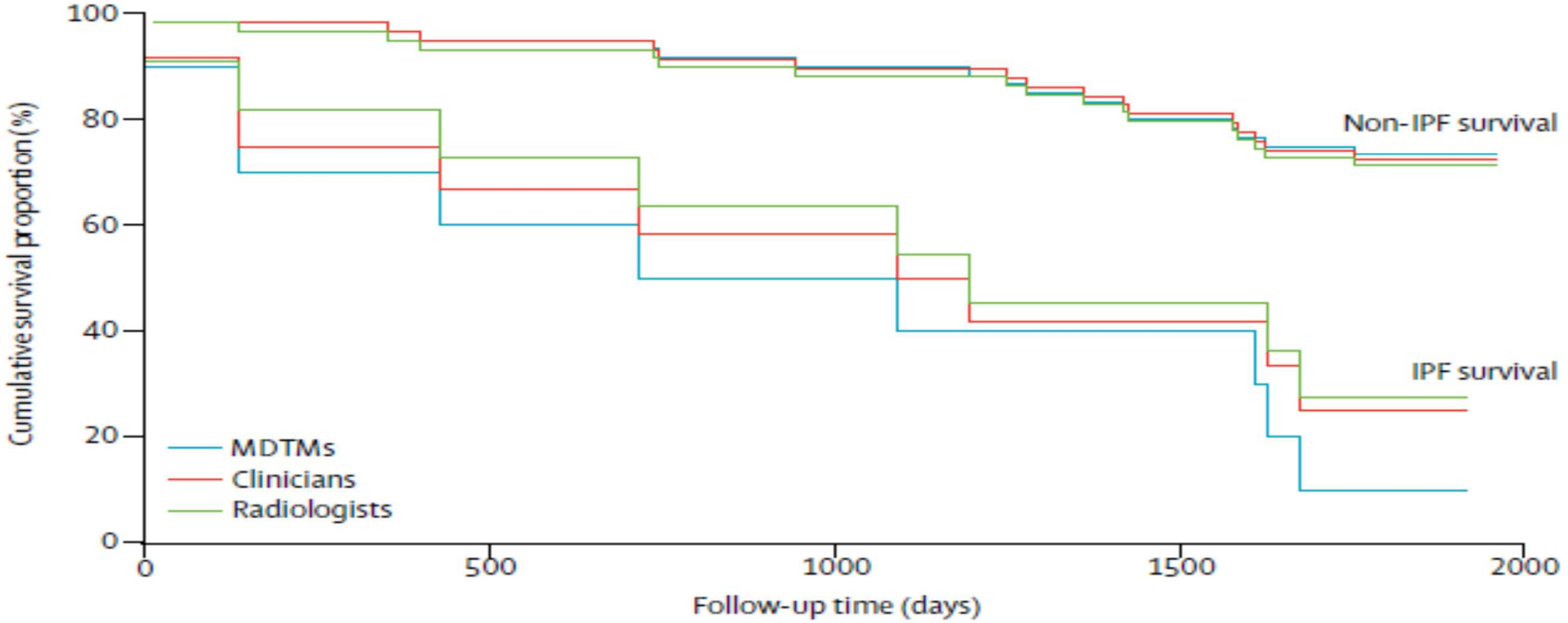
Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study

imon L F Walsh, Athol U Wells, Sujal R Desai, Venerino Poletti, Sara Piciucchi, Alessandra Dubini, Hilario Nunes, Dominique Valeyre, ierre Y Brillet, Marianne Kambouchner, António Morais, José M Pereira, Conceição Souto Moura, Jan C Grutters, Daniel A van den Heuvel, endrik W van Es, Matthijs F van Oosterhout, Cornelis A Seldenrijk, Elisabeth Bendstrup, Finn Rasmussen, Line B Madsen, Bibek Gooptu, abine Pomplun, Hiroyuki Taniguchi, Junya Fukuoka, Takeshi Johkoh, Andrew G Nicholson, Charlie Sayer, Lilian Edmunds, Joseph Jacob, laria A Kokosi, Jeffrey L Myers, Kevin R Flaherty, David M Hansell

Résultats et interprétation

- Concordance inter-DMD acceptable pour ILD et bonne pour FPI
- Dc IPF plus confiant et plus souvent avec DMD que les cliniciens et les radiologues
- Qualité différente des DMD +++ (modalités et … personnes)
- DMD peu performante pour Dc PHS et NSIP

  → manque de recommandations diagnostiques pour ces entités



***igure*: Kaplan-Meier of survival differences between patients assigned a diagnosis of idiopathic pulmonary brosis and those assigned other diagnoses (not idiopathic pulmonary fibrosis)**

