New guidelines for the diagnosis of Idiopathic Pulmonary Fibrosis

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Conflicts of Interest

I declare

NO conflicts of interest
CLASSIFICATION OF ILDs

ACUTE
[AIP, EAA, VASCULITIS]

SUBACUTE
[DIP, COP, EAA]

EPISODIC
[EP, EAA, VASCULITIS, COP]

CHRONIC WITH SYSTEMIC DISEASE
[CVD, VASCULITIS, SARCOIDOSIS, TS, IBD, HES, COP*, LCH*]

CHRONIC WITHOUT SYSTEMIC DISEASE
(Idiopathic interstitial Pneumonias, PAP, PVOD, IPHsid)

CHRONIC
KNOWN ETIOLOGY
(Environmental, Occupational, Drugs)
Estimated Relative Distribution of Specific ILDs in the US

- Sarcoidosis, 20%
- CTD-ILD, 20%
- Chronic hypersensitivity pneumonitis, 20%
- Idiopathic pulmonary fibrosis, 20%
- Other ILDs, 10%
- Pneumocystis, 10%
Idiopathic interstitial pneumonias (IIP)

- Idiopathic pulmonary fibrosis/Usual interstitial pneumonia (IPF/UIP)
- Nonspecific interstitial pneumonia (NSIP)
- Cryptogenic organizing pneumonia (COP/OP)
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- Acute interstitial Pneumonia (AIP)
- RARE IIPs: LIP, PPFE

- 55% Idiopathic pulmonary fibrosis/Usual interstitial pneumonia (IPF/UIP)
- 25% Nonspecific interstitial pneumonia (NSIP)
- 3% Cryptogenic organizing pneumonia (COP/OP)
- 3% Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- 15% Acute interstitial Pneumonia (AIP)
- 3% RARE IIPs: LIP, PPFE
Diffuse Parenchymal Lung Disease (DPLD)

- DPLD of known cause, e.g., drugs or association, e.g., collagen vascular disease
- Idiopathic interstitial pneumonias
  - Idiopathic pulmonary fibrosis
  - Desquamative interstitial pneumonia
  - Acute interstitial pneumonia
  - Nonspecific interstitial pneumonia (provisional)
- Granulomatous DPLD, e.g., sarcoidosis
- Other forms of DPLD, e.g., LAM, HX, etc
  - IIP other than idiopathic pulmonary fibrosis
    - Respiratory bronchiolitis interstitial lung disease
    - Cryptogenic organizing pneumonia
    - Lymphocytic interstitial pneumonia
    - Pleuroparenchymal fibroelastosis

10-20% UNCLASSIFIABLE

The overlap in longitudinal disease behavior between IPF and other progressive fibrotic disorders.
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. Duddien, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schönemann, 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
2011 ATS/ERS Diagnostic Criteria for IPF

Exclusion of known causes of ILD*

AND

UIP pattern on HRCT without surgical biopsy

OR

Definite/possible UIP pattern on HRCT with a surgical lung biopsy showing definite/probable UIP

*also known as diffuse parenchymal lung disease, DPLD
Most common first symptoms of ILD
(600 US residents responded to the survey)

77% Shortness of breath
53% Cough
38% Fatigue

Patients diagnosed with IPF
(47% of respondents)

Median time to diagnosis: 7 months
For 28% of patients, the diagnostic process took over 2 years

Median number of physician visit: 3
14% of patients saw more than 6 physicians

56% of patients were initially misdiagnosed
most frequent misdiagnoses: asthma, pneumonia, bronchitis and allergies.
Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper


This Review provides an updated approach to the diagnosis of idiopathic pulmonary fibrosis (IPF), based on a systematic search of the medical literature and the expert opinion of members of the Fleischner Society. A checklist is provided for the clinical evaluation of patients with suspected interstitial pneumonia (UIP). The role of CT is expanded to permit diagnosis of IPF without surgical lung biopsy in select cases when CT shows a probable UIP pattern. Additional investigations, including surgical lung biopsy, should be considered in patients with either clinical or CT findings that are indeterminate for IPF. A stepwise, systematic approach is particularly important when deciding to perform additional diagnostic assessments. Establishing a working diagnosis of IPF if lung tissue is unavailable. A working diagnosis of IPF should be reviewed at regular intervals since the diagnosis might change as new data are presented to establish confident and working diagnoses of IPF.

