Convegno di presentazione della versione italiana delle linee guida per la diagnosi di fibrosi polmonare idiopatica

Linee guida ufficiali ATS/ERS/JRS/ALAT per la pratica clinica

1 Febbraio 2020

Hotel Enterprise Milano
LA METODOLOGIA

Sebastiano Emanuele Torrisi
Regional Centre for Interstitial and Rare Lung Diseases, Department of Clinical and Experimental Medicine, University of Catania
Methodology of
What is a Guideline?

A guideline asks a clinical question, summarizes the body of relevant evidence, and then uses that evidence summary to inform recommendations.
The team
2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Chair**
    - Dr. Ganesh Raghu, Pulmonologist, Seattle, WA, USA
  - **Co-chairs**
    - Dr. Jeffrey L. Myers, Pathologist, Ann Arbor, MI, USA
    - Dr. Martine Remy-Jardin, Radiologist, Lille, France
    - Dr. Luca Richeldi, Pulmonologist, Rome, Italy
  - **Project manager and lead methodologist**
    - Dr. Kevin C. Wilson, Pulmonologist, Boston, MA, USA
  - **Methodology team**
    - Dr. Thomas Bice, Pulmonologist, Chapel Hill, NC, USA
    - Dr. Abjihit Duggal, Pulmonologist, Cleveland, OH, USA
    - Dr. George Mansur, Internal Medicine, St. Louis, MO, USA
2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - Guideline Panel – North America
    - Ganesh Raghu, Pulmonologist, Seattle, WA, USA
    - Jeff L. Myers, Pathologist, Ann Arbor, MI, USA
    - William D. Travis, Pathologist, New York, NY, USA
    - Fernando Martinez, Pulmonologist, New York, NY, USA
    - Harold Collard, Pulmonologist, San Francisco, CA, USA
    - Kevin Flaherty, Pulmonologist, Ann Arbor, MI, USA
    - David Lederer, Pulmonologist, New York, NY, USA
    - Sonye K. Danoff, Pulmonologist, Baltimore, MD, USA
    - Kevin Brown, Pulmonologist, Denver, CO, USA
    - Chris Ryerson, Pulmonologist, Vancouver, BC, Canada
    - Sudhakar Pipavath, Radiologist, Seattle, WA, USA
    - Ella Kazerooni, Radiologist, Ann Arbor, MI, USA

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018
2018 Diagnosis of Idiopathic Pulmonary Fibrosis
An Official ATS-ERS-JRS-ALAT Clinical Practice Guideline*

- **IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)**
  - **Guideline Panel – Europe**
    - Martine Remy-Jardin, Radiologist, Lille, France
    - Luca Richeldi, Pulmonologist, Rome, Italy
    - Athol Wells, Pulmonologist, London, UK
    - Gisli Jenkins, Pulmonologist, Nottingham, UK
    - Juergen Behr, Pulmonologist, Munich, Germany
    - Vincent Cottin, Pulmonologist, Lyon, France
    - Ferrin Morell, Pulmonologist, Barcelona, Spain
    - Demosthenes Bouros, Pulmonologist, Athens, Greece
    - Andrew Nicholson, Pathologist, London, UK
    - Simon Walsh, Radiologist, London, UK

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018
IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)

- Guideline Panel – Mexico and Japan
  - Moises Selman, Pulmonologist, Mexico
  - Ivette Buendia-Roldan, Pulmonologist, Mexico
  - Takeshi Johkoh, Radiologist, Japan
  - Yoshikazu Inoue, Pulmonologist, Japan
  - Arata Azuma, Pulmonologist, Japan
  - Masanori Kitaichi, Pathologist, Japan

- Reference Librarian
  - Shandra L. Knight, Medical Librarian, Denver, CO, USA

- Patient Representative
  - Liam Galvin, Ireland

* Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018
IPF Committee: Multidisciplinary (ATS, ERS, JRS, ALAT)

- Expert Advisors
  - Drs. Mary Armanios and David Schwartz (Genetic Factors)
  - Dr. Virginia Steen (Rheumatology)
  - Drs. Sharf Keshavjee, Walter Weden, Michael Mulligan (Thoracic Surgery)
  - Drs. Atul Mehta and Venerino Poletti (Interventional Bronchoscopy, Lung Cryobiopsy)
Panel Composition
Multi-disciplinary and multi-society

Discuss evidence and make recommendations

ATS

ERS

JRS

ALAT

Discuss evidence only

Methodology Team
19 pulmonologists
5 radiologists
4 pathologists

Expert Advisors

Richeldi L. ERS 2018
1\textsuperscript{st} step: Questions
Why are research questions so important?

