Guidelines for Diagnosis and Treatment of IPF

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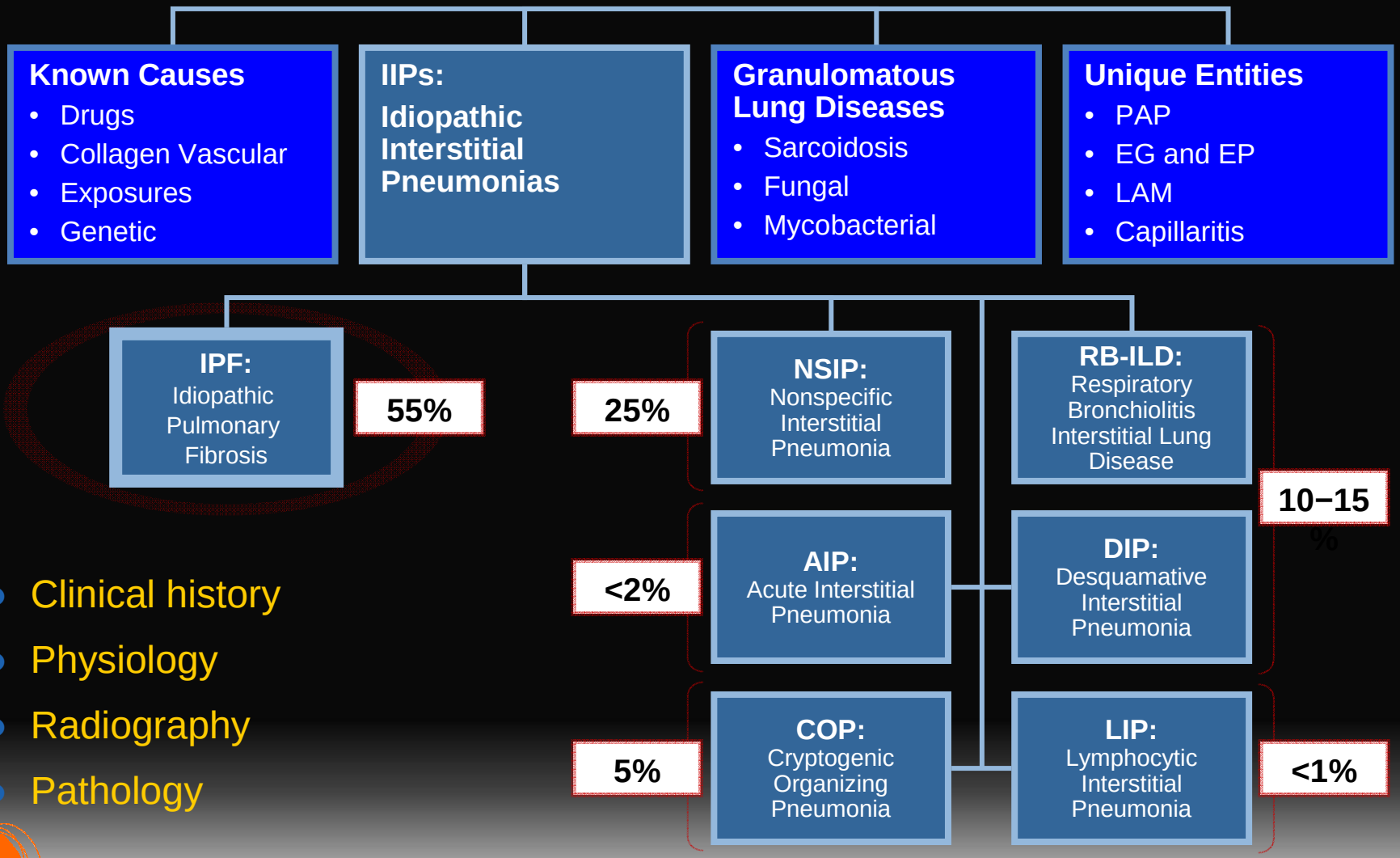
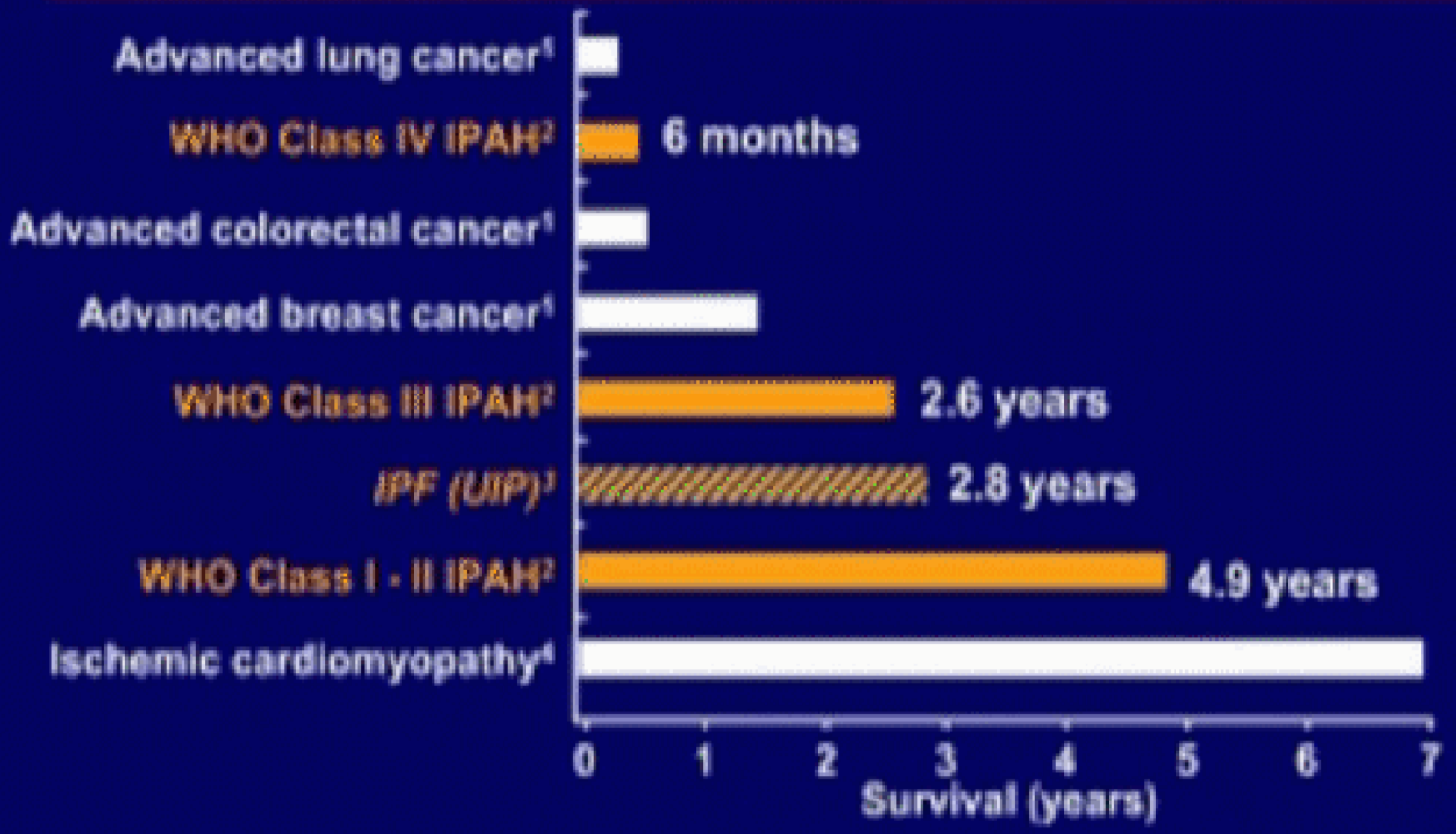
Classification of Interstitial Lung Disease



- Clinical history
- Physiology
- Radiography
- Pathology

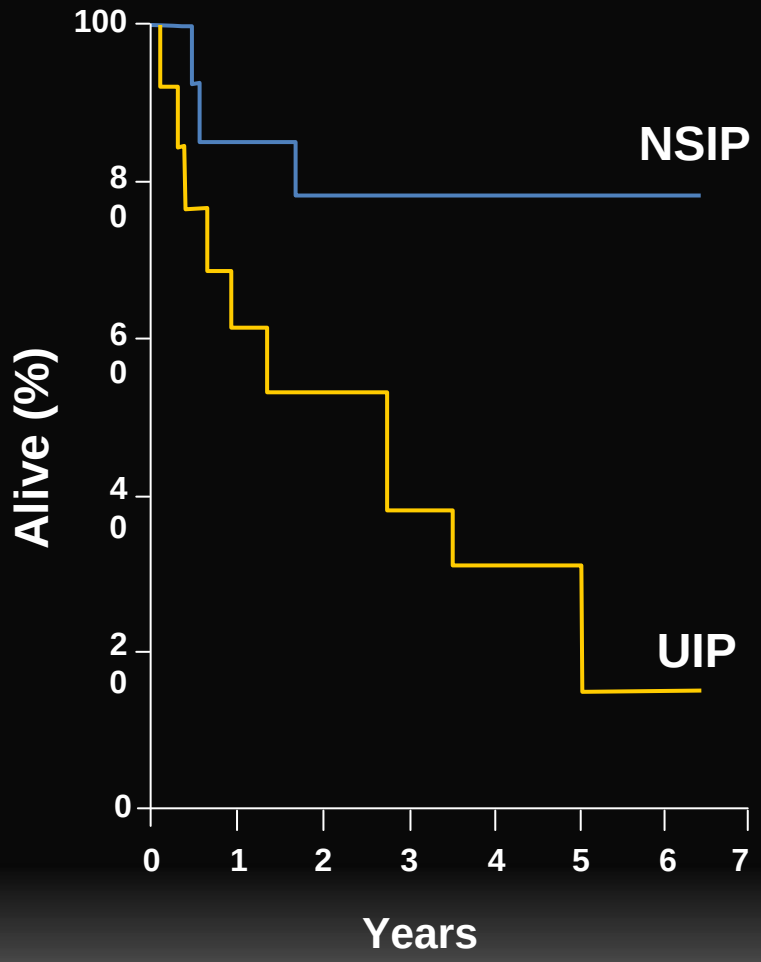
American Thoracic Society/European Respiratory Society. Am J Respir Crit Care Med 2002;165:277-304.

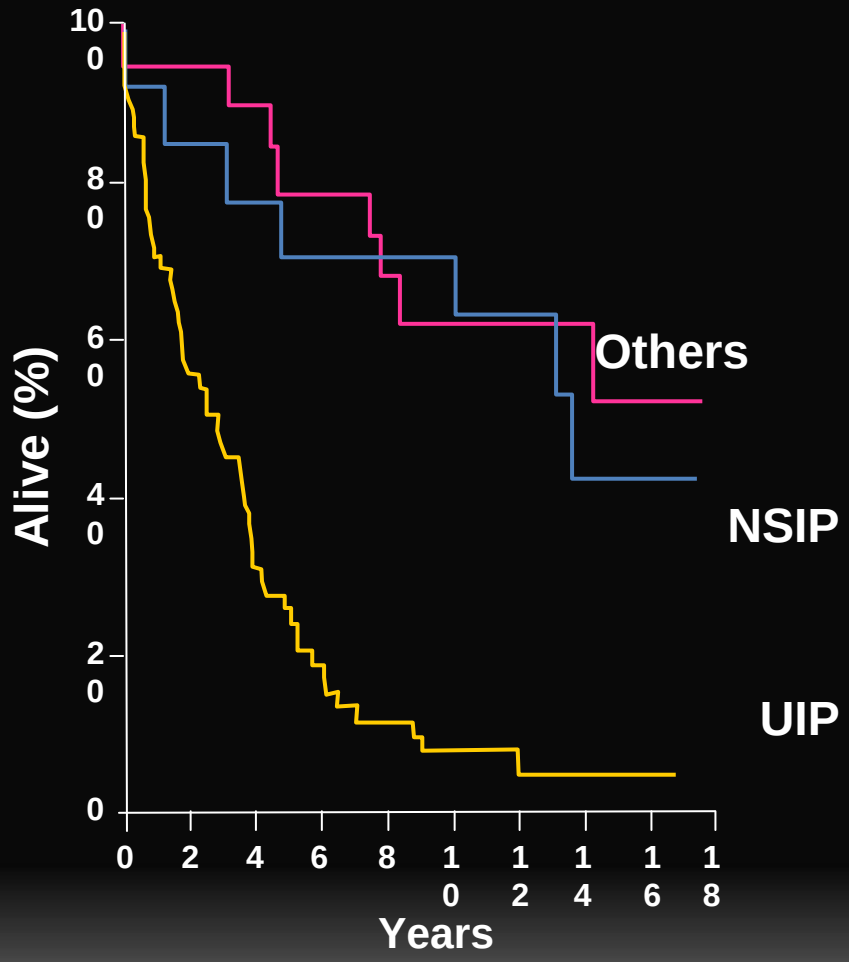
Prognosis of IPF: Comparable to IPAH and advanced cancers



1.Kato I, *et al. Cancer* 2001; 92:2211-9. 2.D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9. 3. Bjoraker JA, *et al. Am J Respir Crit Care Med* 1998; 157:199-203. 4.Felker GM, *et al. N Engl J Med* 2000; 342:1077-84.