Introduction

The approval of medical treatments for idiopathic pulmonary fibrosis (IPF) marks a new era in addressing this deadly disease: offering hope to patients, their physicians, a clearer path forward for comparison of therapies, and potential for new biological insights. This new approach offers clinicians the opportunity to rethink approaches to diagnosis. The diagnostic criteria for IPF, published by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (LATA) in 2011 have been crucial for defining IPF and for guiding appropriate recruitment for new clinical trials. In turn, these trials, with large numbers of well-characterised patients, have provided remarkable new clinically relevant information about disease progression and longitudinal behaviour. The specific inclusion and exclusion criteria used in these studies also highlight the limitations of current diagnostic guidelines, and indicated opportunities for improvement.

The diagnosis of IPF requires the collaboration of multiple specialists, the ability to interpret and communicate complex clinical data patterns, and to integrate clinical findings or sometimes conflicting information. This process requires the ability to interpret the history and physical exam in the context of the patient’s clinical condition. The radiologist interprets the pattern present on high-resolution CT images of the chest and, if needed, the pathologist interprets the histopathological pattern seen in biopsy samples. All the information gained must be shared in a common language to enable clinical decision making. Since so-called classic clinical stories and patterns are uncommon, some degree of clinical uncertainty is often present, and acknowledgment of this uncertainty and a clear plan to address it are essential.

For this Review, we identified specific questions pertaining to the diagnosis of IPF (panel 1), and did a search of the medical literature to identify evidence related to the topics identified and that had been published after the 2011 ATS/ERS/JRS/LATA guidelines. Using this research and the expert opinion of members of the Fleischner Society, we provide IPF diagnostic criteria that we believe will be useful for clinicians, clinical trialists, trial sponsors, and other interested groups.

Systematic review

An international multidisciplinary committee, including 17 members of the Fleischner Society with expertise in interstitial lung disease (ILD) and evidence-based medicine (eight pulmonologists, six radiologists, and three pathologists), and a medical librarian expert (SLK), developed the key questions believed to be important for the diagnosis of IPF (panel 1). Several face-to-face meetings were held, in addition to monthly conference calls. We did a literature search with the assistance of a medical librarian (search strategy and selection criteria and appendix). The committee was divided into subgroups assigned to specific topics.

Key messages

- A confident diagnosis of IPF (idiopathic pulmonary fibrosis) can be made in the correct clinical context when CT imaging shows a pattern of typical or probable UIP (usual interstitial pneumonia).
- If the clinical context is indeterminate for IPF, or the CT pattern is not indicative of typical or probable UIP, biopsy should be considered to confirm the presence of an histological pattern, and a confident diagnosis of IPF could then be made on the basis of a multidisciplinary evaluation.
- If diagnostic tissue is not available, a working diagnosis of IPF could be made after a careful multidisciplinary evaluation.
- All patients with an IPF diagnosis, particularly those with a working diagnosis, should have this diagnosis reviewed at regular intervals.
Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline


This official clinical practice guideline of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) was approved by the ATS, JRS, and ALAT May 2018, and the ERS June 2018
ΕΡΩΤΗΣΕΙΣ-ΠΡΟΤΑΣΕΙΣ ΟΔΗΓΙΩΝ

• ΓΕΝΙΚΕΣ-MOTHERHOOD

• EVIDENCE BASED
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Number of authors</td>
<td>34</td>
<td>17</td>
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<tr>
<td>Overlapping authors</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Endorsing scientific societies</td>
<td>Multiple</td>
<td>Single</td>
</tr>
<tr>
<td>Multidisciplinary nature</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Question-based structure</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systematic search of the literature</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evidence-based approach (Institute of Medicine standards)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PICO questions/format</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expert opinion-based approach</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Grading of recommendations</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Published in a peer-reviewed journal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Implementation and interest to all stakeholders (policy makers, regulating agencies, IPF community-at-large)</td>
<td>Yes</td>
<td>?</td>
</tr>
</tbody>
</table>

*Eur Respir J 2018; 52: 1801485*
The new guidelines for IPF diagnosis (ATS/ERS/JRS/ALAT 2018)

Committee decision after voting

- **Strong for**
- **Conditional for**
- **Strong against**
- **Conditional against**
- **Abstain**
## Table 2. Implications of Strong and Conditional Recommendations

<table>
<thead>
<tr>
<th>Category</th>
<th>Strong Recommendation (“We recommend . . .”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients</td>
<td>The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>For policy makers</td>
<td>The recommendation can be adapted as policy in most situations, including for use as performance indicators.</td>
</tr>
</tbody>
</table>
Conditional Recommendation ("We suggest . . .")

