Idiopathic pulmonary fibrosis

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Interstitial lung disease

- Known cause or association:
  - Connective tissue diseases
  - Occupational causes
  - Drug side effects

- Idiopathic interstitial pneumonias

- Granulomatous:
  - Sarcoidosis
  - Hypersensitivity pneumonitis
  - Infections

- Other forms of ILD:
  - Lymphangioleiomyomatosis
  - Pulmonary Langerhans’ cell histiocytosis
  - Eosinophilic pneumonia
  - Pulmonary alveolar proteinosis

- Idiopathic pulmonary fibrosis
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Lymphocytic interstitial pneumonia

- Non-specific interstitial pneumonia
- Respiratory bronchiolitis-ILD
- Acute interstitial pneumonia
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:

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The authors thank Drs. Thomas Colby, David Hansell, Masanori Kitaichi, and William Travis for their critical review of the manuscript.
Idiopathic pulmonary fibrosis (IPF)

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

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

International Consensus Statement, AJRCCM 2000
Prognosis of IPF: Comparable to IPAH and advanced cancers

- Advanced lung cancer
- WHO Class IV IPAH: 6 months
- Advanced colorectal cancer
- Advanced breast cancer
- WHO Class III IPAH: 2.6 years
- IPF (UIP): 2.8 years
- WHO Class I - II IPAH: 4.9 years
- Ischemic cardiomyopathy

References:
Survival for UIP vs NSIP / Others

Idiopathic Pulmonary Fibrosis
Evidence Based Guidelines for Diagnosis and Management*

Definition: Idiopathic Pulmonary Fibrosis

- Specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause
- Occurring in adults; limited to the lungs
- Histologic and/or radiologic pattern of Usual Interstitial Pneumonia (UIP)
- Requirement
  - Exclusion of other forms of Idiopathic interstitial pneumonia and Interstitial lung diseases associated with environmental exposure, medication, or systemic disease

* Under Review (External)
Loss of the Lobule: Formation of the Fibroblastic Focus

UIP/IPF

Fibrosis

FF: Fibroblastic Focus
Idiopathic Pulmonary Fibrosis
Evidence Based Guidelines for Diagnosis and Management*

Clinical presentation
- Older age (6th – 7th 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 = 14-42.7/100,000

* Under Review (External)
Lung function testing in ILD

- Resting PFTs and TLCO measurement at presentation, provide a reasonable measure of disease severity.
- In IPF and fibrotic-NSIP, TLCO levels at presentation are a more reliable guide to outcome than other resting PFTs variables.
- A TLCO level of less than 40% is indicative of advanced disease in fibrotic idiopathic interstitial pneumonia.
- In IPF a fall from baseline of >10% in FVC or >15% in TLCO in the first 6–12 months identifies patients with a much higher mortality.
- Desaturation during the 6 MD at presentation is a stronger prognostic determinant in IPF than resting lung function.
POTENTIAL RISK FACTORS FOR IPF

- Cigarette Smoking
- Exposure to Commonly Prescribed Drugs
- Chronic Aspiration
- Environmental Factors
- Infectious Agents
- Genetic Predisposition to IPF.
- **Familial IPF (FPF)** is defined as at least two members of a primary biological family (parent, child, sibling) having clinical features of IPF that are confirmed histologically.
The Selman hypothesis

- Histopathologic, CT, treatment data……

- *Inflammation in UIP an epiphenomenon*

- Pathogenesis is epithelial/fibrotic

- Earliest event is epithelial damage, which induces……
Pathogenesis of UIP

**UIP**

- Multiple microscopic foci of injury occurring over many years
- Focal fibroblast proliferation (fibroblastic foci)
- Collagen deposition
- Progressive clinical course
- Death

? inflammation

Fibroblastic Foci

UIP pattern

Fibroblastic Foci

Courtesy T.V. Colby
• It remains unclear whether this pathology begins as UIP and remains unchanged with disease progression or

• begins as a cellular pattern that progresses to UIP over time.
A study by Flaherty sheds light on the natural history of UIP

This prospective study evaluated multiple open lung biopsies involving more than one lobe of the lung in 109 patients with IIPs.

• 47% of patients (mean age, 63.3 years) exhibited histopathology of UIP in all lobes.
• 26% of patients (mean age, 56.9 years) exhibited NSIP in at least one lobe and UIP in at least one lobe, indicating the presence of two different idiopathic pulmonary processes in the lung at the same time.
• 26% of patients (mean age, 53.1 years), NSIP was found in all lobes.
• Ten percent of patients had two or more biopsy specimens obtained from the same lobe; among these patients, 73% of the lobes had coexistent NSIP with UIP.