Survival for UIP vs NSIP / Others





Daniil ZD, et al. *Am J Respir Crit Care Med.* 1999;160:899-905.

Bjoraker JA, et al. *Am J Respir Crit Care Med.*1998;157:199-203.

Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management

Idiopathic Pulmonary Fibrosis

- Clinical presentation
  - Older age (6^{th} – 7^{th} decades of life)
  - Men > women
  - Unexplained chronic exertional dyspnea, crackles, finger clubbing
- Incidence and prevalence
  - No large-scale studies to base formal estimates
  - Incidence = 6.8-16.3/100,000
  - Prevalence = 14-42.7/100,00

Clinical findings in IPF

- Age: 66 yr (40 - 70), two- thirds > 60 yr
- Dyspnea on exertion > 6 mo 95%
- Cough 90%
- Fine crackles 90%
- Clubbing 60-70%
- Weight loss, malaise, fatigue 30-50%
- Fever rare

American Thoracic Society

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment

International Consensus Statement

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999 AND BY THE ERS EXECUTIVE COMMITTEE, OCTOBER 1999

This statement was prepared by an ad-hoc committee of the Assembly on Clinical Problems. Members of the committee are:

TALMADGE E. KING, JR., M.D., *Chair*
ULRICH COSTABEL, M.D.
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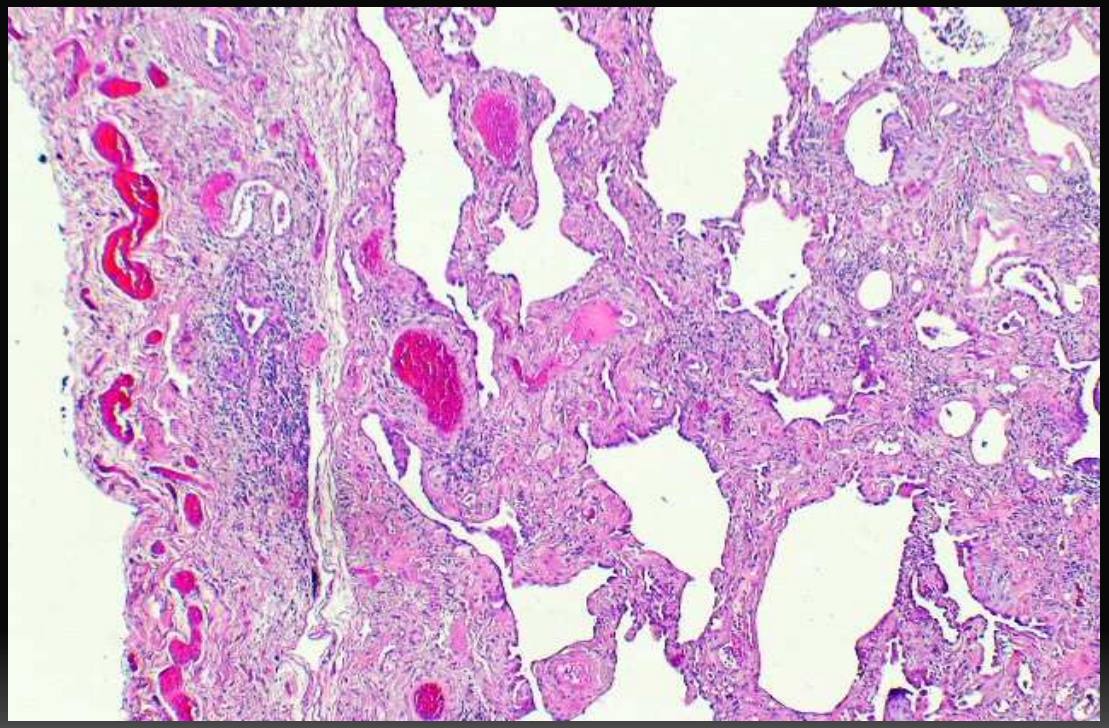
The authors thank Drs. Thomas Colby, David Hansell, Masanori Kitaichi, and William Travis for their critical review of the manuscript.

Am J Respir Crit Care Med 2000; 161: 646–664

Idiopathic pulmonary fibrosis (IPF)

"Specific form of chronic fibrosing interstitial pneumonia limited to the lung, associated with UIP on lung biopsy."



International Consensus Statement, *AJRCCM* 2000

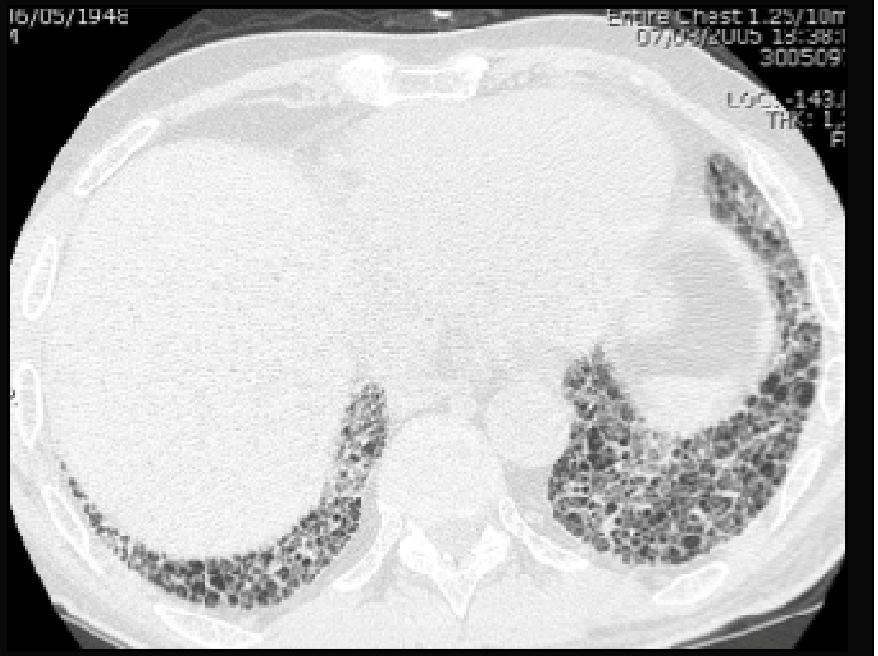
IPF diagnosis *in the absence* of SLB

All four major criteria:

1. exclude all known causes
2. appropriate lung function
3. imaging
4. BAL or TBB excluding other diseases

3/4 minor criteria:

1. age >50 yr
2. slow onset
3. disease duration at least 3 months
4. crackles on auscultation



peripheral/basal
honeycombing
little/no ground-glass

International Consensus Statement, *AJRCCM* 2000

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

This Official Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) Was Approved by the ATS Board of Directors, November 2010, the ERS Executive Committee, September 2010, the JRS Board of Directors, December 2010, and the ALAT Executive Committee, November 2010

This Statement has been formally endorsed by the Society of Thoracic Radiology and by the Pulmonary Pathology Society

Am J Respir Crit Care Med 2011; 183: 788-824

Grading quality of evidence and strength of recommendations

GRADE Working Group

Clinical guidelines are only as good as the evidence and judgments they are based on. The GRADE approach aims to make it easier for users to assess the judgments behind recommendations

BMJ 2004; 328: 1-8

American Thoracic Society Documents

An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations

Holger J. Schünemann, Roman Jaeschke, Deborah J. Cook, William F. Bria, Ali A. El-Solh, Armin Ernst, Bonnie F. Fahy, Michael K. Gould, Kathleen L. Horan, Jerry A. Krishnan, Constantine A. Manthous, Janet R. Maurer, Walter T. McNicholas, Andrew D. Oxman, Gordon Rubenfeld, Gerard M. Turino, and Gordon Guyatt, on behalf of the ATS Documents Development and Implementation Committee

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, DECEMBER 2005

Am J Respir Crit Care Med 2006; 174: 605-614

ORGANIZATIONS THAT HAVE ENDORSED GRADE

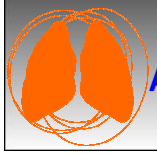
GRADING THE EVIDENCE

- For each question, the committee graded the quality of the evidence available (high, moderate, low, or very low), and made a recommendation for or against.
- Recommendations were decided based on majority vote.
- Recommendations were either “strong” or “weak”.

Open and explicit vote of each member on each recommendation (reported in the document)

GRADING the evidence

Quality of Evidence	Study Design	- Lower if:	- Higher if:
High	Randomized controlled trial	Study quality -1 Serious limitation -2 Very serious limitation -1 Important inconsistency Directness -1 Some uncertainty -2 Major uncertainty -1 Sparse or imprecise data -1 High probability of reporting bias	+1 Strong association, no plausible confounders +2 Very strong association, no major threats to validity +1 Evidence of a dose response gradient +1 All plausible confounders would have reduced the effect
Moderate	Downgraded randomized controlled trial or upgraded observational study		
Low	Well done observational study with control groups		
Very low	Any other evidence (e.g. case reports, case series)		



ATS/ERS/JRS/ALAT IPF GUIDELINES

Schünemann H et al. *AJRCCM* 2006

PROVIDING RECOMMENDATIONS

Strong recommendation

Patients: most people in this situation would want the recommended course of action and only a small proportion would not.

Clinicians: most patients should receive the recommended course of action.

Policy makers: the recommendation can be adopted as a policy in most situations.

Weak recommendation

Patients: the majority of people in this situation would want the recommended course of action, but many would not.

Clinicians: be more prepared to help patients to make a decision that is consistent with the patient's own values.

Policy makers: there is a need for substantial debate and involvement of stakeholders.

Schünemann *AJRCCM* 2006

RECOMMENDATIONS

The strength of the recommendations is either strong or weak based on the quality of evidence and the voting of the committee members.

<u>Thus the recommendations are either:</u>

1) STRONG -YES,

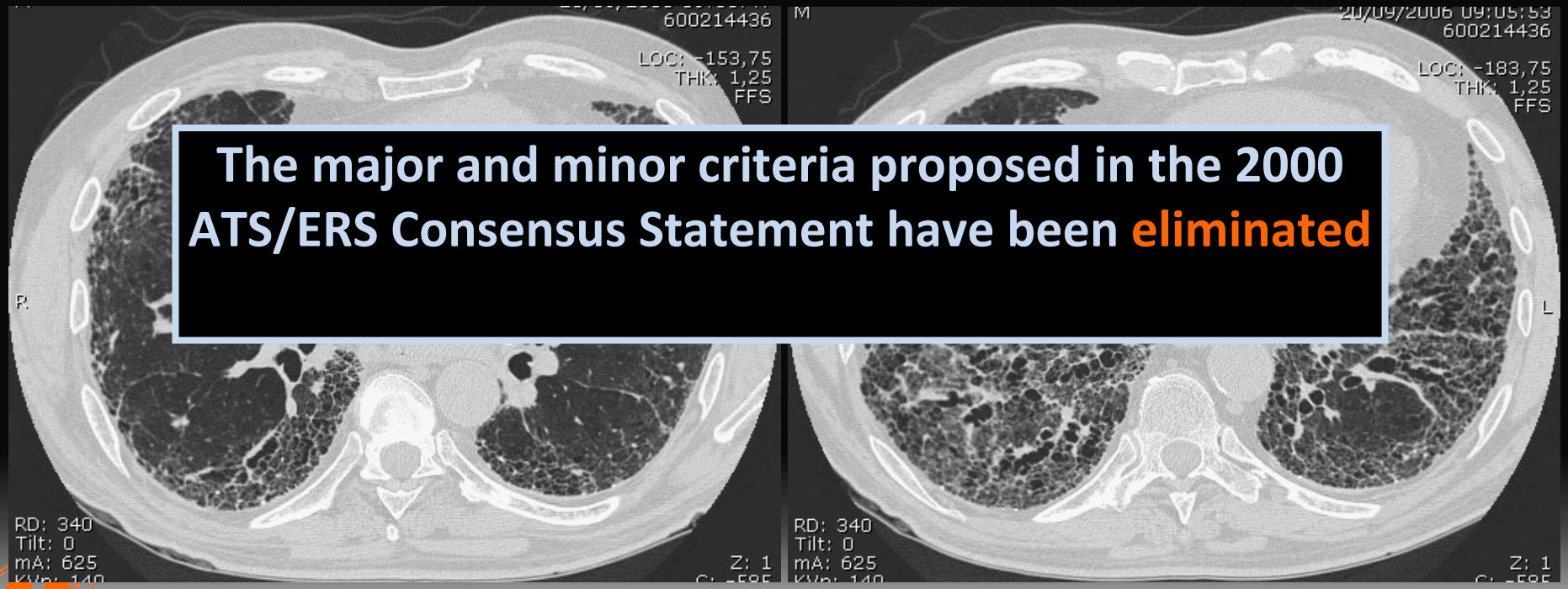
2)STRONG -NO,

3) WEAK- YES, or

4) WEAK- NO.

