ACUTE MANAGEMENT OF INTERSTITIAL LUNG DISEASE

Stephen R Selinger MD
CASE PRESENTATION
CASE PRESENTATION

- 58 year old woman admitted to ICU after failure to extubate postoperatively
- 17 year history of antisynthetase syndrome with ILD
- Low dose prednisone and cellcept
- Baseline functional without home oxygen
- Mechanical fall on DOA
- ORIF under general anesthesia
CASE PRESENTATION

• Inability to extubate due to hypoxemia
BASELINE CT

First Annual Symposium:
Successful Management of Lung Disease
ACUTE Management of ILD

• Classification of ILD
• Idiopathic Interstitial Pneumonias
• ILDs commonly associated with Hospitalization
  – Cryptogenic Organizing Pneumonia
• Deterioration with known lung disease
• Exacerbations of UIP
• New Therapy for UIP
Diseases of the Interstitial Compartment

• Idiopathic
  – Idiopathic interstitial pneumonias

• Known Cause
  – Diffuse alveolar damage
  – Granulomatous disorders
  – Inhalational disorders
    • Pneumoconiosis
    • Extrinsic allergic alveolitis
  – Neoplastic disorders
    • Lymphangitic Carcinoma
    • Lymphangioleiomyomatosis
    • Pulmonary langerhans cell histiocytosis
  – Medication
  – CTD
  – Infectious disorders
  – Vascular diseases
American Thoracic Society Documents


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

This official statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) was approved by the ATS Board of Directors, June 2013, and by the ERS Steering Committee, March 2013
# Histologic and Clinical Classification of the Idiopathic Interstitial Pneumonias

<table>
<thead>
<tr>
<th>Histologic Patterns</th>
<th>Clinical, Radiological and Pathological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Interstitial Pneumonia</td>
<td>Idiopathic Pulmonary Fibrosis or Cryptogenic Fibrosing Alveolitis</td>
</tr>
<tr>
<td>Nonspecific Interstitial Pneumonitis</td>
<td>Nonspecific Interstitial Pneumonitis</td>
</tr>
<tr>
<td>Organizing Pneumonia</td>
<td>Cryptogenic Organizing Pneumonia</td>
</tr>
<tr>
<td>Diffuse Alveolar damage</td>
<td>Acute Interstitial Pneumonia</td>
</tr>
<tr>
<td>Respiratory Bronchiolitis</td>
<td>Respiratory Bronchiolitis Interstitial Lung Disease</td>
</tr>
<tr>
<td>Desquamative Interstitial Pneumonia</td>
<td>Desquamative Interstitial Pneumonia</td>
</tr>
<tr>
<td>Lymphocytic Interstitial Pneumonia</td>
<td>Lymphocytic Interstitial Pneumonia</td>
</tr>
</tbody>
</table>
## RESPONSIVENESS TO IMMUNOSUPRESSION

<table>
<thead>
<tr>
<th>DISEASE PROCESS</th>
<th>RESPONSE TO STEROIDS AND OTHER IMMUNOSUPPRESSANTS/</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual interstitial pneumonia</td>
<td>None: worse outcomes with steroids and azathioprine</td>
<td>Median survival 2-3 years</td>
</tr>
<tr>
<td>Nonspecific Interstitial pneumonitis</td>
<td>Responsive</td>
<td>Guarded 15-25% 5 year mortality</td>
</tr>
<tr>
<td>Acute Interstitial pneumonitis</td>
<td>Nonresponsive</td>
<td>High acute mortality</td>
</tr>
<tr>
<td>Cryptogenic Organizing Pneumonia</td>
<td>Responsive</td>
<td>Good</td>
</tr>
<tr>
<td>Desquamative Interstitial pneumonitis</td>
<td>Smoking cessation Steroids likely beneficial</td>
<td>Good 70-100% 10 year survival</td>
</tr>
<tr>
<td>Lymphoid Interstitial Pneumonitis</td>
<td>Variable</td>
<td>Variable 37% mortality</td>
</tr>
</tbody>
</table>
# Histology Associated with Known Diseases