Flaherty KR et al Am J Respir Crit Care Med 2001
Idiopathic UIP and idiopathic NSIP, sharing a common clinical phenotype, form a spectrum of disease with a common pathogenesis.
A continuum that separates air from blood
- Type I and II epithelial cells
- Basement membrane
- Endothelial cells

Blood vessel

**Injury to epithelial and endothelial cells**
- Microinjury
- Larger area injury (macroinjury)
- Massive injury (acute exacerbation)

**Possible causes**
- Smoking
- Viruses
- Wood and metal dust
- Gastro-oesophageal reflux
- Oxidants
- Ageing

**Consequences of injury**
- Type II epithelial cell mediator release:
  - Growth factors
  - Metalloproteinases
  - Chemokines
  - Coagulation factor X
- Leakage of protein including coagulant factors into the airspace from the blood
**Figure d:**
- Organization of intra-alveolar exudate
- Migration of fibroblasts into the area of injury
- Accumulation of myofibroblasts from:
  - Resident fibroblasts
  - Circulating fibrocytes
  - Epithelial to mesenchymal cell transition

**Figure e:**
- Organizing clot incorporates into interstitium
- Accumulating myofibroblasts (fibroblastic foci)
- Failure of type II cells to restore integrity of epithelial cell layer

**Possible predispositions to type II cell dysfunction:**
- Viral inclusions (EBV and herpes)
- Gene variants (surfactant proteins C and A2, and telomerase)
- Irrevocable loss of basement membrane
Multiple molecular pathways and mechanisms for the elaboration and resorption of wounds

- **Injury**: Particulates, chemicals, autoimmune events, viruses

- **Activation**
  - Coagulation cascades
  - Oxidant-antioxidant cascades
  - Fibrocytes, inflammatory cells
  - Th1/Th2 immune cascades

- **Imbalance**
  - Profibrotic mediators: CTGF, TGF-β, PDGF, thrombia, FXa
  - Antifibrotic mediators: PGE₂, IFN-γ

- **Endothelium Epithelium Fibroblasts**
  - EMT, transdifferentiation, proliferation, extracellular matrix production, apoptosis

- **Fibrosis**: Excessive extracellular matrix deposition
Herpes viruses, microaspiration, cigarette smoke, short telomeres, others

Injury  Apoptosis

Alveolar epithelium

Proliferation, migration, activation

Dysregulation of developmental pathways

CXCL12

TGF-β

Fibrocytes

Myofibroblast focus

EMT

TGF-β

PDGF

Resident fibroblasts

Extracellular matrix accumulation

Selman 2011
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. Duddon, 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
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

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

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)
GRADE approach

- Identifies all outcomes that are important to patients
- Differentiates the critical outcomes from the important (but not critical) ones
- Recommendations depend on the evidence for patient important outcomes and the quality of evidence for each of those outcomes.
- 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”. 
## GRADING the evidence

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable</td>
<td>The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely weak recommendations are warranted.</td>
</tr>
<tr>
<td>Quality of the evidence</td>
<td>The higher the quality of evidence, the more likely is a strong recommendation.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak recommendation warranted.</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention - that is, the more resources consumed - the less likely is a strong recommendation warranted.</td>
</tr>
</tbody>
</table>
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.
“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

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

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

# HRCT Criteria for UIP Pattern

<table>
<thead>
<tr>
<th>UIP (all <strong>four</strong> features)</th>
<th>Possible UIP (all three features)</th>
<th>Inconsistent with UIP (any of the seven features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural, basal predominance</td>
<td>Subpleural, basal predominance</td>
<td>Upper or mid lung predominance</td>
</tr>
<tr>
<td>Reticular abnormality</td>
<td>Reticular abnormality</td>
<td>Peribronchovascular predominance</td>
</tr>
<tr>
<td><strong>Honeycombing</strong> with or without traction bronchiectasis</td>
<td>Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td>Extensive ground glass abnormality (extent &gt; reticular abnormality)</td>
</tr>
<tr>
<td>Absence of features listed as inconsistent with UIP pattern (see third column)</td>
<td></td>
<td>Profuse micronodules (bilateral, predominantly upper lobes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discrete cysts (multiple, bilateral, away from areas of honeycombing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diffuse mosaic attenuation / air-trapping (bilateral, in 3 or more lobes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consolidation in bronchopulmonary segment(s)/lobe(s)</td>
</tr>
</tbody>
</table>