	Clinicians (HR, 95% CI, p value)	Radiologists (HR, 95% CI, p value)	MDTM (HR, 95% CI, p value)
Team 1	2·09 (0·90–4·86, p=0·085)	2·80 (1·17–6·73, p=0·021)	2·67 (1·21–6·02, p=0·016)
Team 2	2·95 (1·33–6·59, p=0·008)	4·08 (1·84–9·04, p=0·001)	3·44 (1·54–7·68, p=0·003)
Team 3	3·75 (1·65–8·51, p=0·002)	2·78 (1·11–6·97, p=0·030)	5·30 (2·26–12·41, p<0·001)
Team 4	3·34 (1·38–8·00, p=0·007)	4·49 (1·71–12·29, p=0·003)	3·99 (1·49–10·66, p=0·006)
Team 5	2·03 (0·87–4·69, p=0·100)	2·58 (1·08–6·21, p=0·033)	2·61 (1·12–6·06, p=0·025)
Team 6	4·14 (1·72–9·97, p=0·002)	2·11 (0·91–4·89, p=0·082)	3·36 (1·40–8·07, p=0·007)
Team 7	2·96 (1·43–6·55, p=0·007)	1·28 (0·53–3·06, p=0·583)	2·43 (1·09–5·41, p=0·030)

Results for the multidisciplinary team meetings (MDTMs), clinicians, and radiologists are based on the whole patient cohort (n=70). HR=hazard ratio.

Table 5: **Univariate Cox regression analysis for mortality according to clinician, radiologist, and MDTM diagnoses of idiopathic pulmonary fibrosis versus not idiopathic pulmonary fibrosis**

TABLE 3. IDIOPATHIC INTERSTITIAL PNEUMONIAS: CLASSIFICATION ACCORDING TO DISEASE BEHAVIOR*

Clinical Behavior	Treatment Goal	Monitoring Strategy
Reversible and self-limited (e.g., many cases of RB-ILD)	Remove possible cause	Short-term (3- to 6-mo) observation to confirm disease regression
Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)	Initially achieve response and 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., some fibrotic NSIP)	Maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)	Stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

Travis AJRCCM 2013

	I-PINS	PIC/FPI
Frequency	14-36%	47-64%
Presentation	Subacute or chronic	Chronic
Age	43-58 years old	60-65 years old
gender ratio	M ≤ F	M > F
Smoking habits	S ≤ NS	S > NS
Digital clubbing	10-35%	25-50%
Auto-antibodies	23-43%	10-20%
BAL	Lymphocytosis variable, often elevated	Lymphocytosis < 20-30%
Prognosis	Fairly « good » Response to CS and IS Survival: 45-90% à 5 ans	Bad No response to Cs nor IS Survival: 20-43% at 5 years

ATS/ERS consensus. *Am J Respir Crit Care Med* 2002 et 2013
Travis et al. *Am J respir Crit Care Med* 2008
Nunes et al. *ERJ 2015*

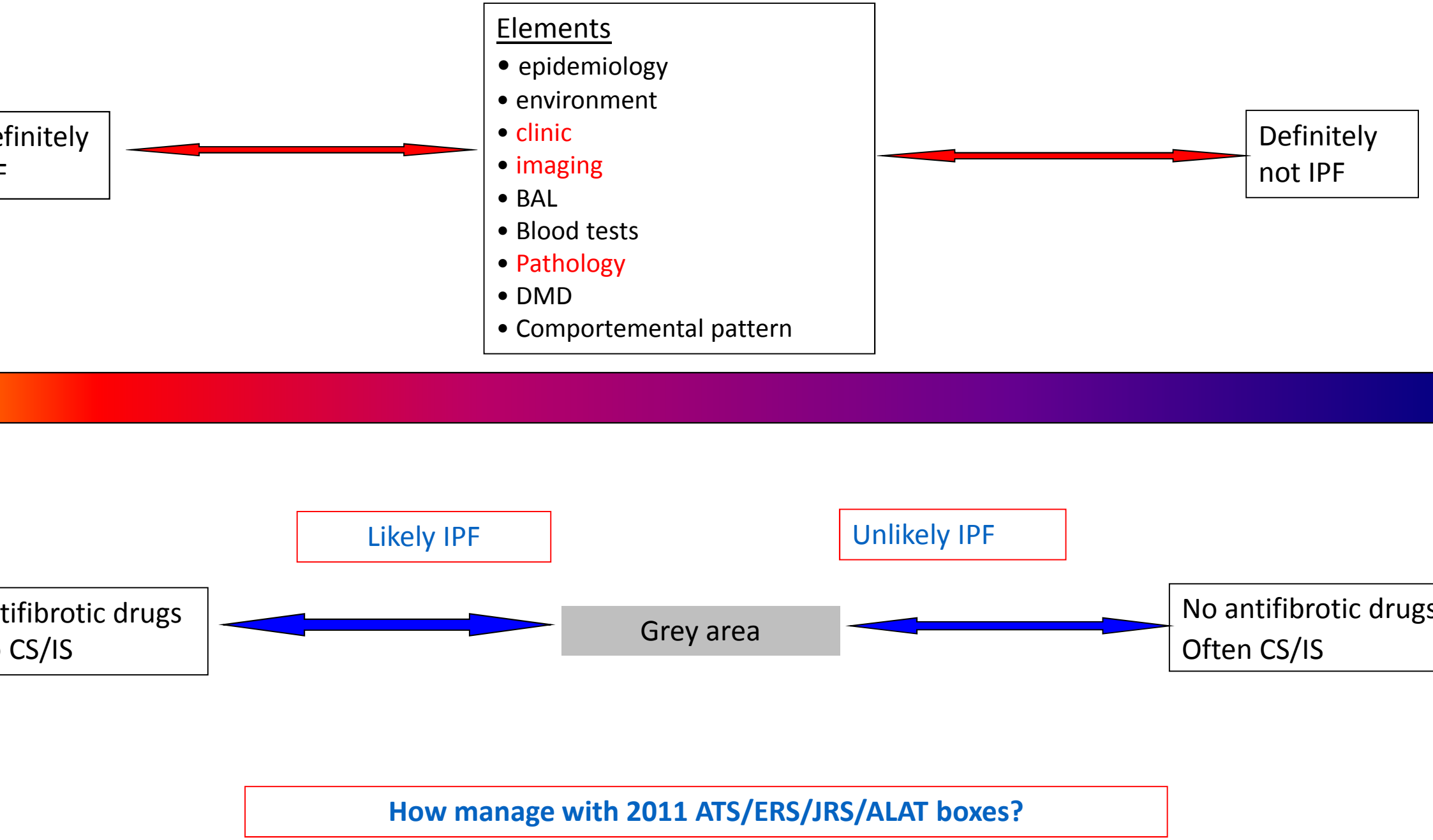
	I-NSIP	IPF/UIP
Sub-pleural predominance	p++	+++
Sub-pleural sparing	++	0
Peri-bronchovasculaire predominance	++	0
GG	+++	+
Reticulations	+++	+++
Condensations	++	0
HC	+	++