“Well-crafted questions guide the systematic planning of research. Formulating your questions precisely enables you to design a study with a good chance of answering them.”

Light, Singer, Willet, by Design 1990
Characteristics of a good question

«FINER»
F=feasible
I=interesting
N=novel
E=ethical
R=relevant
The co-chairs and methodologist drafted key clinical questions in a **PICO (Population, Intervention, Comparator, and Outcome) format**

The questions were then discussed, modified, and approved by the full guideline panel with input from the expert advisers at a face-to-face meeting held at the 2017 ATS International Conference in Washington, D.C. in May, 2017.

The evidence was assessed for all outcomes identified by the panel, but only those assigned a priority of critical (i.e., median rating of 7-9) were used to rate the quality of evidence.
Questions

«The co-chairs and methodologist drafted key clinical questions in a PICO format»
What is PICO format?

• A useful model to help structure an answerable question
• Used to formulate clinical questions
• Breaks down the question into four key elements
Asking the clinical question: the PICO format

- **P**: Population
- **I**: Intervention or Interest area
- **C**: Comparison intervention or status
- **O**: Outcome
<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient, Population or Problem</strong></td>
<td><strong>Intervention or exposure</strong></td>
<td><strong>Comparison</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>What are the characteristics of the patient or population?</td>
<td>What do you want to do with this patient (e.g. treat, diagnose, observe)?</td>
<td>What is the alternative to the intervention (e.g. placebo, different drug, surgery)?</td>
<td>What are the relevant outcomes (e.g. morbidity, death, complications)?</td>
</tr>
</tbody>
</table>
Questions
Approved
Face-to-face
meeting at 2017
ATS Conference

- Exclusion of potential causes of ILD.
- Serological testing for CTD.
- Cellular analysis of BAL fluid.
- Surgical lung biopsy.
- Transbronchial biopsy.
- Transbronchial cryobiopsy.
- Multi-disciplinary discussion.
- Serum diagnostic biomarkers.
The published literature was searched by the librarian (SK) in the following databases:

Medline, Excerpta Medica Database (EMBASE), and Cochrane Database of Systematic Reviews

Table E3. Search strategy/results for bronchoalveolar lavage

<table>
<thead>
<tr>
<th></th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bronchoalveolar lavage/ or bronchoalveolar lavage fluid/</td>
<td>25167</td>
</tr>
<tr>
<td>2</td>
<td>((lavage$ or wash$) adj2 (lung$ or bronch$ or pulmonary$)).mp.</td>
<td>39697</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>39697</td>
</tr>
</tbody>
</table>
3rd step Evidence synthesis

- For controlled studies, relative risk (RR) was used to report the results for dichotomous outcomes and the mean difference (MD) was used to report the results for continuous outcomes.

- For uncontrolled studies, generic inverse variance was used if possible, but studies were often pooled without weighting (i.e., generic inverse variance cannot be used if an individual study has a result of 0% or 100%, which was often the case).
The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach

<table>
<thead>
<tr>
<th>Underlying Methodology</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>High</td>
</tr>
<tr>
<td>Downgraded RCTs or upgraded observational studies</td>
<td>Moderate</td>
</tr>
<tr>
<td>Well-done observational studies with control groups</td>
<td>Low</td>
</tr>
<tr>
<td>Others (e.g., case reports or case series)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: RCT = randomized controlled trial.*
The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach

### Quality of Evidence

<table>
<thead>
<tr>
<th>Initial assumption based upon the study design:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Randomized trial</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>--</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Well-done observational study with control groups</td>
</tr>
<tr>
<td><strong>Very low</strong></td>
<td>Other evidence, such as case reports, case series, etc.</td>
</tr>
</tbody>
</table>

### Downgrade the quality of evidence if:

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
</tr>
</thead>
</table>

### Upgrade the quality of evidence if:

<table>
<thead>
<tr>
<th>Strong association (i.e., large magnitude of effect)</th>
<th>Dose-response gradient</th>
<th>Plausible confounders would have the opposite effect</th>
</tr>
</thead>
</table>