*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)

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

* Under Review (External)
<table>
<thead>
<tr>
<th><strong>UIP</strong> (all <strong>four</strong> criteria)</th>
<th><strong>Probable UIP</strong> (all <strong>three</strong> criteria)</th>
<th><strong>Possible UIP</strong> (any of the six criteria)</th>
<th><strong>Not UIP</strong> (any of the six criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a predominantly subpleural/paraseptal distribution</td>
<td>□ Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a subpleural/paraseptal distribution</td>
<td>□ Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation</td>
<td>□ Hyaline membranes</td>
</tr>
<tr>
<td>□ Presence of patchy involvement of lung parenchyma by fibrosis</td>
<td>□ Absence of either patchy involvement or fibroblastic foci, but not both</td>
<td>□ Absence of other criteria for UIP (see UIP pattern column)</td>
<td>□ Organizing pneumonia</td>
</tr>
<tr>
<td>□ Presence of fibroblast foci</td>
<td>□ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>□ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>□ Marked interstitial inflammatory cell infiltrate away from honeycombing</td>
</tr>
<tr>
<td>□ Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)</td>
<td>□ Honeycomb changes only</td>
<td>□ Honeycomb changes only</td>
<td>□ Predominant airway centered changes</td>
</tr>
<tr>
<td>OR</td>
<td>□ Honeycomb changes only</td>
<td>□ Honeycomb changes only</td>
<td>□ Other features suggestive of an alternate diagnosis</td>
</tr>
<tr>
<td>□ Honeycomb changes only</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Am J Respir Crit Care Med 2011; 183: 788-824*
Idiopathic Pulmonary Fibrosis
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Surgical Lung Biopsy Specimens: Histopathology of UIP Pattern

* Under Review (External)
HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

PRESERVED LUNG

HONEYCOMB

Am J Respir Crit Care Med 2011; 183: 788-824
HISTOPATHOLOGICAL CRITERIA FOR 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?
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?
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.
<table>
<thead>
<tr>
<th>HRCT Pattern</th>
<th>Surgical Lung Biopsy Pattern (when performed)</th>
<th>Diagnosis of IPF?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UIP</strong></td>
<td><strong>UIP</strong> Probable UIP Possible UIP Non-classifiable fibrosis</td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
<tr>
<td><strong>Possible UIP</strong></td>
<td><strong>UIP</strong> Probable UIP Possible UIP Non-classifiable fibrosis</td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td></td>
<td>Probable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
<tr>
<td><strong>Inconsistent with UIP</strong></td>
<td><strong>UIP</strong> Probable UIP Possible UIP Non-classifiable fibrosis</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>Probable UIP Possible UIP Non-classifiable fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not UIP</td>
<td>No</td>
</tr>
</tbody>
</table>

*UIP = usual interstitial pneumonia*
“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.
Diagnostic algorithm for IPF

Suspected IPF

Identifiable cause for ILD?
(CTD, drugs, exposures, ...)

Identifiable cause for ILD? YES
(NOT/UIP)

Identifiable cause for ILD? NO
(Chest HRCT)

Chest HRCT NOT UIP
Possible UIP / Probable UIP
Inconsistent with UIP
Surgical lung biopsy

Surgical lung biopsy NOT UIP
Possible UIP / Probable UIP
Non classifiable fibrosis
MDD
IPF
IPF / Not IPF

Identifiable cause for ILD? NO
MDD
IPF
IPF / Not IPF

Not UIP

Identifiable cause for ILD? NOT/IPF
Not UIP

Identifiable cause for ILD? NOT/IPF
Not IPF
NATURAL HISTORY OF IPF

DISEASE PROGRESSION

TIME

RAPID PROGRESSION

ACUTE WORSENING

SLOW PROGRESSION

STABLE

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

A change in absolute FVC of 10%, with or without a concomitant change in DLco, or a change in absolute DLco of 15%, with or without a concomitant change in FVC, is a surrogate marker of mortality and is evidence of disease progression, in the absence of an alternative explanation.

Under review – external reviewers
Recommendation

The committee recommends that FVC and DLco measurements be performed during routine monitoring, in accordance with ATS standards, to follow trends.

Under review – external reviewers
Emphysema plus fibrosis

- Spurious preservation of lung volumes
- Devastating reduction in gas transfer
- In this scenario, the patient may die with normal or mildly reduced lung volumes
Recommendation

The physiologic effect ...of emphysema on ...serial changes in pulmonary function....is likely to be a confounder. Thus, changes in FVC may not be reliable as an indicator of disease progression. Under these circumstances, a combination of FVC and DLco may be useful in assessing progression of disease.