ATS/ERS consensus. *AJRCCM* 2002 et 2013
Travis et al. *Am J Respir Crit Care Med* 2002
Kligerman et al. *Radiographics* 2009
Sumikawa et al. *Radiology* 2006
Sumikawa et al. *Radiology* 2014

Autres questions

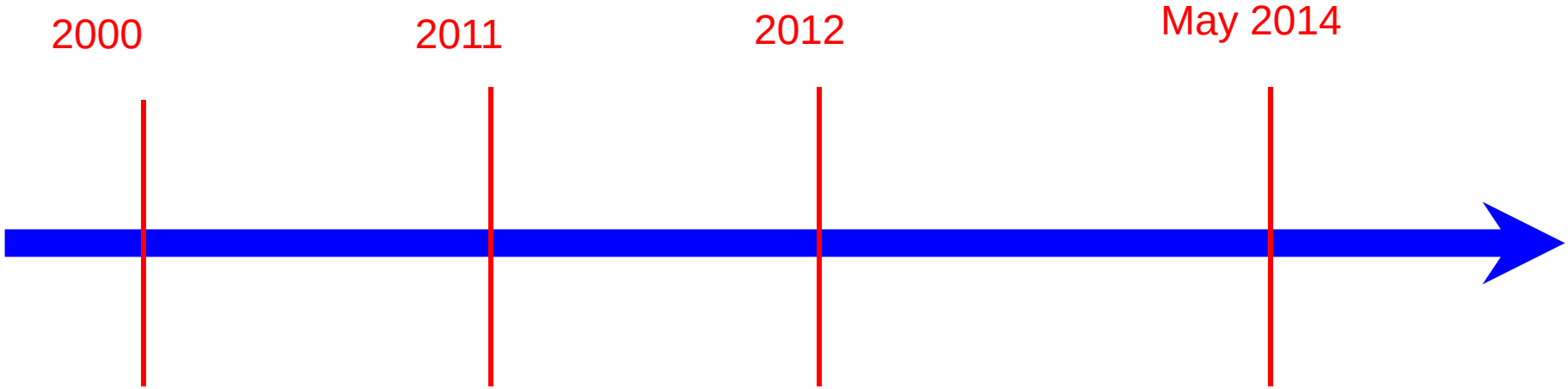
- Cryobiopsie? Dc pour patients plus fragiles?
- Biomarkers: SPD, MMP, ostéopontine?

Tomassetti Am J Respir crit Care Med 2016; Guiot Lung


efinitely
F
Elements
• epidemiology
• environment
• clinic
• imaging
• BAL
• Blood tests
• Pathology
• DMD
• Comportemental pattern
Definitely not IPF
Likely IPF
Unlikely IPF
tifibrotic drugs
CS/IS
Grey area
No antifibrotic drugs
Often CS/IS
How manage with 2011 ATS/ERS/JRS/ALAT boxes?

mpact of treatment recent knowledge on PF diagnosis paradigm

EMA approval for PFD and national guidelines in EU



Consensus statement
On IPF

- Guidelines
- CAPACITY Lancet
- BIBF NEJM

Triple therapy
Warfarin
deleterious

Discosure of
PFD ASCEND and
Nintedanib BIBF
trials

IPF≠NSIP
Tt idem

Grading IPF
diagnosis proba
MDD

Triple therapy
harmful in IPF

Increasing need for clearer diagnosis criteria

Treatment options

- Lung transplantation
- Antifibrotic drugs
- Other treatments
- Palliative care

Lung transplantation (1)