For patients

The majority of individuals in this situation would want the suggested course of action, but a sizeable minority would not.

For clinicians

Διαφορετικές επιλογές θα είναι κατάλληλες για διαφορετικούς ασθενείς, και πρέπει να βοηθήσεις τον κάθε ασθενή να αποφασίσει ανάλογα με τις αξίες του και τις προτιμήσεις του. Ο γιατρός αναμένεται να αφιερώσει περισσότερο χρόνο με τους ασθενείς προκειμένου να αποφασίσουν.

For policy makers

Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.
• IPF is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause.
• It occurs primarily in older adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of UIP.
• It should be considered in all adult patients with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing, that occur without constitutional or other symptoms that suggest a multisystem disease.
DIAGNOSTIC APPROACH OF IIPs

History, physical exam, serology, PFTs, CXR

NOT IIP
e.g., CTD-ILD, drug-induced ILD, environmental ILD.

POSSIBLE IIP

HRCT

Definite IPF in HRCT with compatible clinical picture

Atypical clinical or HRCT picture

TBB / BAL?

Findings diagnostics of other ILD, e.g., Histiocytosis.

Surgical biopsy

Suspicion of other ILD

TBB, BAL or other exam

UIP

NSIP

RB-ILD

DIP

AIP

COP

RARE

Non-classified
We recommend taking a detailed history of both medication use and environmental exposures at home, work, and other places the patient frequently visits to exclude potential causes of ILD (motherhood statement).

- **AGE** (>50 years)
- **GENDER** (male > female)
- **SMOKING** (frequently)
- **DRUGS** (exclude)
- **Sx DURATION** (months-years)
- **EXPOSURE** (organic/inorganic dust)
- **FAMILIAL PULMONARY FIBROSIS** (5-8%)

*Am J Respir Crit Care Med 2018; 198: Sept 1st.*
**DIAGNOSTIC APPROACH OF IIPs**

**History, physical exam, serology, PFTs, CXR**

**NOT IIP**
e.g., CTD-ILD, drug-induced ILD, environmental ILD.

**POSSIBLE IIP**

**HRCT**

Definite IPF in HRCT with compatible clinical picture

Atypical clinical or HRCT picture

Findings diagnostics of other ILD, e.g., Histiocytosis.

Surgical biopsy

**UIP**

**NSIP**

**RB-ILD**

**DIP**

**AIP**

**COP**

**RARE**

Non-classified

Suspicion of other ILD

TBB, BAL or other exam

NON DIAGNOSTIC

TBB / BAL?
Digital clubbing

Happy Father’s Day, Hippocrates!

Hippocrates was the first to describe **clubbed fingers**, an important diagnostic sign in chronic lung disease.

> 50% OF THE PATIENTS
Fine end inspiratory basal crackles (velcro). Λεπτοί τελοεισπνευστικοί μη μουσικοί ρόγχοι

EDITORIAL

Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?

Vincent Cottin and Jean-François Cordier
How Does the Digital Stethoscope Work?

AI analyses the sound and shows the results on apps.

LiPo Rechargeable Battery

BLE 5 iOS & Droid

1-Button User Interface

100 hours between charges

Send lung sound to apps
Digital Auscultation Aids

Data sources

- Patient demographics
- Medical history
- Patient-reported symptoms
- Lung auscultation (4-6 points)

Probabilistic scores for all compatible diagnostic hypotheses
Pulmonary fibrosis, COPD, asthma, CHF, etc...
DIAGNOSTIC APPROACH OF IIPs

History, physical exam, serology, PFTs, CXR

NOT IIP

e.g., CTD-ILD, drug-induced ILD, environmental ILD.

POSSIBLE IIP

HRCT

Definite IPF in HRCT with compatible clinical picture

Atypical clinical or HRCT picture

Findings diagnostics of other ILD, e.g., Histiocytosis.