Confidence in the accuracy of the study results

Richeldi L. ERS 2018
Guideline Development
Two processes in parallel

Methodology team
PICO questions
- Bronchoalveolar lavage (BAL) vs no BAL
- Surgical lung biopsy (SLB) vs no SLB
- Transbronchial biopsy (TBBx) vs no TBBx
- Cryobiopsy (CB) vs no CB
- Multi-disciplinary discussion (MDD) vs no MDD
- Peripheral blood biomarkers (BM) vs no BM

Remainder of panel
Other content
- Motherhood statements
- Diagnosis based upon HRCT & histopathology
- Diagnostic criteria
- Diagnostic algorithm

Richeldi L. ERS 2018
Evidence to Recommendations
Face-to-face meeting at 2017 ERS Congress

- Approval of non-PICO content
- Then, presentation of evidence → committee discussion → recommendation formulation → voting

Recommendations for or against an intervention are based upon:
- balance of benefits vs harms and burdens
- quality of evidence
- patient values and preferences
- feasibility
- costs
Recommendations

Guideline recommendations are rated:

- **Quality of evidence**: Conveys how much confidence the committee has in the accuracy of the study results.

- **Strength of the recommendation**: Conveys how certain the committee is that the upsides of the recommended course of action outweigh the downsides.
**Strength of Recommendations**

- Certainty that upsides of the recommended course of action outweigh downsides

<table>
<thead>
<tr>
<th><strong>Strong</strong></th>
<th><strong>Conditional</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>It is the correct course of action for &gt;95% of patients</td>
<td>It is the correct course of action for &gt;50% of patients, but may not be correct for a sizeable minority</td>
</tr>
<tr>
<td>“Just do it”</td>
<td>“Slow down, think about it, discuss it with the patient”</td>
</tr>
<tr>
<td>Willing to tell a colleague that he/she is wrong for not following the recommendation</td>
<td>Not willing to tell a colleague that he/she is wrong for not following the recommendation. It is a matter of style. There is equipoise</td>
</tr>
<tr>
<td>Appropriate for a performance measure</td>
<td>Not appropriate for a performance measure</td>
</tr>
</tbody>
</table>

Richeldi L. ERS 2018
Strength of Recommendations

- Certainty that upsides of the recommended course of action outweigh downsides

<table>
<thead>
<tr>
<th>Strong</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is the correct course of action for &gt;95% of patients</td>
<td>It is the correct course of action for &gt;50% of patients, but may not be correct for a sizeable minority</td>
</tr>
<tr>
<td>“Just do it”</td>
<td>“Slow down, think about it, discuss it with the patient”</td>
</tr>
<tr>
<td>Willing to tell a colleague that he/she is wrong for not following the recommendation</td>
<td>Not willing to tell a colleague that he/she is wrong for not following the recommendation. It is a matter of style. There is equipoise</td>
</tr>
<tr>
<td>Appropriate for a performance measure</td>
<td>Not appropriate for a performance measure</td>
</tr>
</tbody>
</table>
Sample Recommendation

We recommend treatment X rather than treatment Y for patients with condition Z

(conditional recommendation, low quality of evidence)
Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Jehkoh, Andrew G Nicholson, Shandra L Knight, Suhaib Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

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 usual 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 multidisciplinary approach is particularly important when deciding to perform additional diagnostic assessments, integrating biopsy results with clinical and CT features, and establishing a working diagnosis of IPF if lung tissue is not available. A working diagnosis of IPF should be reviewed at regular intervals since the diagnosis might change. Criteria are presented to establish confident and working diagnoses of IPF.
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

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhaib Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

IPF diagnosis: flexibility is a virtue

In 2011, the joint guidelines of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Thoracic Association of Latin America provided the first truly international evidence-based statement on the diagnosis of idiopathic pulmonary fibrosis (IPF). Although this statement undoubtedly underpinned international collaboration in science and interventional trials, the rigour of the 2011 diagnostic criteria effectively disenfranchised a large subgroup of patients with IPF, in whom a surgical lung biopsy (SLB) could not be done and no definite diagnosis could be made. The concept of probable IPF was not explored in the 2011 guidelines, and the conclusion is crucial, given the Fleischner statement that “if diagnostic tissue is not available, a working diagnosis of IPF may be made after careful multidisciplinary evaluation.”