- The only curative treatment
- Improves survival: mean 5-year survival rate =50-56%
- Due to age and comorbidities, can be offered only in a minority of patients (21/244 i.e. 8.6% in the COFI cohort)
  - Absolute contraindications: recent history of malignancy; untreatable significant dysfunction of any major organ (other than lung); chronic infection; BMI>35; non adherence to treatments; some psychiatric or psychologic conditions; absence of adequate or reliable social support; substance abuse or dependence…
  - Relative contraindications: age>65 years; severe symptomatic osteoporosis…
- Should be offered at time to all patients with an expectable benefit
  - Time of referral
  - Time of listing
- « at time » depends upon the delay for obtaining a transplant: scores (for ex GAP) are helpgul to predict survival expectancy

Weill The Journal of Heart and Lung Transplantation 2015; Kistler BMC Pulm Med 2014; Thabut 2009

Antifibrotic drugs

- Pirfenidone
- Nintedanib
- Combination therapy
- New trials

Summary of national IPF guidelines issued

Country	Date	Treatment recommendation
Denmark[1]	2012	• Pirfenidone in patients with FVC >50% or DLco >30% predicted • Recommendation against triple therapy in newly diagnosed patients
Ireland[2]	2012	• Pirfenidone weakly recommended • New patients should not be initiated on regimens incl. prednisolone and azathioprine
Germany[2]	2013	• Pirfenidone weakly recommended • Strong recommendation against triple therapy in definitive IPF
Spain[2]	2013	• Pirfenidone first line for all patients with FVC >50% predicted • In patients who progress, there is the possibility of pirfenidone combination regimens
Sweden[2]	2013	• Pirfenidone first line in patients with FVC >50% predicted • Triple therapy should not be offered to any new patients
Austria[2*]	2013	• Pirfenidone is the standard of care in mild to moderate IPF • Triple therapy should not be offered to any new patients
UK[2]	2013	• Pirfenidone recommended for patients with FVC 50–80% predicted
France[3]	2013	• Pirfenidone recommended in mild to moderate disease • Triple therapy should not be offered to any new patients
Netherlands[2]	2014	• Pirfenidone recommended in mild to moderate disease • Triple therapy should not be offered to any new patients
Italy[4]	2015	• Pirfenidone in patients with FVC >50% and DLco >35% predicted • Prednisone-azathioprine not recommended; NAC monotherapy is not efficacious

recommendations based on an expert
s statement
rapy: prednisone, azathioprine, N-acetylcysteine (NAC)
usion capacity of the lung for carbon monoxide;
ed vital capacity

1. Danish Lung Diseases Society 2014 www.lungemedicin.dk (accessed Marc
2. Xaubet A et al. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:2
3. Cottin V et al. Rev Mal Respir 2013;30:8
4. Tomassetti S et al. Rassegna di Patologia dell'Apparato Respiratorio 2015;30(S

Table 2. Comparison of Recommendations in the 2015 and 2011 Idiopathic Pulmonary Fibrosis Guidelines

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

Raghu AJRCCM 2015

Pirfenidone

- Efficacy (from CAPACITY and ASCEND and some other studies)
  - Reduces progression of disease (FVC; 6MWT; PFS)
  - Improves survival
  - No efficacy on AE, QOL, dyspnea perception
- Tolerance
  - Generally well-tolerated
  - No severe direct adverse effect;
  - mainly GI and phototoxicity; elevated liver enzymes
- Precautions/contra-indications
  - Intake during meals and sun protection (clothes; sun screen etc…); decrease of doses when side effects: stop smoking habits; don't associate omeprazole (esomeprazole can be used)
  - Contra-indications: hepatic insufficiency; drugs (strong CYP1A2 inhibitors: fluvoxamine; enoxacin; to a less degree: ciprofloxacin)
  - Monitor liver function

Noble Lancet 2011; King AJRCCM 2014; Aravena PLOS one 2015; Funke-Chambour Swiss Med Wkly 2015

Nintedanib

- Data from phase II TOMORROW trial and phase III INPULSIS 1 and 2 trials; some post-hoc studies
- Efficacy
  - Reduces disease progression
  - Might (not confirmed)
    - Delay time to first AE
    - Improve QOL
- Tolerance
  - No severe adverse complication
  - Mainly GI (diarrhea +++)
  - Elevated liver enzymes
- Precautions
  - Patients at risk for bleeding (surgery etc…) or with full anticoagulation therapy
  - Interruption if occurrence of MI; in case of GI perforation
  - Caution after recent abdominal surgery; with co-administration P-gp inhibitors (ketoconazole; erythromycine) or inducers (carbamazepine; phenytoine; hypericum)
  - Contraindicated in case of moderate to severe hepatic impairment
  - Use of antidiarrheic drugs