Suspicion of other ILD

TBB, BAL or other exam

NON DIAGNOSTIC

Surgical biopsy

UIP, NSIP, RB-ILD, DIP, AIP, COP, RARE, Non-classified
Serologic Tests Can Help Identify Other Conditions

We recommend serological testing to exclude connective tissue disease (CTD) as a potential cause of the ILD (motherhood statement).

Connective tissue diseases

- ANA, RF & anti-CCP (ERS/ATS guidelines)
- CK and aldolase
- Anti-myositis panel with Jo-1 antibody
- ENA panel
  - Scl-70, ACA
  - Ro (SSA), La (SSB)
  - MPO/PR3 (ANCA)
  - Smith, RNP
  - ESR, CRP

Hypersensitivity pneumonitis

Hypersensitivity panel (if exposure history)

Positive autoantibodies were found in 22% of patients with IPF and 21% of healthy controls. There were no differences in the types of autoantibodies found between patients with idiopathic pulmonary fibrosis and healthy controls.
DIAGNOSTIC APPROACH OF IIPs

History, physical exam, serology, PFTs, CXR

NOT IIP
e.g., CTD-ILD, drug-induced ILD, environmental ILD.

POSSIBLE IIP

HRCT

Definite IPF in HRCT with compatible clinical picture

Atypical clinical or HRCT picture

Findings diagnostics of other ILD, e.g., Histiocytosis.

TBB / BAL?

NON DIAGNOSTIC

Suspcion of other ILD

TBB, BAL or other exam

Surgical biopsy

UIP
NSIP
RB-ILD
DIP
AIP
COP
RARE
Non-classified
What are the features of an HRCT?

- **Type of HRCT**: Non-contrast
- **Resolution**: 1 mm Slices, High-Resolution Reconstruction Algorithm
- **View**: Axial, Coronal
- **Position**: (Prone), Supine
- **Breathing**: Inspiratory, Expiratory

(ATS/ERS/JRS/ALAT 2018)
<table>
<thead>
<tr>
<th>Recommended Scanning Protocol</th>
<th>Advantages of Updated Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Noncontrast examination</td>
<td></td>
</tr>
<tr>
<td>2. Volumetric acquisition with selection of:</td>
<td>A. Acquisition covering the entire lung volume (vs. analysis of 10% of lung volume with sequential scanning)</td>
</tr>
<tr>
<td>• Sub-millimetre collimation</td>
<td>• No risk of missing subtle infiltrative abnormalities</td>
</tr>
<tr>
<td>• Shortest rotation time</td>
<td>• Possibility of multiplanar reformations, helpful for analysis of the ILD pattern and predominant distribution of lung changes</td>
</tr>
<tr>
<td>• Highest pitch</td>
<td>• Possibility of post-processing to optimize detection of subtle hypoattenuated lesions (minimum intensity projection) and micronodular infiltration (maximum intensity projection)</td>
</tr>
<tr>
<td>• Tube potential and tube current appropriate to patient size:</td>
<td>• Possibility of detection of additional lesions (e.g., incidental identification of lung nodule or focal consolidation in lung fibrosis that may correspond to lung carcinoma)</td>
</tr>
<tr>
<td>• Typically 120 kVp and 9240 mAs</td>
<td>• Optimal to assess progression or improvement in patient's follow-up</td>
</tr>
<tr>
<td>• Lower tube potentials (e.g., 100 kVp) with adjustment of tube current encouraged for thin patients</td>
<td>B. Dramatic increase in temporal resolution and speed of data acquisition</td>
</tr>
<tr>
<td>• Use of techniques available to avoid unnecessary radiation exposure (e.g., tube current modulation)</td>
<td>• Motion-free images</td>
</tr>
<tr>
<td>3. Reconstruction of thin-section CT images (91.5 mm):</td>
<td>C. Availability of numerous dose-reduction tools</td>
</tr>
<tr>
<td>• Contiguous or overlapping</td>
<td></td>
</tr>
<tr>
<td>• Using a high-spatial-frequency algorithm</td>
<td>A. Expiratory scans useful to detect air trapping</td>
</tr>
<tr>
<td>• Iterative reconstruction algorithm if validated on the CT unit (if not, filtered back projection)</td>
<td>B. Prone scans allow analysis of peripheral lung changes without dependent lung atelectasis that may be mistaken for abnormal lung infiltration or mimic disease (e.g., pseudohoneycombing when combined with paraseptal emphysema)</td>
</tr>
<tr>
<td>4. Number of acquisitions:</td>
<td>C. Inadequate inspiration increases lung attenuation (which should not be interpreted as ground-glass attenuation) and is responsible for dependent lung atelectasis (which may mimic abnormal lung infiltration or mask subtle abnormalities)</td>
</tr>
<tr>
<td>• Supine: inspiratory (volumetric)</td>
<td>A. Considerable dose reduction compared to sequential scanning</td>
</tr>
<tr>
<td>• Supine: expiratory (can be volumetric or sequential)</td>
<td></td>
</tr>
<tr>
<td>• Prone: only inspiratory scans (can be sequential or volumetric); optional (see text)</td>
<td></td>
</tr>
<tr>
<td>• Inspiratory scans obtained at full inspiration</td>
<td></td>
</tr>
<tr>
<td>5. Recommended radiation dose for the inspiratory volumetric acquisition:</td>
<td></td>
</tr>
<tr>
<td>• 1–3 mSv (i.e., “reduced” dose)</td>
<td></td>
</tr>
<tr>
<td>• Strong recommendation to avoid “ultralow-dose CT” (&lt;1 mSv)</td>
<td></td>
</tr>
</tbody>
</table>
CRITERIA ARE PRESENTED TO ESTABLISH CONFIDENT AND WORKING DIAGNOSIS OF IPF.