"The diagnosis of IPF *requires*:

a)exclusion of other known causes of interstitial lung disease
b)the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy
c)specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy"



The major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated

Am J Respir Crit Care Med 2011; 183: 788-824

IPF diagnosis *in the absence* of SLB

All four major criteria:

1. exclu all known cau s
2. ab lung f
3. in
4. BAL c er diseases

3/4 minor crit

1. age
2. sl
3. dis ration at months
4. crackles on auscultatio

International Consensus Statement, *AJRCCM* 2000

HRCT CRITERIA FOR UIP PATTERN

UIP
(all **four** features)

- Subpleural, basal predominance
- Reticular abnormality
- **Honeycombing** with or without traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern (see third column)

Possible UIP
(all three features)

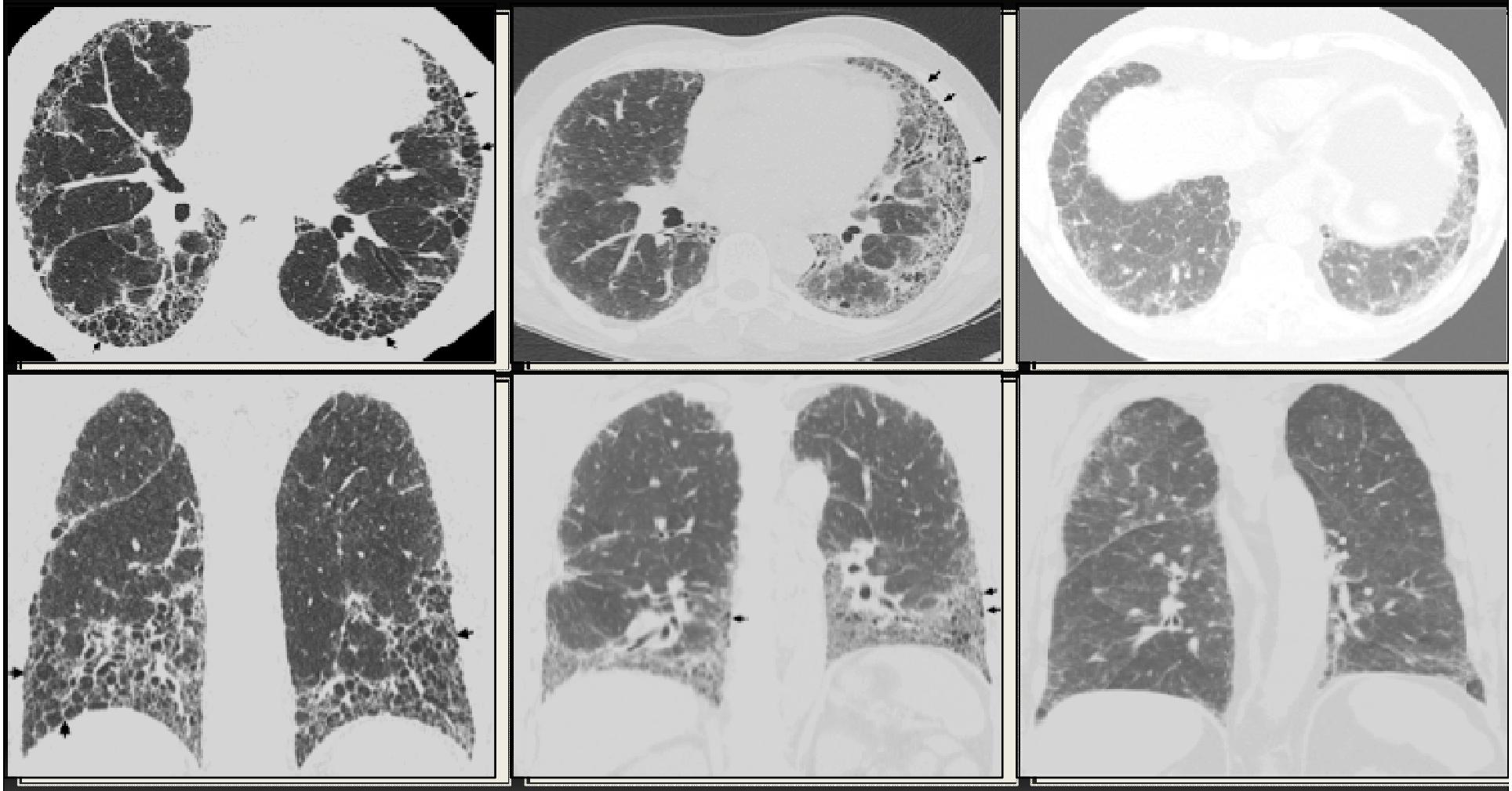
- Subpleural, basal predominance
- Reticular abnormality
- Absence of features listed as inconsistent with UIP pattern (see third column)

Inconsistent with UIP
(**any** of the seven features)

- 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 3 or more lobes)
- Consolidation in bronchopulmonary segment(s)/lobe(s)

Am J Respir Crit Care Med 2011; 183: 788-824

HRCT UIP PATTERN



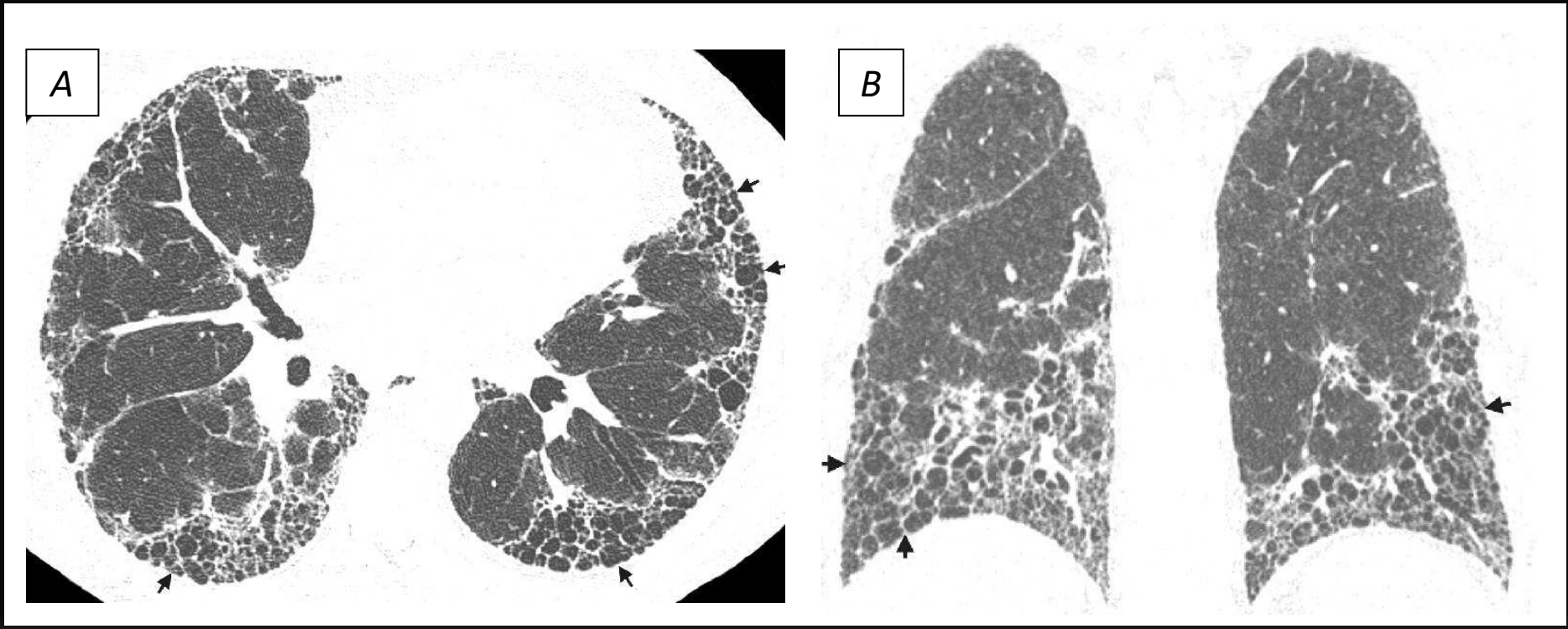
DEFINITE UIP **DEFINITE UIP** **POSSIBLE UIP**

Am J Respir Crit Care Med 2011; 183: 788-824

Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

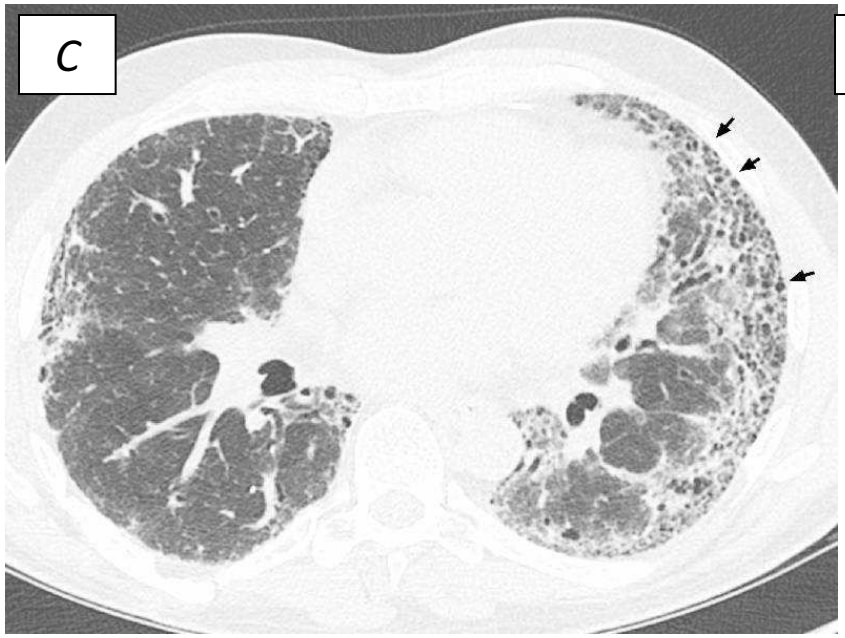
HRCT Images: UIP Pattern *(Extensive honeycombing)*

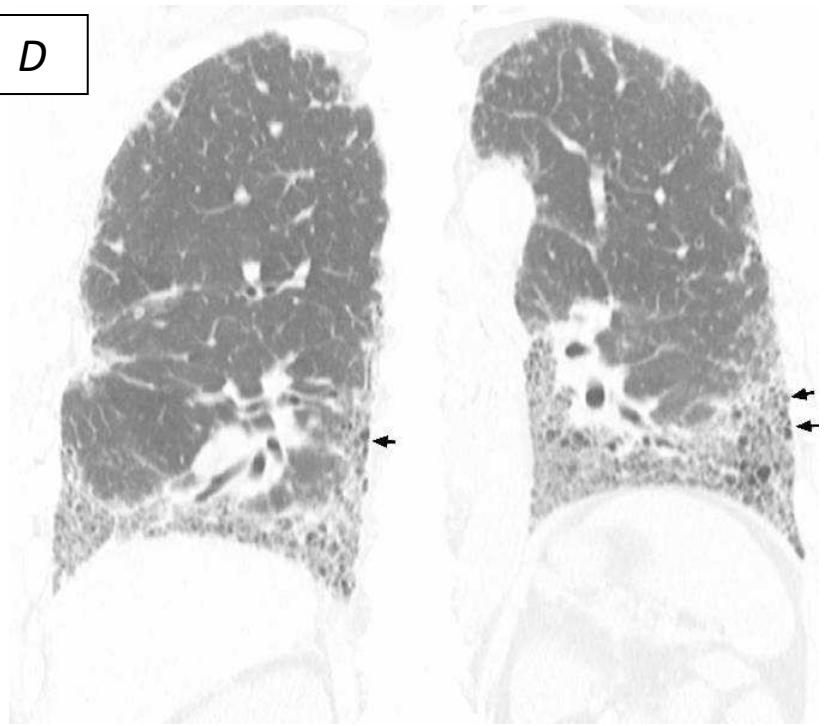


Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

HRCT Images: UIP Pattern *(Less severe honeycombing)*



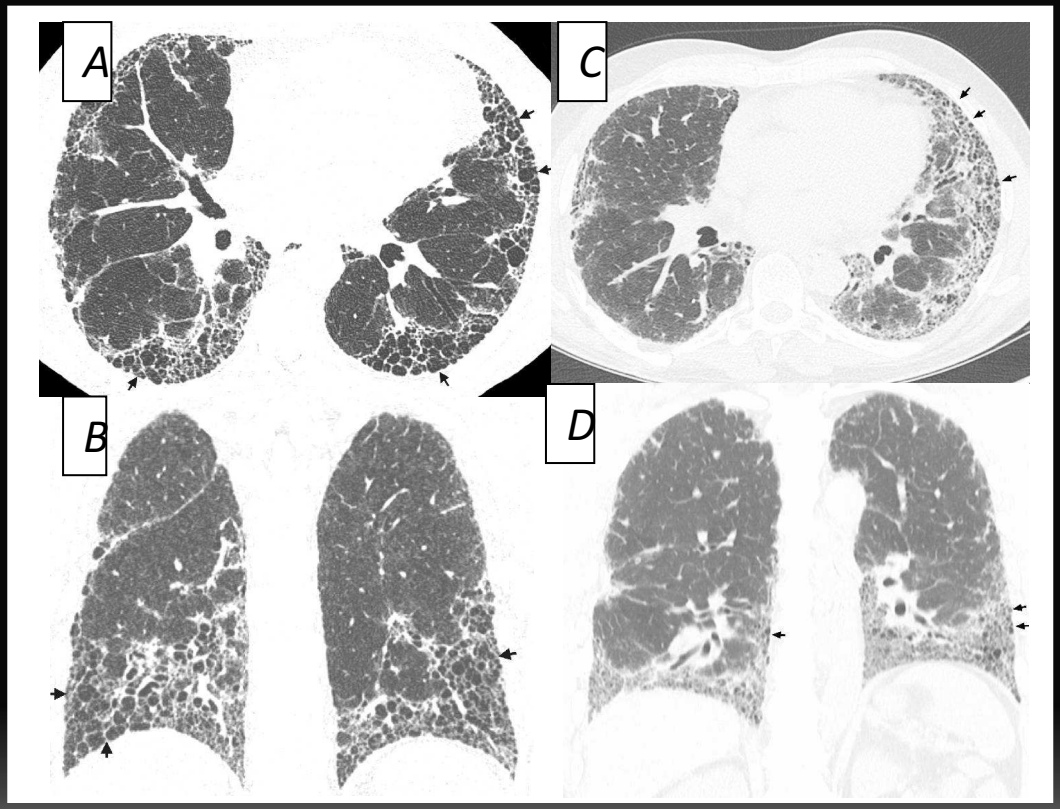


Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

HRCT Images: UIP Pattern
(Extensive honeycombing)