Richeldi NEJM 2011; Richeldi NEJM 2014; Keating Drugs 2015

Combination therapy

- Combination regimens
  - IPF nature is pleiotropic with a complex pathogenesis
  - Pirfenidone and nintedanib respectively prevent 50% of FVC decline
  - New trials are based on the study of new drugs in association with one effective antifibrotic drug
  - In medium-term future, after probant studies, the use of combination regimens might be expected to be the standard of treatment
- Association of pirfenidone and nintedanib
  - Preliminary data in a short series concerning only safety and pharmacokinetics
  - Adverse effects frequent but only mild or moderate; never severe: most often GI
  - Impact of PFD on nintedanib pharmacokinetics
  - No available data about efficacy

Wuyts Lancet RM 2014; Ogura ERJ 2015

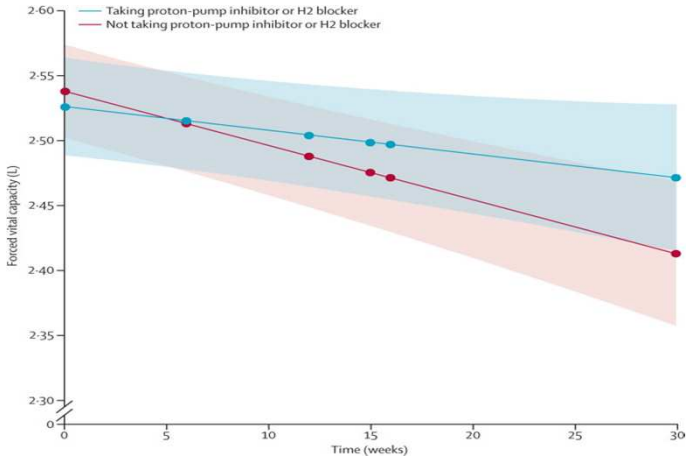
Trials with new antifibrotic drugs

- IPF is still a very severe condition despite available treatments
- There is a need for new treatments
- Patients, even under treatment, have to be informed about participation in new trials http://clinicaltrials.gov/

Other treatments

- PPI
- Supportive treatments
  - O2 supplementation
  - Treatment of dyspnea, anxiety and depression
  - Rehabilitation
  - Psycho-social support
- Formal palliative care

PPI: retrospective and in vitro studies



- Retrospective studies suggest that PPI might slower IPF course and delay AE
- In vitro study
- Esomebrazole might have direct antiinflammatory, antioxydant, antiproliferative and antifibrotic effects

Lee AJRCCM; Lee Lancet RM 2013; Ghebremariam J Transl Med 2015; Ghrebe AJRCCM 2016

Supportive care: O2 supplementation; treatment of dyspnea, anxiety and depression (1)

- O2 supplementation
  - One retrospective study *(Douglas, AJRCCM 2000; 161)* : no effect on survival in IPF
  - No benefit on dyspnea (Nishiyama, Respir Med 2013; 107)
  - O2 improves 6MWD and dyspnea in patients with desaturation *(Visca, ERJ 2011; 38. FranK, ERJ 2012; 40).* Increase O2 by steps; goal : SaO2 > 88-90%
- Morphinic at low dose can improve dyspnea. Surveillance ++
- Anxiety
  - Supportive groups improve anxiety, depression and dyspnea, which are often associated *(Danoff, Curr Opin Pulm Med 2013; 19. Ryerson, J Pain Symptom Manage 2012; 43)*
- Medical treatment of depression may soothe dyspnea perception.

Supportive care: respiratory rehabilitation in IPF

- RR improves 6MWD, symptoms and QoL *(Holland, Thorax; 2008: 63. Nishiyama, Respirology; 2008: 13. Huppmann, ERJ; 2013: 42)*
- Long-term benefit : less pronounced than in COPD
- Modalities ?
  - In dedicated RR Centres : *Huppmann, ERJ 2013; 42*
  - At home : *Rammaert; Rev Mal Respir 2011* (improvement of endurance and exercise limitation)
- Lack of standardized protocole protocol for RR in IPF: must include : retraining at exercise, tobacco weaning, psycho-social help, supportive care

Palliative care in IPF

- Despite improvements in therapy, IPF will progress until advanced disease and death for most patients
- Advanced IPF is very similar to advanced lung cancer according to survival expectancy, QOL and many other questions
- Studies have shown a clear benefit with systematic early integration of palliative care in advanced cancer
  - Improvement of QOL and survival; reduction of inappropriate hospitalizations
  - Palliative care is currently considered a standard in oncology care
- There are not yet significant prospective studies in IPF; but retrospective studies and a limited prospective one show and suggest that:
  - Only a very limited proportion of IPF patients (and too lately) currently benefit from palliative care
  - Early palliative care is probably beneficial in advanced IPF (with evidence a better breathlessness mastery)
- Therefore, studies are warranted to assess how systematic early integration of palliative care in advanced IPF treatment could impact QOL, survival, hospitalizations, redaction of anticipated directives, location of death and specify how to organize at best palliative care in IPF
- Essai PALIF (PHRC)