Under review – external reviewers
Recommendation

The optimal time interval for repetition of FVC and DLco has not been formally investigated. **It is appropriate to routinely monitor ... at three to six monthly intervals** ...(but)...a flexible approach...is required with a lower threshold...(for repeat FVC and DLco)... in the presence of progressive dyspnoea

*Under review – external reviewers*
Recommendation

Longitudinal measurements of other clinical and physiological variables (e.g. TLC, P(A-a)O2, 6 minute walk test variables) is not recommended for routine use in monitoring

Under review – external reviewers
Diagnostic Criteria

- Previous or concurrent diagnosis of IPF
- Unexplained worsening or development of dyspnea within 30 days
- HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background consistent with UIP pattern
- No evidence of pulmonary infection by endotracheal aspirate or BAL
- Exclusion of alternative causes, including the following:
  - Left heart failure
  - Pulmonary embolism
  - Identifiable cause of acute lung injury
1. Acute exacerbations of IPF represent a distinct, pathobiological manifestation of the primary disease process, characterized by idiopathic lung injury.

2. Acute exacerbations of IPF may represent clinically occult but biologically distinct conditions that go undiagnosed (e.g., viral infection, aspiration).

3. Acute exacerbations of IPF may be the sequelae of an acute direct stress to the lung, with a subsequent acceleration of the already abnormal fibroproliferative process intrinsic to IPF.
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
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
Categories

- Strong positive
- Weak positive
- Weak negative
- Strong negative
Three or the four categories obvious

- **Strong positive**: routine treatment/best current treatment/virtually all patients would want the treatment if informed to physician levels

- **Strong negative**: the treatment should not be used and if used, you are flagrantly violating guidelines
“Weak” = “no definitive conclusion”

- There is some evidence for an intervention but not yet enough to view it as routine

- Weak positive = the majority of patients would want the intervention, but it is not routine/ appropriate in all cases.
The problem is “weak negative”

- Sometimes no means yes
- There are data to suggest that an intervention might be effective.
- However, based upon cost, toxicity, strength of evidence, the treatment should not be used in the majority of cases but in a selected minority
- Of course, this could be a large minority
Considering medical treatment for typical IPF
Strong negatives

- Corticosteroid monotherapy
- Colchicine
- Cyclosporine A
- Combined steroid/immunosuppression
- Bosentan
- Etanercept
There are no strong positives
There are no weak positives which is an interesting comment on the mind set of the committee

This implies that the majority of patients would not want a speculative cheap non-toxic treatment in IPF, based on some supportive data
Weak negatives

- Combined acetylcysteine/ azathioprine/ prednisolone
- Acetylcysteine monotherapy
- Anticoagulation
- Pirfenidone
<table>
<thead>
<tr>
<th>Evidence</th>
<th>Long term oxygen</th>
<th>Lung transplant</th>
<th>Mechanical ventilation</th>
<th>Rehabilitation</th>
<th>Treatment of PH</th>
<th>Steroids in AE</th>
<th>Asymptomatic GER</th>
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<tbody>
<tr>
<td>STRENGTH</td>
<td></td>
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<td>STRONG</td>
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<td>M/H</td>
<td>L/V</td>
<td>M/H</td>
<td>L/V</td>
<td>M/H</td>
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<td>WEAK</td>
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<td>M/H</td>
<td>L/V</td>
<td>M/H</td>
<td>L/V</td>
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</tbody>
</table>