IF A DIAGNOSTIC TISSUE IS NOT AVAILABLE, A WORKING DIAGNOSIS OF IPF COULD BE MADE AFTER A CAREFUL MDD.

ALL PATIENTS ESPECIALLY THOSE WITH A WORKING DIAGNOSIS SHOULD HAVE THIS DIAGNOSIS REVIEWED AT REGULAR INTERVALS.
FLEISCHNER society 2017 white paper
Diagnostic criteria for IPF. Lancet RM 2017

• **HRCT categories**
  - Typical UIP
  - Probable UIP ("possible" in ATS/ERS 2011)
  - Indeterminate for UIP
  - Consistent with alternative diagnosis *(inconsistent with UIP)*

• **Histopathologic categories**
  - UIP
  - Probable UIP
  - Indeterminate for UIP
  - Consistent with alternative diagnosis
V. Tzilas, D. Valeyre, A. Tzouvelekis,*D. Bouros

Taking a giant step in the diagnosis of idiopathic pulmonary fibrosis

Lancet Respir Med 2017
Published Online
November 10, 2017
http://dx.doi.org/10.1016/PII
See Online/Review
http://dx.doi.org/10.1016/PII
**Diagnostic categories of UIP based on CT patterns**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
<td>Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis</td>
</tr>
</tbody>
</table>

Figure 4: High-resolution computer tomography in idiopathic pulmonary fibrosis. Predominantly basal and subpleural reticular fibrosis with honeycombing.

www.thelancet.com/respiratory Published online November 15, 2017
### Probable UIP CT pattern

**Distribution**

Basal and subpleural predominant; distribution is often heterogeneous

**Features**

- Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*
- Honeycombing is absent; absence of features to suggest an alternative diagnosis

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*Associated with idiopathic pulmonary fibrosis (IPF) and other forms of idiopathic interstitial pneumonias (IIPs).
Usual interstitial pneumonia pattern in the diagnosis of idiopathic pulmonary fibrosis?

Probable UIP has high positive predictive value for IPF
Diagnostic categories of UIP based on CT patterns

CT pattern indeterminate for UIP

Distribution

Variable or diffuse

Features

Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern

www.thelancet.com/respiratory Published online November 15, 2017
CT features most consistent with non-IPF diagnosis

**Distribution**

Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing

**Features**

Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts
Inconsistent With UIP

Distinct lobular pattern + HC

Slide courtesy D BOUROS
Fibrotic NSIP: subpleural sparing
MTX toxicity: GGO > reticular, peribronchovascular
Positive Predictive Value of UIP on HRCT for IPF

UIP pattern (honeycombing) on HRCT:
• PPV for IFP 90-100%

UCSF study: other HRCT classifications
• Possible UIP: 63% (94% Mayo)
• Inconsistent with UIP: 23%
  — Even if inconsistent, still can be IPF

Wells A, Respir Res. 2013;14(suppl 1):S2
**DIAGNOSTIC APPROACH OF IIPs**

**History, physical exam, serology, PFTs, CXR**

- **NOT IIP**
  - e.g., CTD-ILD, drug-induced ILD, environmental ILD.