Temel NEJM 2010; Smith JCO 2012; Zimmerman Lancet 2014; Lindell Chest 2015; Higginson Lancet RM 2014; Rajala 201

Specific conditions

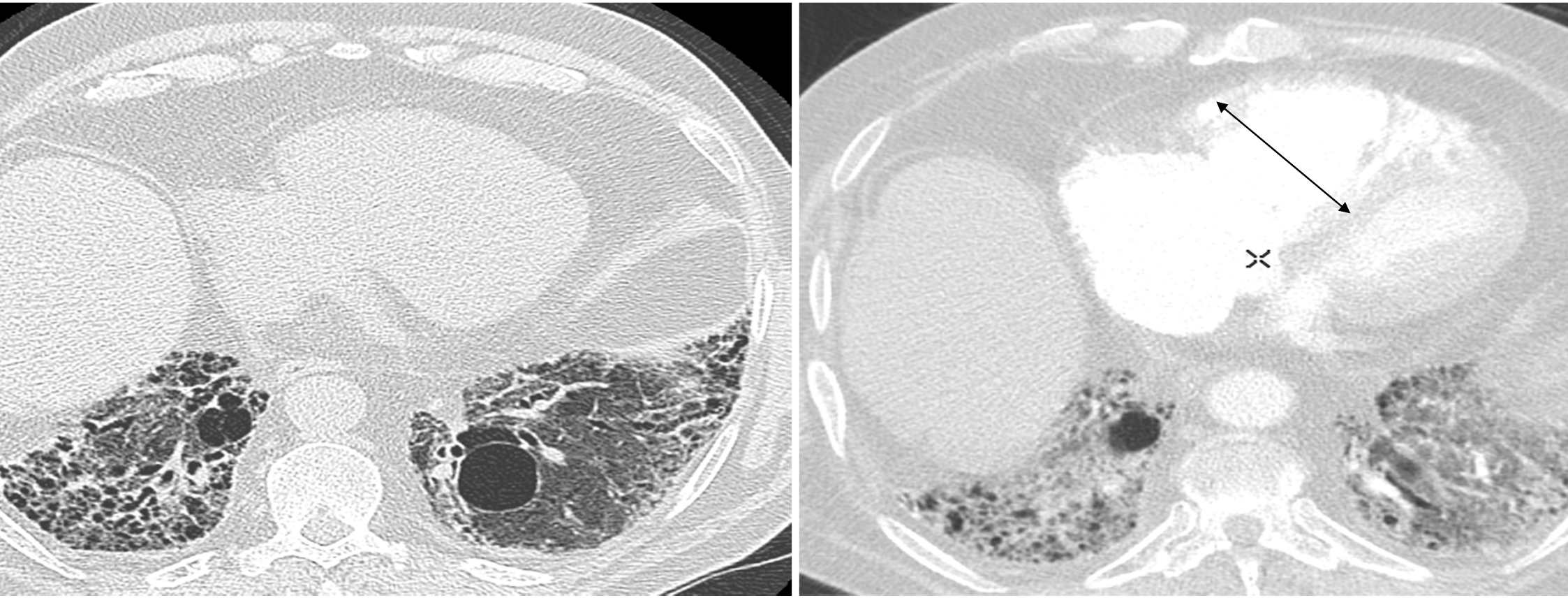
- Acute exacerbation
- Comorbidities
- Sleep apnea syndrome
- Pulmonary hypertension
- Associated emphysema/COPD
- Lung cancer
- Elderly patients
- Progression of IPF under antifibrotic treatment
- Telomeropathies: impact on post-transplantation survey

Acute exacerbation of IPF

- Annual incidence 5-15%
- Short-term mortality ~50%
- Often treated with high dose corticosteroids and antimicrobials
- Sometimes transplantation (in patients listed at time)
- No validated study