HRCT Images: UIP Pattern
(Less severe honeycombing)



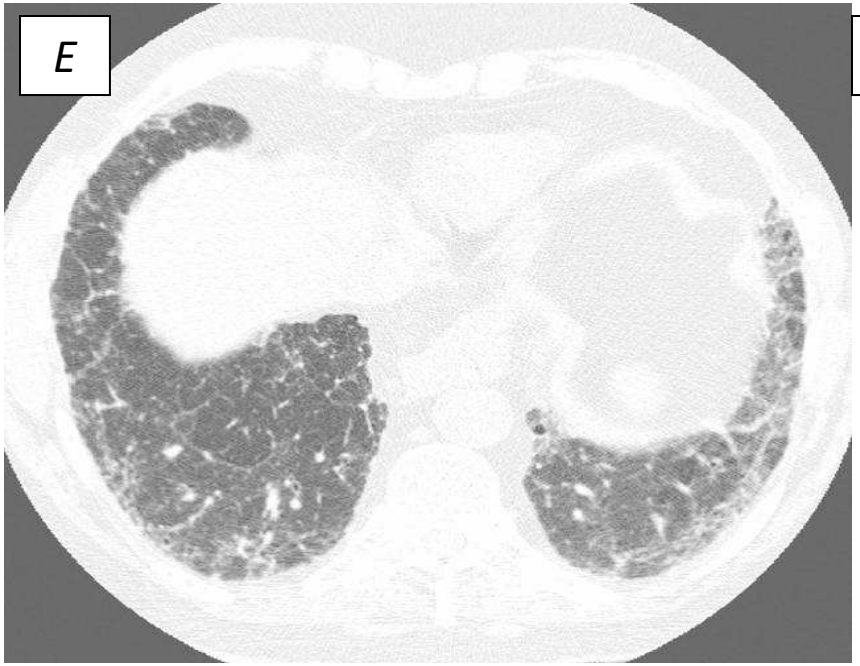
Honeycombing (HRCT)

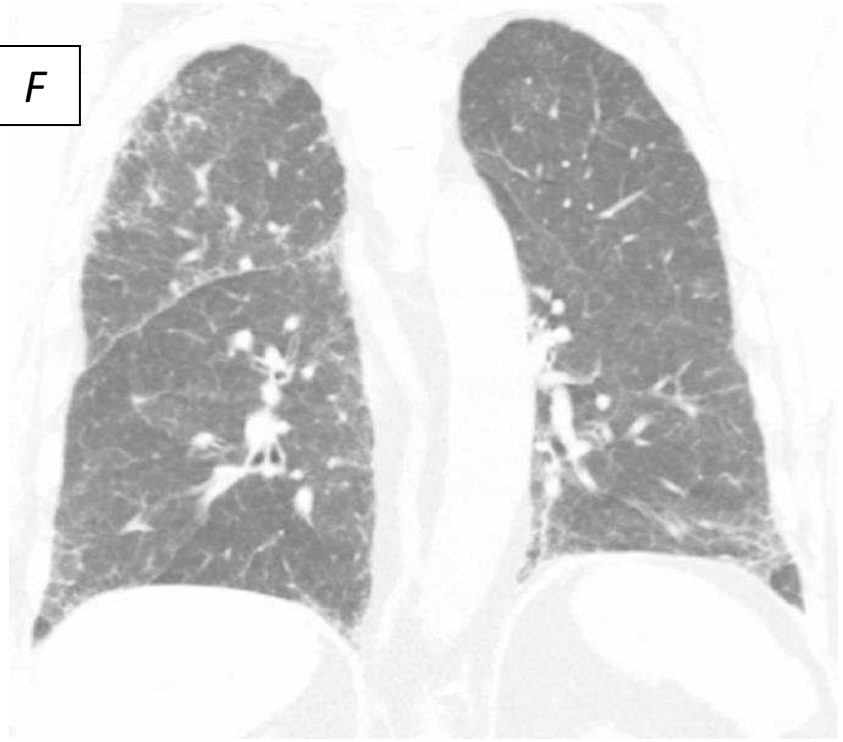
- Clustered cystic air spaces
- Well defined walls
- Typically comparable diameters (3-10 mm; occasionally as large as 2.5 cm)
- Sub pleural

Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

HRCT Images: Possible with UIP pattern *(no honeycombing)*





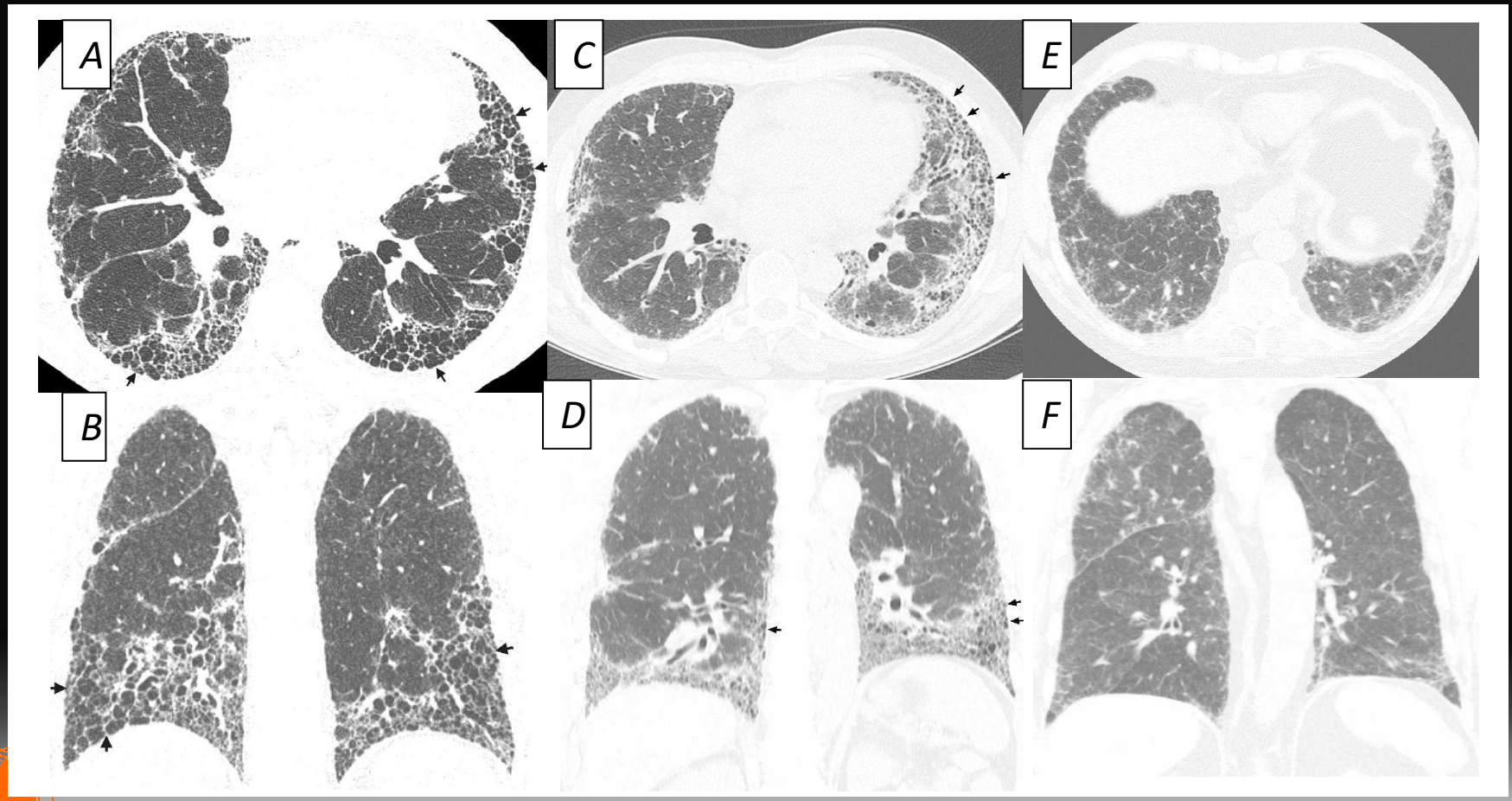
Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

HRCT Images: UIP Pattern
(Extensive honeycombing)

HRCT Images: UIP Pattern
(Less severe honeycombing)

HRCT Images: Possible
with UIP pattern



HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP
(all **four** criteria)

Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a predominantly subpleural/paraseptal distribution

Presence of **patchy involvement** of lung parenchyma by fibrosis

Presence of **fibroblast foci**

Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)

Probable UIP

Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a subpleural/paraseptal distribution

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

Possible UIP
(all **three** criteria)

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)

Not UIP
(**any** of the six criteria)

Hyaline membranes

Organizing pneumonia

Granulomas

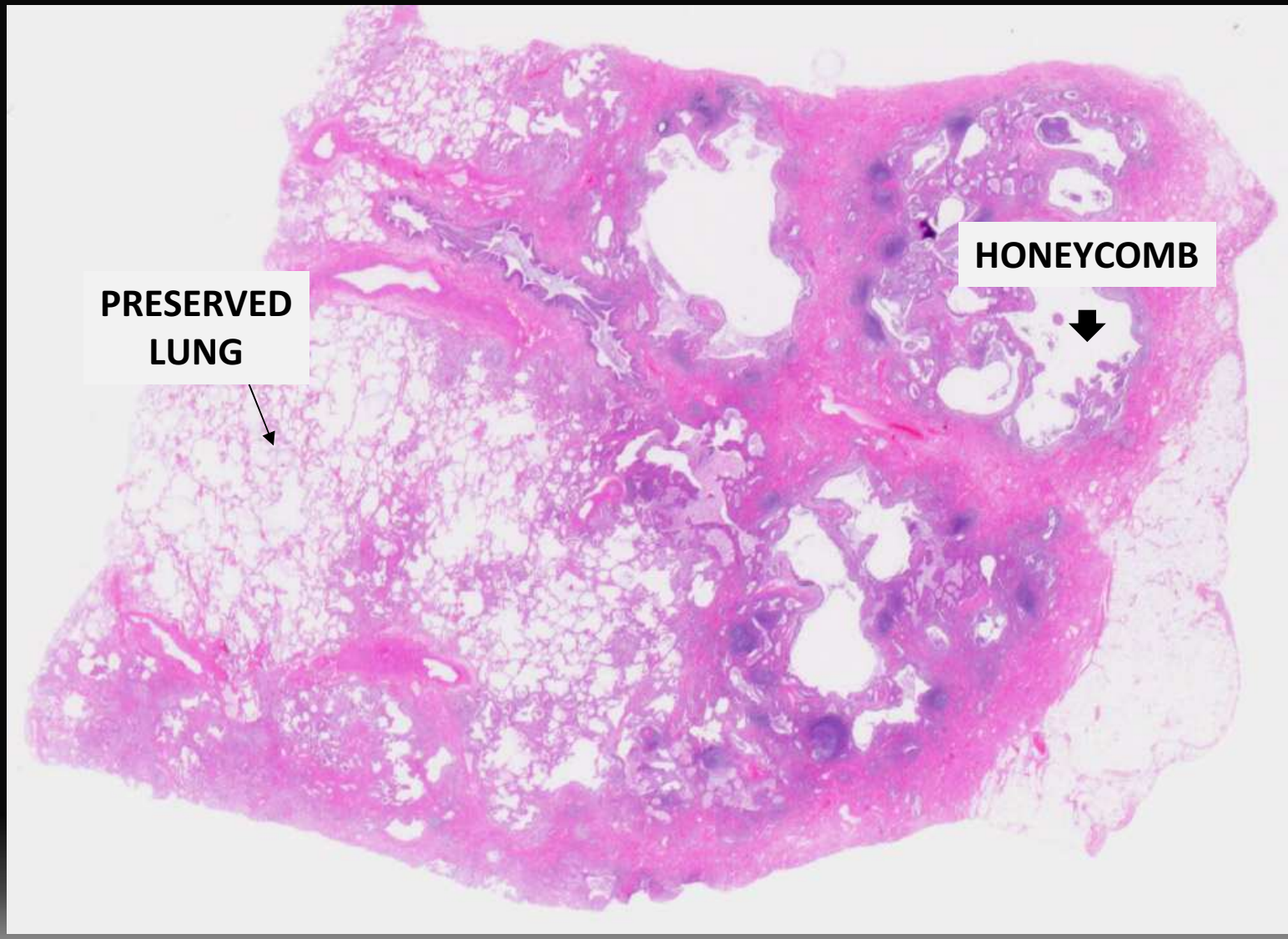
Marked interstitial inflammatory cell infiltrate away from honeycombing