- **POSSIBLE IIP**
  - TBB, BAL or other exam

- **HRCT**
  - Findings diagnostics of other ILD, e.g., Histiocytosis.

- **Atypical clinical or HRCT picture**
  - TBB / BAL?

- **Surgical biopsy**
  - Definite IPF in HRCT with compatible clinical picture
  - Suspicion of other ILD

- **POSSIBLE IIP**
  - TBB, BAL or other exam

- **NON DIAGNOSTIC**
  - Surgical biopsy

- **UIP, NSIP, RB-ILD, DIP, AIP, COP, RARE, Non-classified**
Diagnosis of IPF - 2018 guidelines

For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP:

- We suggest NOT performing cellular analysis of their BAL fluid (conditional recommendation, very low quality of evidence).
- We recommend NOT performing SLB (strong recommendation, very low quality of evidence).
- We recommend NOT performing TBBx (strong recommendation, very low quality of evidence).
- We recommend NOT performing lung cryobiopsy (strong recommendation, very low quality of evidence).
Diagnosis of IPF - 2018 guidelines

For patients with newly detected ILD of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis:

- We suggest cellular analysis of their BAL fluid (conditional recommendation, very low quality of evidence).
- We suggest surgical lung biopsy (SLB) (conditional recommendation, very low quality of evidence).
- The panel made no recommendation for or against transbronchial lung biopsy (TBBx).
- The panel made no recommendation for or against lung cryobiopsy.
We recommend NOT measuring serum MMP (matrix metalloproteinase)-7, SPD (surfactant protein D), CCL (chemokine ligand)-18, or KL (Krebs von den Lungen)-6 for the purpose of distinguishing IPF from other ILDs (strong recommendation, very low quality of evidence).
Diagnosis of IIPs

History, physical exam, serology, PFTs, CXR

Definite IPF in HRCT with compatible clinical picture

Possible IIP

Atypical clinical or HRCT picture

Findings diagnostics of other ILD, e.g., Histiocytosis.

Surgical biopsy

TBB/BAL?

Non diagnostic

Suspicion of other ILD

TBB, BAL or other exam

Non-classified

UIP, NSIP, RB-ILD, DIP, AIP, COP, RARE

NOT IIP

e.g., CTD-ILD, drug-induced ILD, environmental ILD.

HRCT
When can one make a confident diagnosis of IPF without biopsy?
- Clinical context of IPF*, with CT pattern of typical or probable UIP

When is a diagnostic biopsy necessary to make a confident diagnosis of IPF?
- Clinical context of IPF* with CT pattern either indeterminate or suggestive of an alternative diagnosis
- Clinical context indeterminate for IPF† with any CT pattern
Video-Assisted Thoracoscopic Surgery
VATS

The patient is positioned on the operating table as depicted. The three trocars and videoscope used for video thoracoscopic lung biopsy are placed as illustrated.
<table>
<thead>
<tr>
<th>General comments</th>
<th>Definite UIP-IPF</th>
<th>Probable UIP-IPF</th>
<th>Indeterminate for UIP-IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients show features with all four criteria, and do not show features that might suggest an alternative diagnosis (eg, non-UIP)</strong></td>
<td>Patients show features with all four criteria, and do not show features that might suggest an alternative diagnosis (eg, non-UIP)</td>
<td>Patients show either honeycomb fibrosis only, or a severe fibrosing process that falls short of showing all four criteria for definite UIP-IPF and do not show features that might suggest an alternative diagnosis</td>
<td>Patients show evidence of a fibrosing process but with features that are more in favour of either a non-UIP pattern, or UIP in a setting other than IPF</td>
</tr>
<tr>
<td><strong>Specific criteria</strong></td>
<td>Dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; subpleural or paraseptal distribution, or both; fibroblast foci at the edge of dense scars</td>
<td>Honeycomb fibrosis only or; dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; fibroblast foci at the edge of dense scars may or may not be present</td>
<td>Patients have less compelling histological changes than those classified by the final column (eg, occasional foci of centrilobular injury or scarring, rare granulomas or giant cells, only a minor degree of lymphoid hyperplasia or diffuse inflammation, or diffuse homogenous fibrosis favouring fibrotic non-specific interstitial pneumonia); these features, and the differential diagnoses they call to mind, become part of the multidisciplinary discussion and decision with regard to a multidisciplinary diagnosis of IPF, or not</td>
</tr>
</tbody>
</table>
VATS biopsy shows UIP: heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibrosis, fibroblastic foci and honeycomb change.