Ryerson Chest 2015

Exacerbation aiguë de FPI



FPI connue depuis un an
Aggravation respiratoire rapide en avril 2009

Akira M. AJRCCM 2008;178:372

Comorbidities

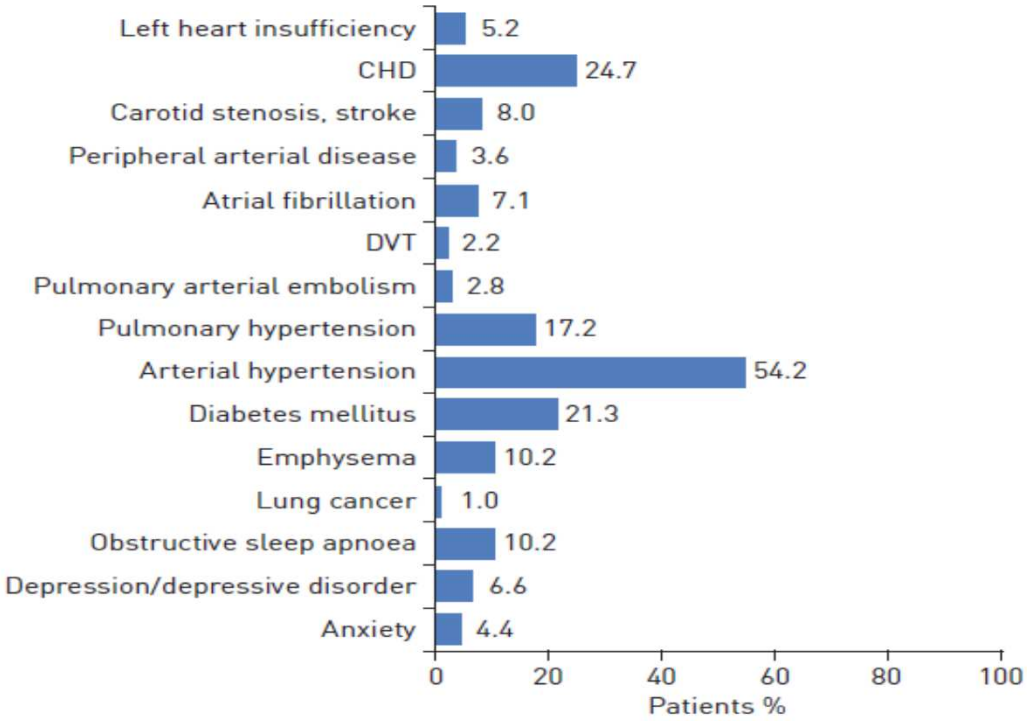


FIGURE 1 Comorbidities at baseline. CHD: coronary heart disease; DVT: deep venous thrombosis.

Comorbidities may impact survival, have to be treated which may interact with IPF treatment; need to consider pharmacokinetics interactions of respective treatments

Behr ERJ 2015

Sleep disorder treatment in IPF

- Rapid eye movement period-induced hypoxemia → O2 supplementation
- OSA is among recognized IPF-associated comorbidities
  - 59-88% in IPF (mild vs moderate to severe OSA)
  - Factors: age; increased BMI; ↓FVC in supine position?
  - Associated to Coronary disease
- CPAP therapy in IPF (few studies)
  - Might improve daily living activities and quality of sleep
  - CPAP may be difficult to initiate, unaccepted or used with a poor compliance in advanced IPF but might be well tolerated when initiated in mild stage IPF
  - Effect on fatigue, QOL, PH incidence, mortality, IPF progression to be assessed

Schiza ERR 2015; Gille ERJ 2017

Schiza ERR 2015; Raghu AJRCCM 2011; Lancaster Chest 2009; Mermigkis Sleep Breath 2010; Mermigkis Sleep Breath 2015

COPD/emphysema

- Post-hoc studies on IPF trials suggest a probable efficacy of antifibrotic drugs in patients with associated COPD/emphysema

Pulmonary hypertension

- Precapillary PH is observed in 10-85% cases, most often in advanced IPF but may be encountered in mild-moderate IPF
- PH has a major adverse impact on morbidity and mortality and is an indication for listing on transplantation program
- Only one randomized, double-blind, placebo controled study with PAH-specific therapy (bosentan) in fibrotic IIP= negative
- Efficacy of Sidenafil or riociguat: possible but still to be confimed
- Recommandations
  - PH Nice congress meeting: « patients with ILD and PH should not receive PAH-specific therapy until any evidence of a benefit »
  - Reversal of hypoxemia
  - Enrollment in well-designed trials

Corte AJRCCM 2014; Cottin ERJ 2013

Lung cancer

- Incidence: up to 13%
- Survival worse in IPF when lung cancer is associated
- Death due to respiratory failure (43%), LC (13%) and treatment adverse effects (17%)
- Treatment is difficult (risks inherent to lobectomy or chemotherapy)
- Intérêt des antifibrosants pour prévenir EA post résection? Rôle PFD?

Tomassetti Chest 2015

IPF in elderly patients

- Context
  - More comorbidities (OSA; GERD; CAD; osteoporosis etc…)
  - Increased risk of drug-drug interactions
  - Monitoring function and 6MWT sometimes difficult
  - No available trial >80 years
- Treatment options
  - Antifibrotic drugs effective and well-tolerated >75 years
  - Transplantation: contraindication over 65 years: « relative »
  - PPI: often
  - Usefulness of supportive measures even though rehabilitation may be difficult
  - Wise balance between antifibrotic, supportive and palliative approaches

Meyer Chest 2015

Treatment after progression of IPF despite antifibrotic drugs

- ntifibrotic drugs reduce but do not stop IPF progression
- s difficult to assess the efficacy of antifibrotic drug in a single patient
- st-hoc analysis of trials indicates that PFD might decrease further IPF progression despite a cent progression and suggests that a progression is not a sufficient reason to withdraw the drug
- us, face to a progression, treatment strategy has to be discussed in MDD to determine the best tion

Patterns in FPF (CT/pathology)