Predominant airway centered changes

Other features suggestive of an alternate diagnosis

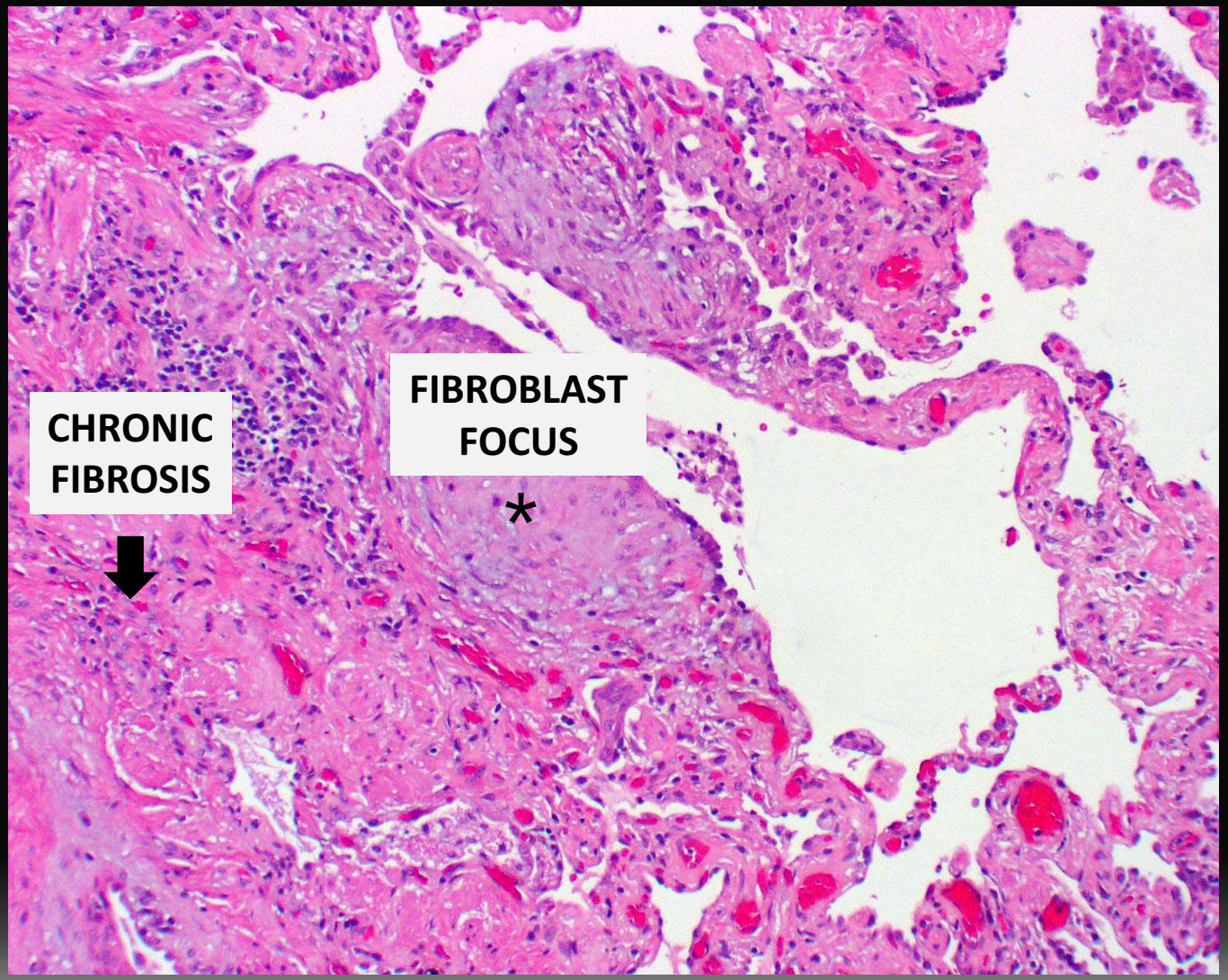
Am J Respir Crit Care Med 2011; 183: 788-824

HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN



Am J Respir Crit Care Med 2011; 183: 788-824

HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN



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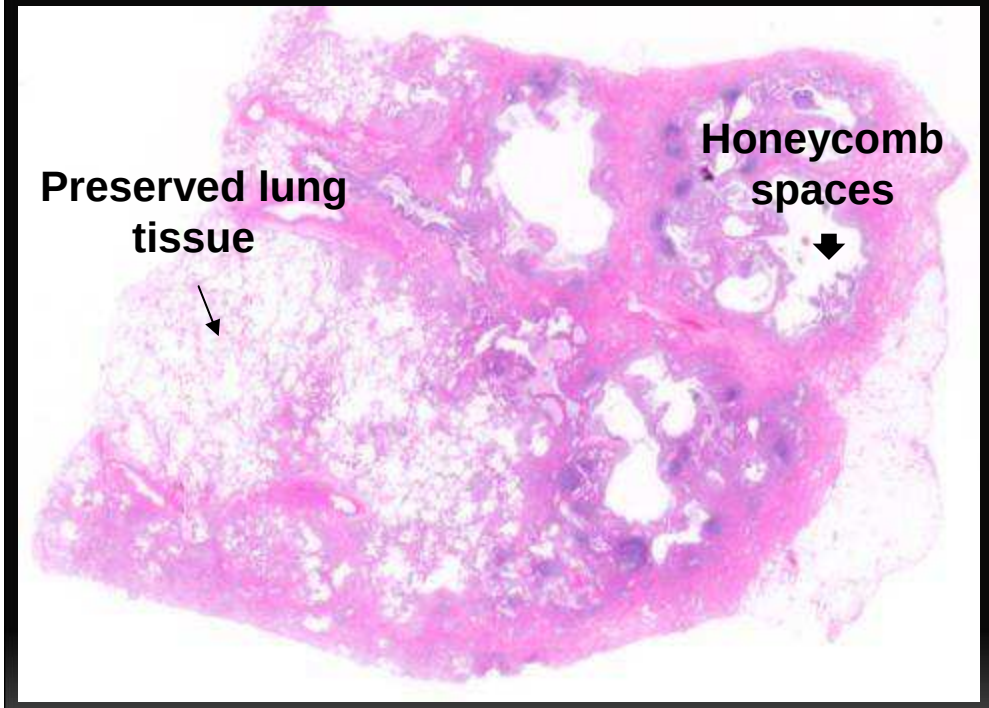
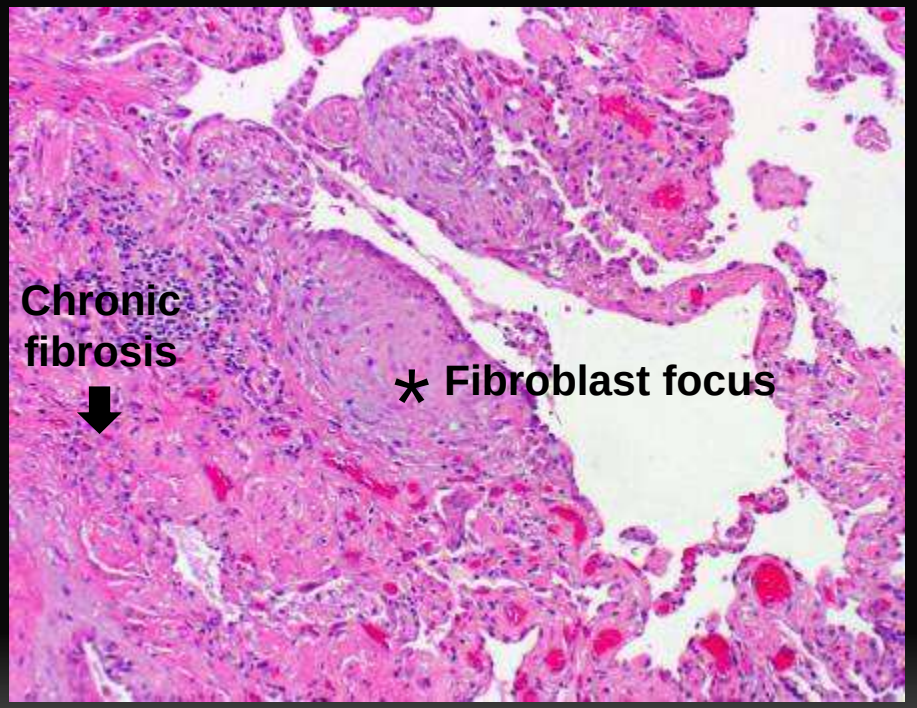
Idiopathic Pulmonary Fibrosis

Evidence Based Guidelines for Diagnosis and Management*

Surgical Lung Biopsy Specimens: Histopathology of UIP Pattern



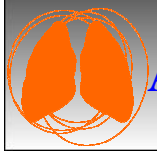


Diagnosis

- Is bronchoalveolar lavage required for the diagnosis of IPF?
- Can transbronchial lung biopsy accurately identify UIP?
- Are autoimmune serologies required for the diagnosis of IPF?
- Is a multidisciplinary approach important to the accurate diagnosis of IPF?

Exclusion of other known causes

- Careful history (including family history), physical examination focusing on co-morbidities, medication use, environmental exposures
- No validated tools. The questionnaire available through the ACCP may be of use
- It is of particular importance to evaluate patients thoroughly for possible chronic HP



Should BAL cellular analysis be performed in the diagnostic evaluation of suspected IPF?

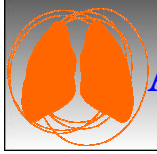
- In the evaluation of patients with suspected IPF, the most important application of BAL is in the exclusion of chronic HP; prominent lymphocytosis (>40%) should suggest the diagnosis.

- **Recommendation**: BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation; low quality evidence).
- **Values:** high value on the additional risk and cost and a low value on possible improved specificity of diagnosis.
- **Remarks:** this recommendation is only for BAL differential cell count ("cellular analysis"). It does not refer to the use of BAL in the evaluation of infection, malignancy, etc.

Should transbronchial lung biopsy be used in the evaluation of suspected IPF?

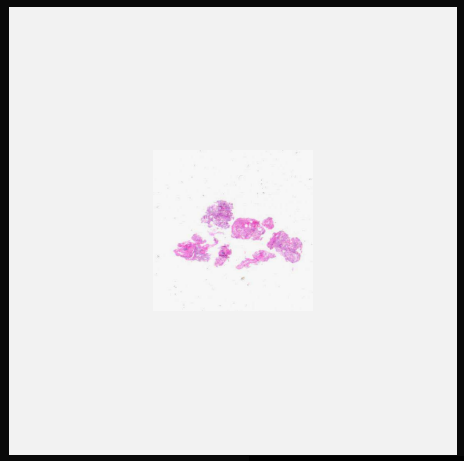
- *Transbronchial lung biopsy is useful in the evaluation of selected conditions (e.g. sarcoidosis). A UIP pattern on HRCT makes these conditions unlikely*

- ***Recommendation**: Transbronchial biopsy should not be used in the evaluation of IPF in the majority of patients, but may be appropriate in a minority (weak recommendation; low quality evidence).*
- ***Values:** high value on the additional morbidity in patients with IPF who will subsequently undergo SLB and low value on possible diagnostic specificity.*