A working diagnosis of IPF is not a definite diagnosis, but it is a provisional diagnosis with a level of diagnostic likelihood such that IPF-specific therapy is the only logical approach. In effect, the Fleischner Society endorses the use of IPF-specific treatment in selected patients with probable UIP on HRCT and no biopsy data. To what extent is there genuine disagreement between the Fleischner Society statement and the revised joint diagnostic guidelines? Initial reaction at the American

In summary, the Fleischner Society statement and the 2018 joint diagnostic guidelines are broadly concordant.
Diagnosing idiopathic pulmonary fibrosis in 2018: bridging recommendations made by experts serving different societies

Luca Richeldi¹, Kevin C. Wilson² and Ganesh Raghu³
Diagnosing idiopathic pulmonary fibrosis in 2018: bridging recommendations made by experts serving different societies

Luca Richeldi¹, Kevin C. Wilson² and Ganesh Raghu³

<table>
<thead>
<tr>
<th>Number of authors</th>
<th>Overlapping authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence-based approach (Institute of Medicine standards)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

| Published in a peer-reviewed journal                     | Yes | Yes |
| Implementation and interest to all stakeholders (policy makers, regulating agencies, IPF community-at-large) | Yes | ? |

# Diagnostic Components for IPF

<table>
<thead>
<tr>
<th>Histopathology pattern</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UIS</strong></td>
<td><strong>Definite UIS</strong></td>
<td></td>
</tr>
<tr>
<td>Dense fibrosis with architecture remodelling</td>
<td>Predominant subpleural or paraseptal distribution of fibrosis</td>
<td>Patchy lung involvement by fibrosis</td>
</tr>
<tr>
<td><strong>Probable UIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honeycomb fibrosis only</td>
<td>Fibroblastic foci may or may not be present</td>
<td></td>
</tr>
<tr>
<td><strong>Indeterminate for UIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis with or without architecture distortion</td>
<td>Occasional foci of centrilobular injury or scarring</td>
<td>Rare granulomas or giant cells</td>
</tr>
<tr>
<td>Some histological features from the UIS pattern</td>
<td>Minor degree of lymphoid hyperplasia or diffuse inflammation</td>
<td>Diffuse homogenous fibrosis favouring fibrotic nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td><strong>Alternative diagnosis</strong></td>
<td><strong>Features most consistent with an alternative diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Histological findings indicative of other diseases</td>
<td>A UIS pattern with ancillary features strongly suggesting an alternative diagnosis</td>
<td>A non-UIS pattern</td>
</tr>
</tbody>
</table>


https://doi.org/10.1183/13993003.0145-2018
## DIAGNOSTIC COMPONENTS FOR IPF

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age limit for increased diagnostic confidence</td>
<td>60 years</td>
<td></td>
</tr>
<tr>
<td><strong>UIP</strong></td>
<td>Subpleural and basal predominance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of honeycombing with or without peripheral traction bronchiectasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Biopsy not recommended</em></td>
<td></td>
</tr>
<tr>
<td><strong>Probable UIP</strong></td>
<td>Subpleural and basal predominance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence of peripheral traction bronchiectasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Biopsy recommended (conditional)</em></td>
<td><em>Biopsy not recommended</em></td>
</tr>
<tr>
<td><strong>Indeterminate for UIP</strong></td>
<td>Subpleural and basal predominant</td>
<td>Variable or diffuse</td>
</tr>
<tr>
<td></td>
<td>May have mild GGO or distortion</td>
<td>Features suggestive of non-UIP pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Biopsy recommended</em></td>
</tr>
<tr>
<td><strong>Alternative diagnosis</strong></td>
<td>Findings suggestive of another diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Biopsy recommended</em></td>
</tr>
</tbody>
</table>

Richeldi L, Wilson K, Raghu G. *Eur Respir J* 2018 6 Sept 2018

https://doi.org/10.1183/13993003.01485-2018

Eur Respir J 2018; 52: 1801485
The guideline panel concluded that biopsy is appropriate for a majority of patients, but may not be appropriate for a sizeable minority (up to 49%); in other words, the guidelines indicate that there is clinical equipoise when deciding whether or not to biopsy a patient with a probable UIP pattern on HRCT.

Richeldi L, Wilson, K, Raghu, G. *Eur Respir J* 2018 in press 6 Sept 2018
Grazie