- All patterns (UIP, NSIP, OP, DIP/BR, DAD), HP et SFE may be observed

Steele et al. *Am J Respir Crit Care Med* 2005
Fernandez et al. *Respir Res* 2012
Diaz de Leon et al. *PLoS ONE* 2011
Nunes et al. *Am J Respir Crit Care Med* 2013

- Diversity of patterns even among a single family

Steele et al. *Am J Respir Crit Care Med* 2005

- CT pattern= inclassifiable: 55%

Lee et al. *Chest* 2012

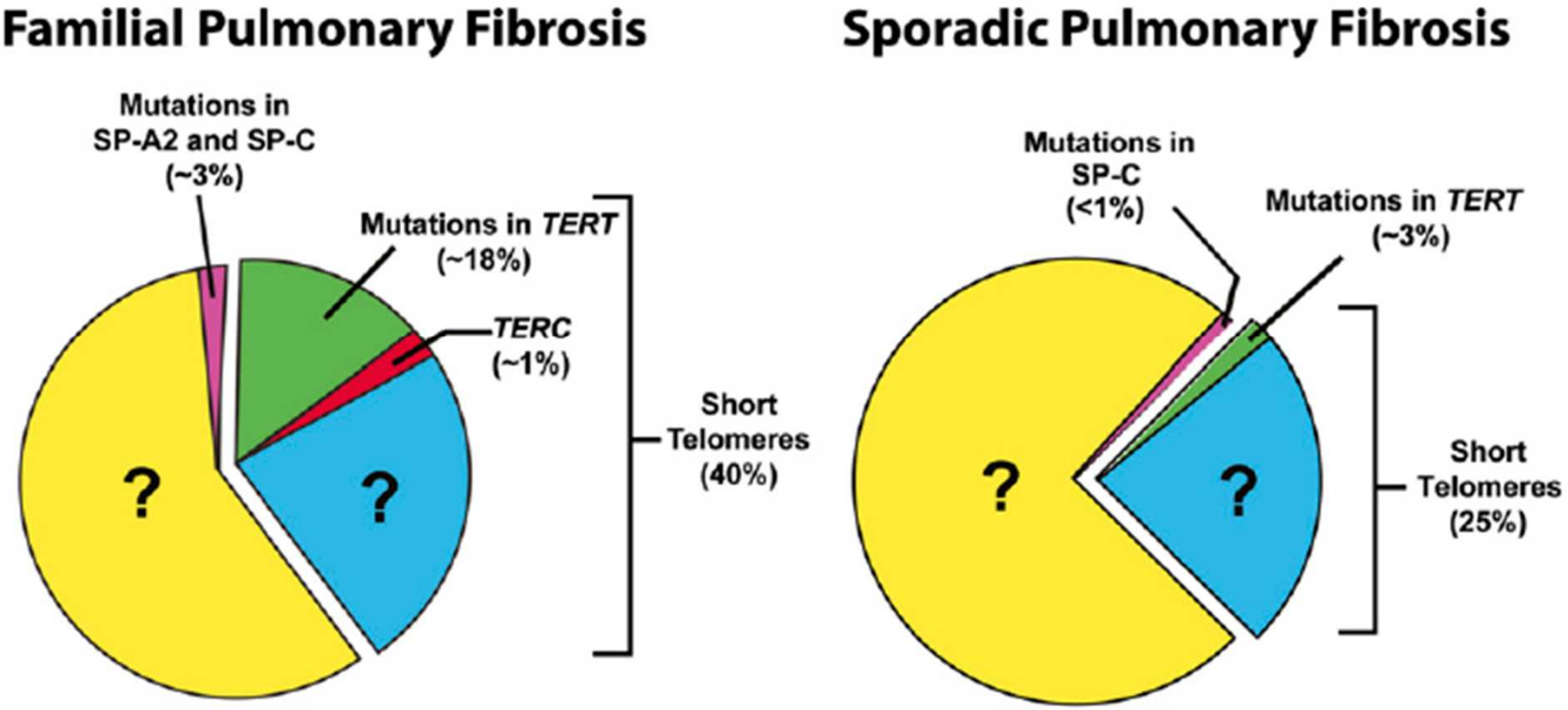
- Pathologic pattern= inclassifiable: 60%

Leslie et al. *Arch Pathol Lab Med* 2012

- Evidence of granulomas: 17%

Diaz de Leon et al. *PLoS ONE* 2011

Familial pulmonary fibrosis



MUC5B 34% 38%

Garcia et al. *PATS* 2011
Seibold et al. *N Engl J Med* 2011

Conclusions

- Effective antifibrotic therapy is now a cornerstone in the treatment of IPF
- LT is the only curative treatment of IPF and needs being proposed when indicated (~10% of patients)
- A personalized approach of IPF care is indispensable taking into account the age, disease stage, multiple comorbidities of patients and the will of patients
- There is a need for new effective drugs or combination of regimens for improving the course of IPF
- Early palliative care in advanced IPF has to be investigated. It is expected to be essential to improve patients care