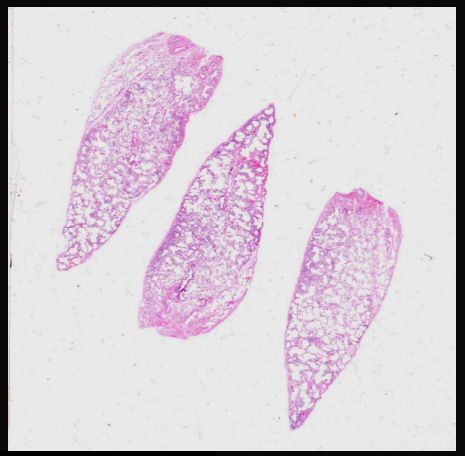


Lung biopsy to diagnose IPF: size does matter

TBBx

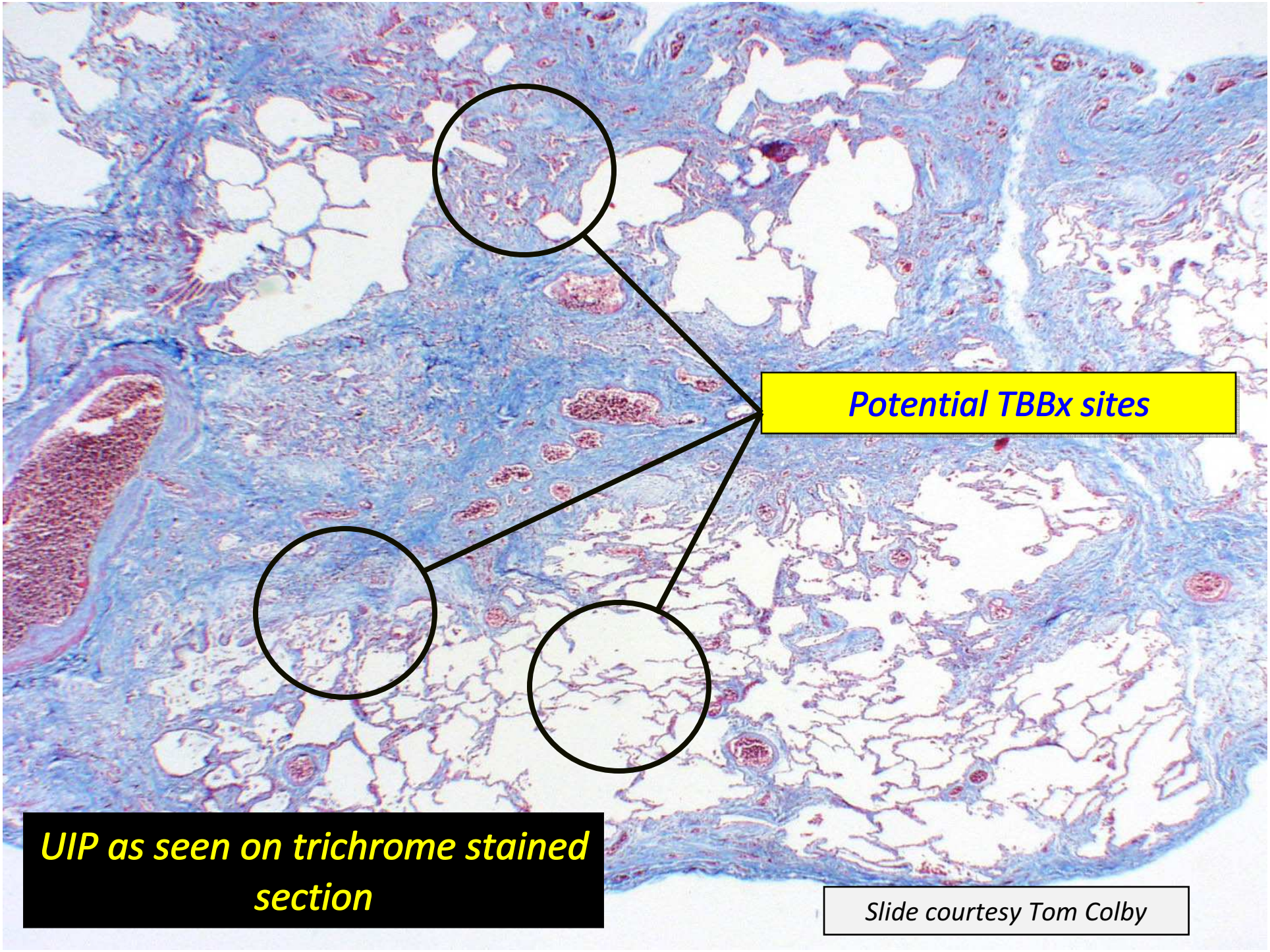


VATS Bx



1X Magnification

Slide courtesy Tom Colby


Potential TBBx sites
UIP as seen on trichrome stained section
Slide courtesy Tom Colby

Should serological testing for CTD be used in the evaluation of suspected IPF?

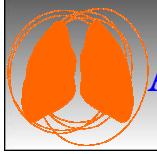
- *CTD can present with a UIP pattern.*
- *ILD can be the sole clinical manifestation of these conditions*
- *ILD can precede the overt manifestation of a specific CTD.*

- ***Recommendation:*** *Serological testing for CTD should be performed in the evaluation of IPF in the majority of patients, but may not be appropriate in a minority (weak recommendation; very low quality evidence).*
- ***Values:*** *High value on distinguishing CTD from IPF and low value on cost.*
- ***Remarks:*** *Serological evaluation should be performed even in the absence of signs or symptoms of CTD and should include RF, anti-CCP, and ANA titer and pattern. The routine use of other serological tests such as antisynthetase antibodies (e.g. Jo-1), creatine kinase and aldolase, Sjogren's antibodies (SS-A, SS-B), and scleroderma antibodies (scl-70, PM-1) is of unclear benefit, but may be helpful in selected cases.*

Should a MDD be used in the evaluation of suspected IPF?

- *Proper communication between the various disciplines involved in the diagnosis of IPF improves inter-observer agreement among experienced clinical experts as to the ultimate diagnosis*

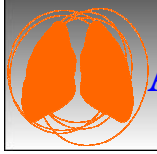
- ***Recommendation:*** *A MD approach should be used the evaluation of IPF (strong recommendation; low quality evidence).*
- ***Values:*** *High value on the accurate diagnosis of IPF and low value on the access to and availability of experts for MDD.*
- ***Remarks:*** *The accuracy of diagnosis improves through MDD.*
- *Timely referral to ILD experts is encouraged*



"Gold standard" for IPF diagnosis

The accuracy of the diagnosis of IPF increases with MDD between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD

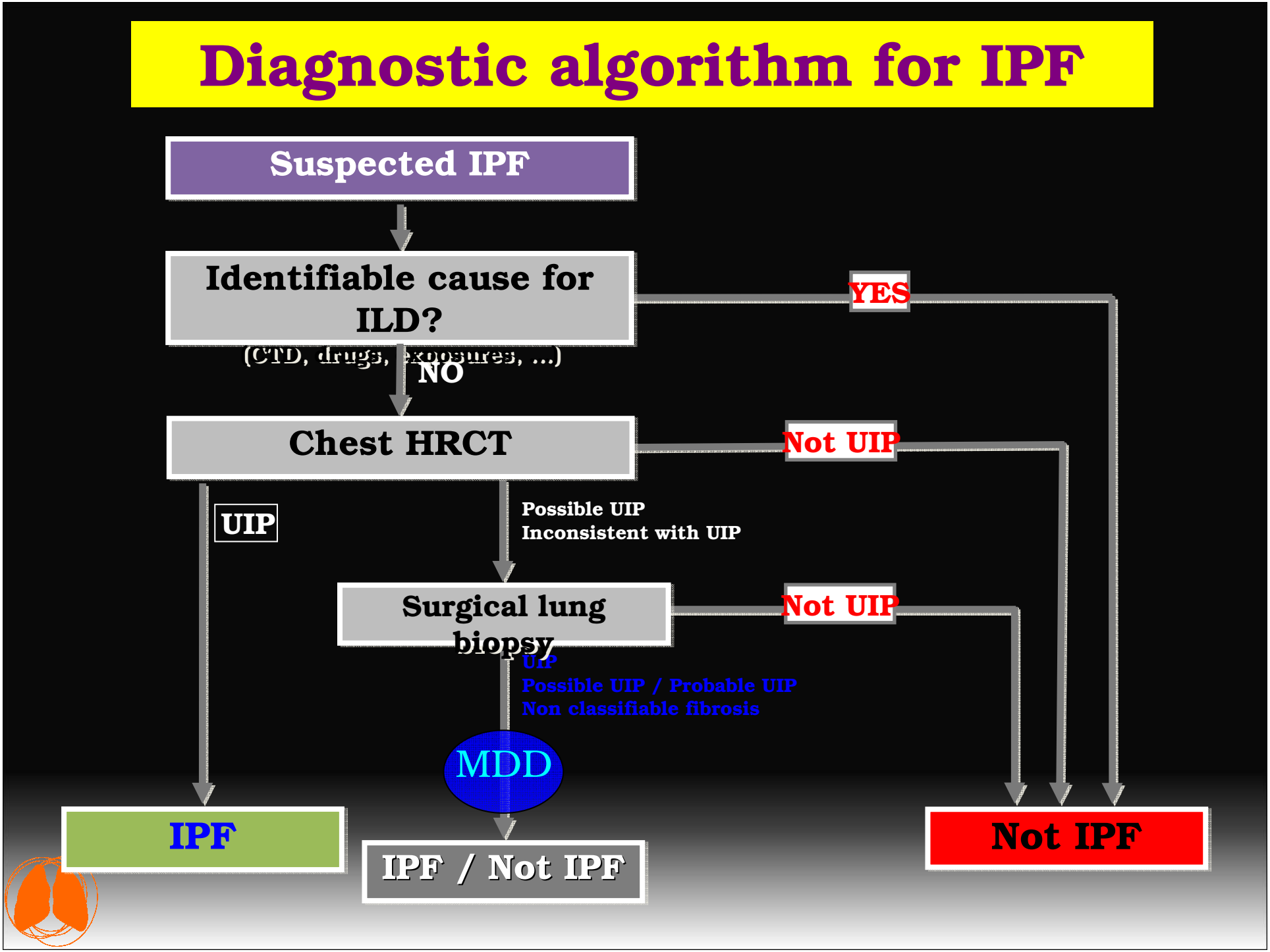
- *MDD should include discussions of the potential for sampling error. In cases with an inconsistent UIP HRCT pattern and UIP pattern clearly present on SLB, the possibility of a diagnosis of IPF still exists and clarification by MDD among ILD experts is indicated.*



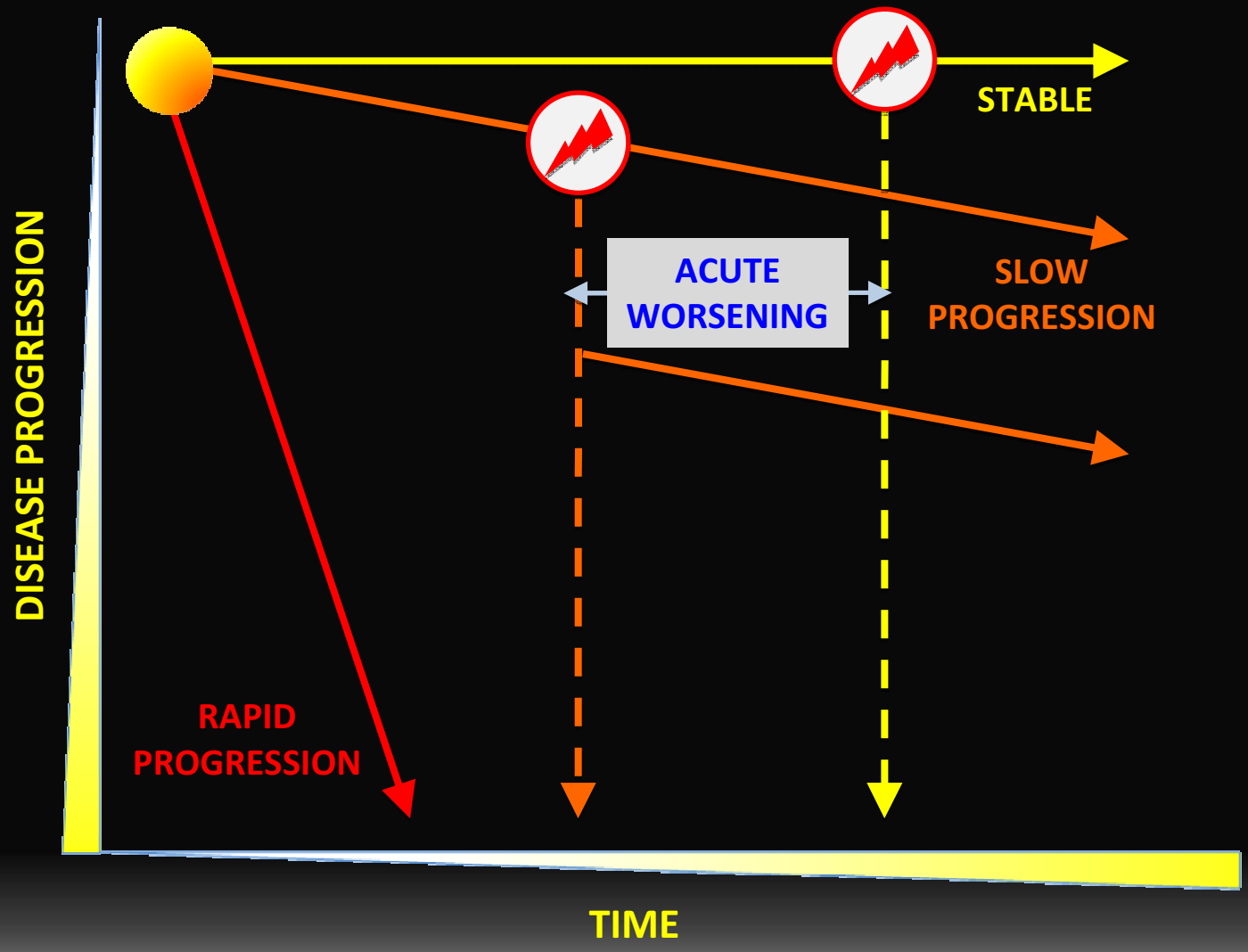
HRCT/SLB pairings

HRCT pattern	SLB pattern (when performed)	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	YES
	Not UIP	NO
Possible UIP	UIP Probable UIP	YES
	Possible UIP Non-classifiable fibrosis	Probable*
	Not UIP	NO
Inconsistent with UIP	UIP	Possible*
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	NO

Diagnostic algorithm for IPF



NATURAL HISTORY OF IPF



Am J Respir Crit Care Med 2011; 183: 788-824 (modified)

American Thoracic Society

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment

International Consensus Statement

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JULY 1999 AND BY THE ERS EXECUTIVE COMMITTEE, OCTOBER 1999

- *Corticosteroid* therapy (prednisone or equivalent) at a dose of 0.5 mg/kg (lean body weight [LBW]) per day orally for 4 wk, 0.25 mg/kg (LBW) per day for 8 wk, and then tapered to 0.125 mg/kg (ideal body weight [IBW]) daily or 0.25 mg/kg (LBW) every other day as initial therapy for IPF. (Lean body weight is the ideal weight expected for a patient of this age, sex, and height)
- *Azathioprine* at 2–3 mg/kg lean body weight (LBW) per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

or

- *Cyclophosphamide* at 2 mg/kg LBW per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

Am J Respir Crit Care Med 2000; 161: 646-664

RECOMMENDATIONS

A strong recommendation implies that most patients would want the recommended course of action.