*Am J Respir Crit Care Med 2011; 183: 788-824*
• 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.
<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (CAPACITY 1)</td>
<td>344</td>
<td>Change in FVC</td>
<td>Negative</td>
</tr>
<tr>
<td>Pirfenidone (CAPACITY 2)</td>
<td>435</td>
<td>Change in FVC</td>
<td>Positive</td>
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<tr>
<td>Pirfenidone (Ogura)</td>
<td>275</td>
<td>Change in FVC</td>
<td>Positive</td>
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<tr>
<td>Pirfenidone (Azuma)</td>
<td>107</td>
<td>Exercise gas exchange</td>
<td>Stopped</td>
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<tr>
<td>Pirfenidone (Nagai)</td>
<td>8</td>
<td>Overall survival, PFTs, CT score</td>
<td>Inconclusive (not RCT)</td>
</tr>
<tr>
<td>Pirfenidone (Raghu)</td>
<td>54</td>
<td>Overall survival and change in PFTs</td>
<td>Inconclusive (not RCT)</td>
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<tr>
<td>Octreotide</td>
<td>25</td>
<td>Multiple</td>
<td>Not reported</td>
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<tr>
<td>Imatinib Mesylate</td>
<td>120</td>
<td>Progression-free survival</td>
<td>Negative</td>
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<tr>
<td>Bosentan (BUILD 1 and 2)</td>
<td>132</td>
<td>Change in 6MW</td>
<td>Negative</td>
</tr>
<tr>
<td>Bosentan (BUILD-3)</td>
<td>616</td>
<td>Progression-free survival or death</td>
<td>Negative</td>
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<td>Etanercept</td>
<td>100</td>
<td>Change in DL$_{CO}$, FVC</td>
<td>Negative</td>
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<tr>
<td>Anticoagulation</td>
<td>56</td>
<td>Survival</td>
<td>Positive</td>
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<tr>
<td>N-acetylcysteine (NAC) (IFIGENIA)</td>
<td>184</td>
<td>Change in FVC, DL$_{CO}$</td>
<td>Positive</td>
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<tr>
<td>Interferon-gamma (INSPIRE)</td>
<td>826</td>
<td>Survival time</td>
<td>Negative</td>
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<tr>
<td>Interferon-gamma (GIPF-001)</td>
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<td>Progression-free survival</td>
<td>Negative</td>
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<tr>
<td>Interferon-beta (1999)</td>
<td>167</td>
<td>Progression-free survival time</td>
<td>Negative</td>
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<tr>
<td>Sildenafil (STEP)</td>
<td>180</td>
<td>Change in 6MWD</td>
<td>Negative</td>
</tr>
</tbody>
</table>
We must continue to search for new therapies, using an oncological model.

We need to reconcile the oncological model (treating multiple mechanisms) and the pharmaceutical model (the search for a miracle drug).
Pirfenidone

- Inhibits TGF-beta, reduces synthesis of collagen I & III, reduces TNF-alpha synthesis.

- True pleiotrophism. Anti-inflammatory, anti-oxidant AND antifibrotic effects

- Historical studies (Raghu, Nagai) suggestive but not controlled. Prevalent disease a particular confounder.
Non-steroid agents for idiopathic pulmonary fibrosis (Review)

The summary of the three estimates (314 pts) suggests that pirfenidone reduces the risk of progression by **30%** (HR 0.70, 95% CI 0.56 to 0.88).
• Well-known pharmacological target in oncology

• Triple inhibitor of tyrosine kinase receptors.

• Was able to prevent the development of lung fibrosis in a bleomycin rat model.
Phase II TOMORROW STUDY:

- 12 mo treatment with BIBF resulted in a clinically important reduction in the rate of decline in lung function in pts with IPF compared to placebo.

- The 150mg twice daily dose provided a 68% reduction in the rate of decline of FVC compared to placebo.

- Acute exacerbations decline to 2.3% compared to 13.8% in placebo.
Referral for lung transplantation in patients with IPF

• The following apply only to patients who fulfill established selection criteria for transplant, thus generally excluding those over the age of 65 years and/or those with significant comorbidity.

• Referral to a transplant centre should be made if the disease is advanced (TLCO < 40% pr) or progressive >10%-15% decline in FVC during 6 months of follow-up).
Lung Transplantation for Idiopathic Pulmonary Fibrosis

David P. Mason, MD, Mariano E. Brizzio, MD, Joan M. Alster, MS, Ann M. McNeill, RN, Sudish C. Murthy, MD, PhD, Marie M. Budev, DO, Atul C. Mehta, MD, Omar A. Minai, MD, Gösta B. Pettersson, MD, PhD, and Eugene H. Blackstone, MD

Departments of Thoracic and Cardiovascular Surgery, Quantitative Health Sciences, and Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic, Cleveland, Ohio


Survival estimates after transplantation for IPF were 95%, 73%, 56%, and 44% at 30 days and 1, 3, and 5 years, somewhat worse than for matched non-IPF patients
Intratracheal Transplantation of Alveolar Type II Cells Reverses Bleomycin-induced Lung Fibrosis

Anna Serrano-Mollar¹,², Maria Nacher¹, Gemma Gay-Jordi¹, Daniel Closa¹, Antoni Xaubet²-³, and Oriol Bulbena¹


This study demonstrates the potential role of alveolar type II cell transplantation in designing future therapies for lung fibrosis.
Stem Cells for Lung Disease

Michael R. Loebinger and Sam M. Janes

Chest 2007;132;279-285