Most UIPs are “IPF”, ALL UIPs ARE NOT IPF

USUAL INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS

KNOWN ETIOLOGY
CVD-PF, DRUGS, HP, Asbestosis etc

Slide courtesy of Demosthenes Bouros
Features most consistent with an alternative diagnosis

Patients show either a UIP pattern with ancillary features strongly suggesting an alternative diagnosis, or a non-UIP pattern (see cell below).

Non-UIP pattern:
patients with features of other fibrotic disorders—eg, fibrotic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, fibrosing organising pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans cell histiocytosis, or smoking-related interstitial fibrosis;
UIP pattern with ancillary features strongly suggesting an alternative diagnosis: eg, prominent diffuse alveolar damage or organising pneumonia (consider acute exacerbation of UIP), granulomas, (consider hypersensitivity pneumonitis, sarcoid, infection), marked interstitial inflammatory cell infiltrate away from areas of UIP (consider hypersensitivity pneumonitis)
Possible UIP pattern

No fibroblastic foci / honeycomb

Courtesy R. Trigidou
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>UIP</strong></td>
<td>Dense fibrosis with architecture remodelling</td>
<td>Definite UIP</td>
</tr>
<tr>
<td></td>
<td>Predominant subpleural or paraseptal distribution of fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patchy lung involvement by fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of fibroblastic foci</td>
<td></td>
</tr>
<tr>
<td><strong>Probable UIP</strong></td>
<td>Honeycomb fibrosis only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibroblastic foci may or may not be present</td>
<td></td>
</tr>
</tbody>
</table>

**Indeterminate for UIP**
- Occasional foci of centrilobular injury or scarring
- Rare granulomas or giant cells
- Minor degree of lymphoid hyperplasia or diffuse inflammation
- Diffuse homogenous fibrosis favouring fibrotic nonspecific interstitial pneumonia

**Alternative diagnosis**
- Histological findings indicative of other diseases

**Features most consistent with an alternative diagnosis**
- A UIP pattern with ancillary features strongly suggesting an alternative diagnosis
- A non-UIP pattern

Eur Respir J 2018; 52: 1801485
Diagnosis of IPF

Diagnosis of IPF requires the following:

1. Exclusion of other known causes (*e.g.*, *domestic and occupational environmental exposures, CTD, drug toxicity*),
   and either #2 or #3:
2. The presence of the HRCT pattern of UIP
3. Specific combinations of HRCT and histopathology patterns

*(ATS/ERS/JRS/ALAT 2018)*
<table>
<thead>
<tr>
<th>HRCT pattern</th>
<th>Histopathology pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIP</td>
</tr>
<tr>
<td>UIP</td>
<td>IPF</td>
</tr>
<tr>
<td>Probable UIP</td>
<td>IPF</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>IPF</td>
</tr>
<tr>
<td>Alternative diagnosis</td>
<td>IPF (Likely)</td>
</tr>
</tbody>
</table>
We suggest multidisciplinary discussion (MDD) for diagnostic decision-making (conditional recommendation, very low quality of evidence).
Approach to the Diagnosis of IPF

Clinical
• History
• Physical
• Laboratory
• PFTs

Radiology
• Chest X-ray
• HRCT

Pathology
• Surgical lung biopsy

Primary care physicians
Pneumonologist
Radiologist
Pathologist

Multidisciplinary discussion
GOLD STANDARD

REFERENCE CENTER
BrainNet allows collaborative problem-solving using direct brain-to-brain communication.

The first “social network” of brains lets three people transmit thoughts to each other’s heads.
QUESTIONS?