A weak positive recommendation implies that the majority of patients would want the intervention, but many would not.

Specifically, a weak negative recommendation implies that the majority of patients would not want the intervention, but many would.

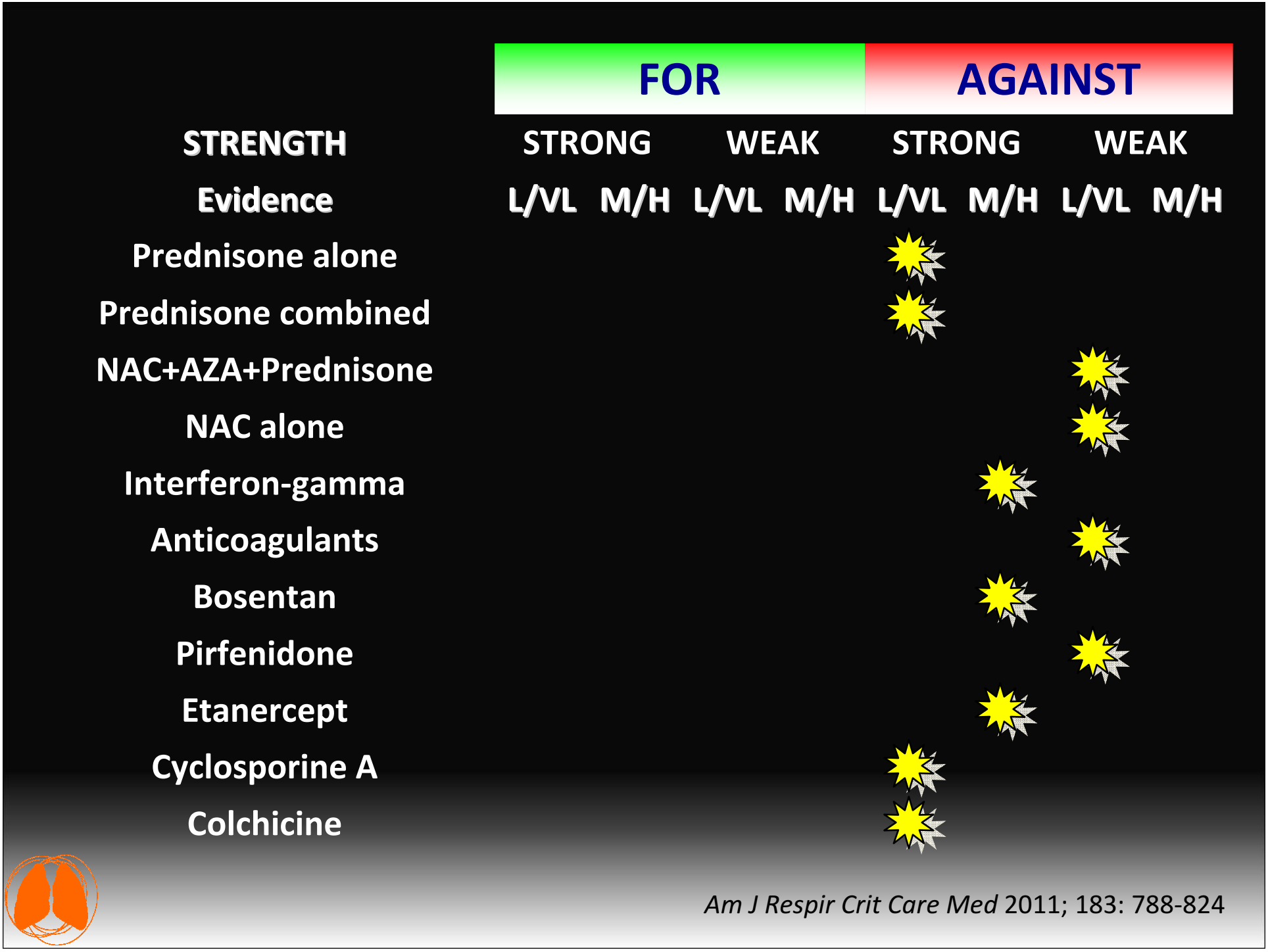
Therapies with a weak recommendation against their use may still be appropriate in selected patients.

Strong no

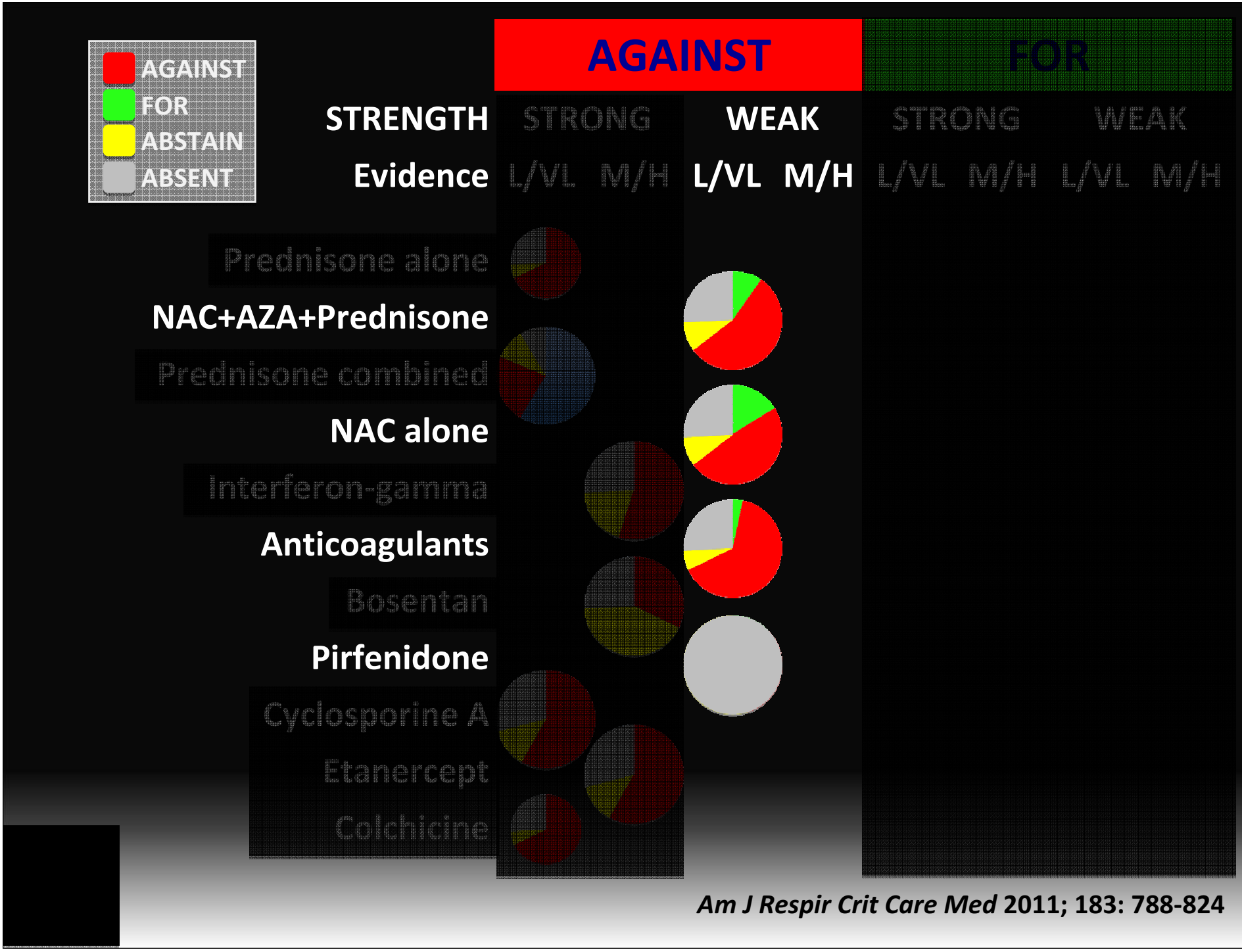
Implication for the patient: *most patients would not want the following treatment intervention and only a small proportion would.*

1) Monotherapy with corticosteroids
2) Colchicine
3) Cyclosporine A
4) Combined corticosteroid and immune modulator therapy
5) Interferon-γ
6) Bosentan
7) Etanercept

Raghu G. *Eur Respir J* 2011; 37: 743-6



Am J Respir Crit Care Med 2011; 183: 788-824



Am J Respir Crit Care Med 2011; 183: 788-824

Recommendations for the treatment of IPF

Treatment	Data quality	Recommendation	Strength
NAC alone	Low	No (5y/15n/3a)	Weak
P/AZA/NAC	Low	No (3y/17n/3a)	Weak
pirfenidone	Low-Moderate	No (4y/10n/17a)	Weak*
anticoagulation	Very low	No (1y/20n/2a/8A)	Weak
P/AZA	Low	No (21n/2a/8a)	Strong
Bosentan	Low	No (10n/13a/8A)	Strong
P/CYCLO	Very low	No (21n/2a/8a)	Strong
Colchicine	Very low	No (21n/2a/8A)	Strong
Corticosteroid	Very low	No (21n/2a/8A)	Strong
Cyclosporin A	Very low	No (18n/4a/9A)	Strong
Etanercept	Low	No (18n/4a/9A)	Strong
Interferon-γ-1a	High	No (17n/6a/8A)	Strong

y=YES, n=NO, a= ABSTAIN-COI, A=ABSENT

NON-PHARMACOLOGICAL THERAPIES

MODALITY	DATA QUALITY	RECOMENDATION	STRENGTH
LTOT	VERY LOW	YES (18y/4a/9A)	STRONG
REHABILITATION	LOW	YES (19y/3a/9A)	WEAK
MV AE-IPF	LOW	NO (2y/19n/2a/8A)	WEAK
LUNG TRANSPL	HIGH	YES (21y/1a/9A)	STRONG

y=YES, n=NO,a= ABSTAIN, A=ABSENT

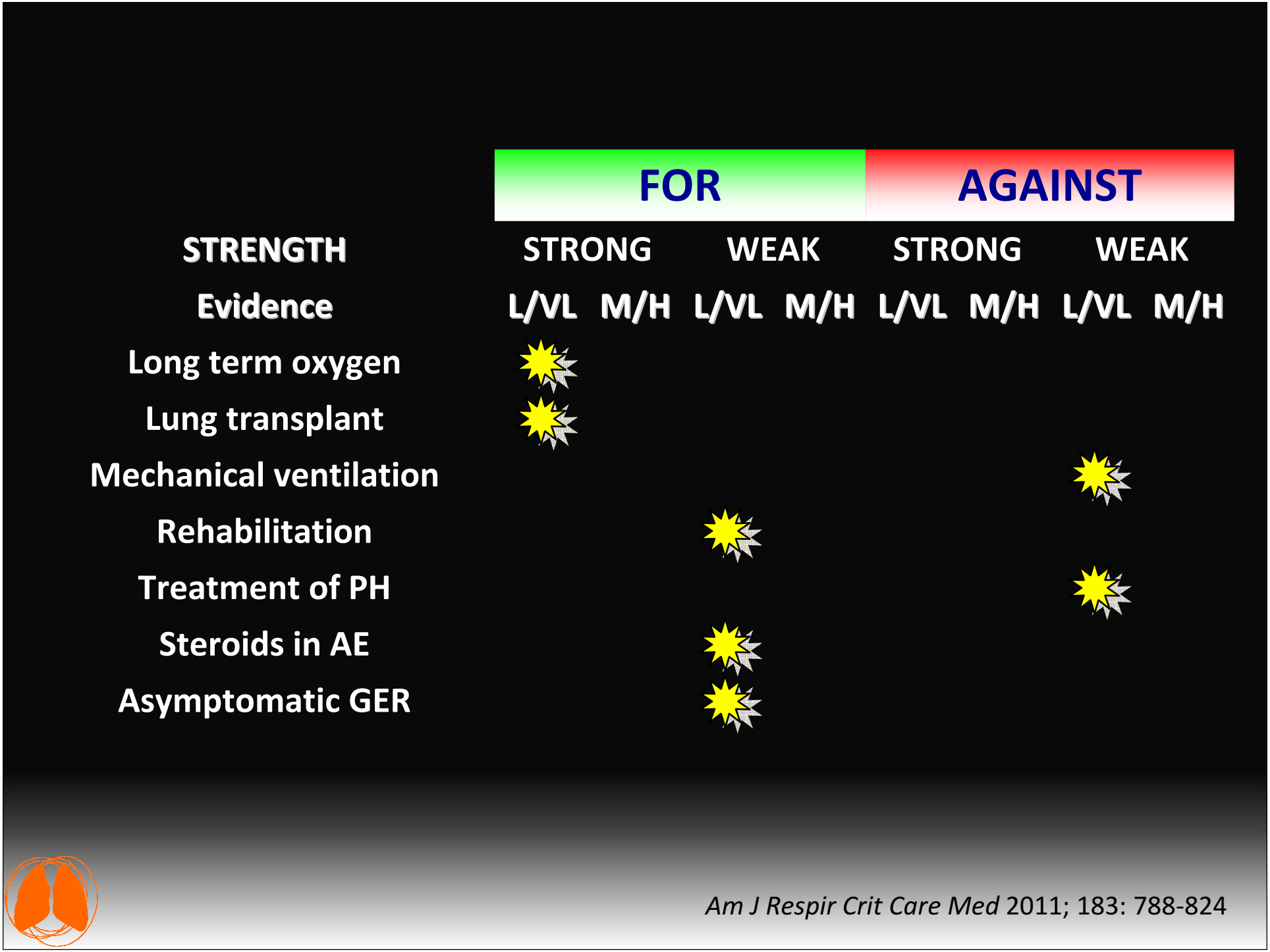
TREATMENT OF SELECTED COMPLICATIONS AND COMORBID CONDITIONS

- Should pulmonary hypertension be treated in patients with IPF?
- Should asymptomatic gastroesophageal reflux disease be medically treated in patients with IPF?
- Should patients with acute exacerbation of IPF be treated with corticosteroids?

TREATMENT OF SELECTED COMPLICATIONS AND COMORBID CONDITIONS

MODALITY	DATA QUALITY	RECOMENDATION	STRENGTH
PH-IPF	VERY LOW	NO (8y/14n/1a)	WEAK
GE REFLUX	VERY LOW	YES (14y/8n/8A)	WEAK
CORTICOIDS AE/IPF	VERY LOW	YES (14y/5n/1a/11A)	WEAK

y=YES, n=NO, a= ABSTAIN, A=ABSENT



Am J Respir Crit Care Med 2011; 183: 788-824

EVIDENCE-BASED TREATMENT RECOMMENDATIONS

Strong yes

Implication for the patient: *most patients would want the following treatment intervention and only a small proportion would not.*

1) Long-term oxygen therapy in patients with IPF demonstrating clinically significant resting hypoxaemia
2) Lung transplantation in appropriate patients

Weak yes

Implication for the patient: *a majority of patients would want the following treatment intervention, but many would not. Not using them may be a reasonable choice in a minority.*

1) Corticosteroids for acute exacerbation of IPF
2) Treatment of asymptomatic gastro-oesophageal reflux
3) Pulmonary rehabilitation

Therapies without a recommendation (newer data published subsequent to final formal face-to-face discussion):

- imatinib, sildenafil, BIBF 1120

Strong no

Implication for the patient: *most patients would not want the following treatment intervention and only a small proportion would.*

1) Monotherapy with corticosteroids
2) Colchicine
3) Cyclosporine A
4) Combined corticosteroid and immune modulator therapy
5) Interferon-γ
6) Bosentan
7) Etanercept

Weak no

Implication for the patient: *the majority of patients would not want the following treatment intervention, but many would, i.e. the following treatment interventions should not be used in the majority of patients with IPF, but may be a reasonable choice in a minority.*

1) Combined prednisone, azathioprine and NAC
2) Monotherapy with NAC
3) Anticoagulation
4) Pirfenidone
5) Pulmonary hypertension associated with IPF
6) Mechanical ventilation in patients with respiratory failure due to IPF

Raghu G. *Eur Respir J* 2011; 37: 743-6

Imatinib Treatment for Idiopathic Pulmonary Fibrosis

Randomized Placebo-controlled Trial Results

Craig E. Daniels[1], Joseph A. Lasky[2], Andrew H. Limper[1], Kathleen Mieras[1], Edith Gabor[2], Darrell R. Schroeder[1], and the Imatinib-IPF Study Investigators*

[1]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; and [2]Division of Pulmonary and Critical Care Medicine, Tulane University, New Orleans, Louisiana

In a randomized, placebo-controlled trial of patients with mild to moderate IPF followed for 96 weeks, **imatinib did not affect survival or lung function.**

Am J Respir Crit Care Med 2010; 181: 604-10

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

This study **did not show a benefit for sildenafil for the primary outcome**. The presence of some positive secondary outcomes creates clinical equipoise for further research.

N Engl J Med 2010; 363: 620-8

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2011 VOL. 365 NO. 12

Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Ulrich Costabel, M.D., Moises Selman, M.D., Dong Soon Kim, M.D., David M. Hansell, M.D., Andrew G. Nicholson, D.M., Kevin K. Brown, M.D., Kevin R. Flaherty, M.D., Paul W. Noble, M.D., Ganesh Raghu, M.D., Michèle Brun, M.Sc., Abhya Gupta, M.D., Nolwenn Juhel, M.Sc., Matthias Klüglich, M.D., and Roland M. du Bois, M.D.

In patients with idiopathic pulmonary fibrosis, BIBF 1120 at a dose of 150 mg twice daily, as compared with placebo, was associated with a **trend toward a reduction in the decline in lung function**, with fewer acute exacerbations and preserved quality of life.

N Engl J Med 2011; 365: 1079-87

FUTURE DIRECTIONS-I

- "Additional high-quality, prospective, controlled, clinical trials of new therapies for IPF are required.
- Successful treatment of IPF will require a combination of therapies targeting multiple pathways involved in fibroproliferation".

FUTURE DIRECTIONS-II

"Future clinical trials should incorporate endpoints of proven clinical value, utilize sophisticated study design and statistical methodology, investigate the impact of potential preventive measures *(e.g. treatment of gastroesophageal reflux),* and consider combinations of promising therapies that work through distinct mechanisms."

FUTURE DIRECTIONS-III

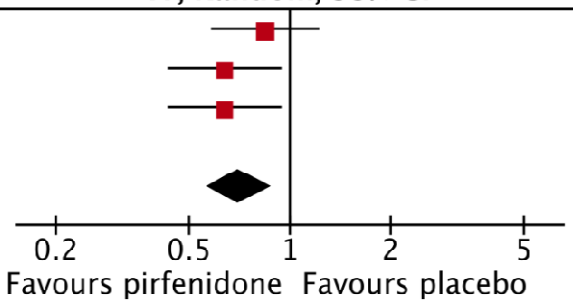
- "Genetic studies and preventive and regenerative strategies, including stem cell transplant-research and gene therapy, hold promise and should be aggressively pursued."

Meta-analysis of pirfenidone treatment effect

Event driven analysis of either 10% decline in FVC or all cause mortality
(Progression Free Survival)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Capacity 1	−0.17	0.19	35.7%	0.84 [0.58, 1.22]
Capacity 2	−0.45	0.2	32.2%	0.64 [0.43, 0.94]
Taniguchi 2010	−0.45	0.2	32.2%	0.64 [0.43, 0.94]
Total (95% CI)			**100.0%**	**0.70 [0.56, 0.88]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.40$, df = 2 (P = 0.50); $I^2 = 0\%$
Test for overall effect: Z = 3.09 (P = 0.002)



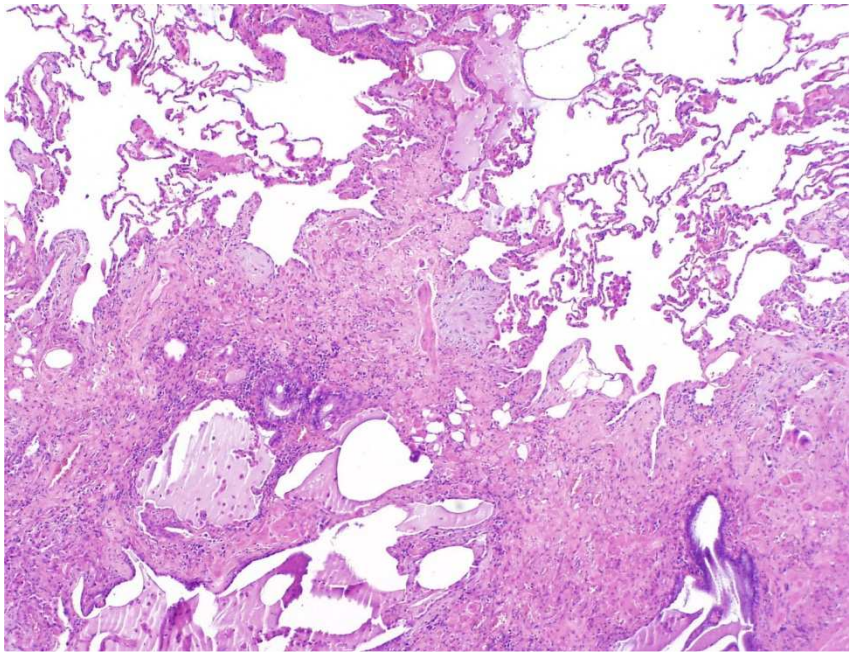
Based in part on unpublished data

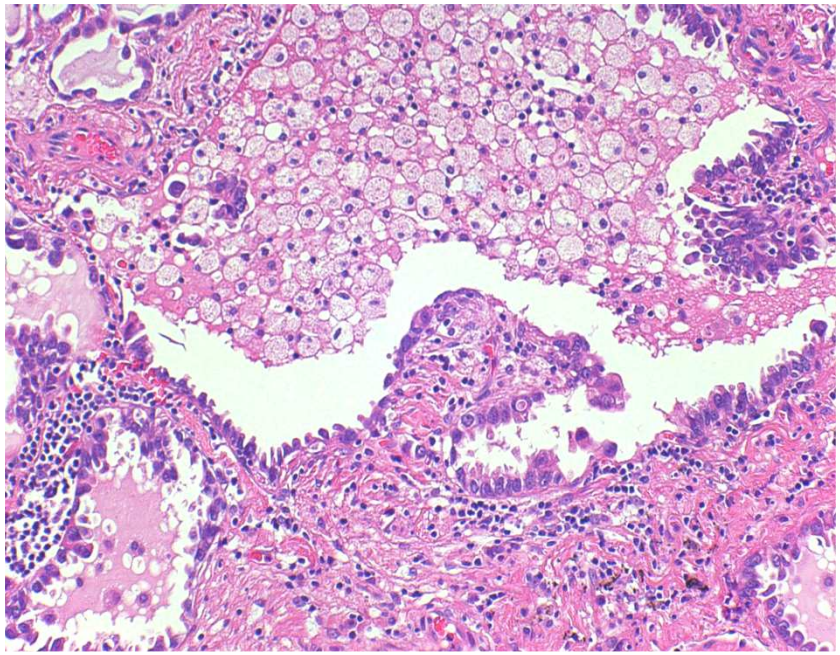
Spagnolo P, Del Giovane C, Luppi F, et al. Cochrane Database Syst Rev 2010;9:CD003134.

PERSPECTIVE

Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology

C. Vancheri*, M. Failla*, N. Crimi* and G. Raghu#





Eur Respir J 2010; 35: 496-504

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

N Engl J Med J 2009; 361: 947-57

Maintenance pemetrexed plus best supportive care versus

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL

Tudor Ciuleanu, Thomas Brodowicz, Christoph Zielinski, Joo Hang Kim, Maciej Krzakowski, Eckart Laack, Yi-Long Wu, Isabel Bover, Stephen Begbie, Valentina Tzekova, Branka Cucevic, Jose Rodrigues Pereira, Sung Hyun Yang, Jayaprakash Madhavan, Katherine P Sugarman, Patrick Peterson, William J John, Kurt Krejcy, Chandra P Belani

Lancet 2009; 374: 1432-40

Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non–Small-Cell Lung Cancer: AVAiL

Martin Reck, Joachim von Pawel, Petr Zatloukal, Rodryg Ramlau, Vera Gorbounova, Vera Hirsh, Natasha Leighl, Jörg Mezger, Venice Archer, Nicola Moore, and Christian Manegold

J Clin Oncol 2009; 27: 1227-34

Conclusions

- ✓ **Little quality evidence** supports the efficacy of "conventional" immunosuppressive therapy for IPF
- ✓ **Pirfenidone: The first EMEA** drug for IPF.
- ✓ Several compounds are in phase 3 clinical trials (BIBF)
- ✓ Participation in **trials** should be discussed as an option for all patients
- ✓ **Comorbidities** associated with IPF, such as cough, GERD, pulmonary hypertension, and sleep apnea should be treated.

Conclusions

- ✓ **Nonpharmacologic therapies are important**
  - *Pulmonary rehabilitation*
  - *Support groups*
  - *Recognition and treatment of depression*
  - *CPAP*
  - *Oxygen*
  - *End-of-life planning*
- ✓ **Patients should be referred early for transplant because of unpredictability of disease progression (eg, acute exacerbations).**

CONCLUSIONS

- Based on the evidence published to date, there is no proven pharmacological therapy for IPF.
- Continued, concerted efforts should be made by physicians, patients, and sponsors to pursue well-designed clinical trials aimed at improving outcomes, including quality of life, in patients with IPF.

Am J Respir Crit Care Med 2011; 183: 788-824