<table>
<thead>
<tr>
<th>Histologic Pattern</th>
<th>Underlying Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>Collagen disease, Chronic HP, Drug, Asbestos,</td>
</tr>
<tr>
<td>Nonspecific Interstitial Pneumonitis</td>
<td>Collagen disease, HP, Drug, Inhalation</td>
</tr>
<tr>
<td>Cryptogenic Organizing Pneumonia</td>
<td>Infection, Collagen disease, Drug, lung transplant</td>
</tr>
<tr>
<td>Desquamative Interstitial Pneumonia</td>
<td>Rheumatoid arthritis, Hepatitis C, Drug</td>
</tr>
<tr>
<td>Lymphoid Interstitial Pneumonia</td>
<td>Sjogrens syndrome, HIV, Bone marrow Transplant</td>
</tr>
</tbody>
</table>
Diagnostic Approach of DILD

History, physical examination, Chest-X ray, lung function tests

Not-IIP
ex: CVD, environmental exposure, drug history etc

IIP

HRCT

Confident CT
Dx of IPF with consistent clinical

Atypical clinical or CT features for IPF

Features diagnostic for another DILD, Ex, PLCH, LAM

Suspected another DILD

TBLB, BAL

If not diagnostic

Surgical lung biopsy

UIP, NSIP, RB-ILD, DIP, DAD, OP, LIP, Not IIP
Radiologic Diagnosis of UIP

<table>
<thead>
<tr>
<th>UIP Pattern</th>
<th>Possible UIP Pattern</th>
<th>Inconsistent with UIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 4 features</td>
<td>All 3 features</td>
<td>Any of the 7 features</td>
</tr>
<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>Honeycombing 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 (greater than 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 lobes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consolidation in bronchopulmonary segment(s)/lobe(s)</td>
</tr>
</tbody>
</table>

UIP
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Successful Management of Lung Disease
NSIP
NSIP
Cryptogenic Organizing Pneumonia
Cryptogenic Organizing Pneumonia
Cryptogenic Organizing Pneumonia
Organizing Pneumonia

- Cryptogenic
- Inhalational
- Postinfectious
- Collagen Disease
- Drugs
- Malignancy
- Radiation
- Transplant
ILDs that Present Acutely

- Acute interstitial pneumonitis
- UIP/IPF
- Cryptogenic organizing pneumonia
- Sarcoidosis
Accelerated Phase Of Chronic Interstitial Lung Disease

- UIP
- NSIP
- Hypersensitivity Pneumonitis
- Cryptogenic Organizing Pneumonia
- Collagen disease
- Pneumoconiosis
Deterioration in ILD

- Underlying disease
- Cor Pulmonale
- Cardiac
- Infection
  - Extrapulmonary
  - Pulmonary
- Pulmonary Embolism
- Drug
Exacerbations of UIP
UIP Exacerbation

- Acute Worsening of unknown Cause in IPF
- Initially described 1993 by Kondoh
  - OLB demonstrated UIP and organizing acute lung injury
- Viral Infection identified in 9% of cases
Diagnostic Criteria of Acute Exacerbation of IPF

- Previous or concurrent diagnosis of IPF
- Unexplained worsening or development of dyspnea
- HRCT with new ground glass
- No evidence of infection on BAL or ET aspirate
- Exclusion of alternative causes
  - CHF
  - Pulmonary Embolus
  - Pneumothorax
  - Identifiable cause of Acute Lung Injury
UIP Exacerbation
Epidemiology

- 1 year incidence 2.3-16%
- Mean Age 70
- Occurs 3-60 months post diagnosis
- Mortality 78%
- Mortality 90% if mechanical ventilation required
- Median survival 2 months from onset
- May proceed death in 47% who die of IPF
- Increased winter months
**UIP Exacerbation**

- Surgery and mechanical stress
  - Surgical Lung Biopsy
  - Nonpulmonary Surgery
  - Lung cancer surgery

- Oxygen

- Drugs
  - Biological agents
  - Chemotherapy
    - specific EGFR tyrosine kinase receptor inhibitors
  - Immunomodulatory agents
AE-IPF
Risk Factors

- More common in progressive disease
- More common males
- Ambient pollution
- Pulmonary hypertension
- GERD (PPI decrease)
  - Pepsin found in BAL
AE-COPD
Clinical Findings

- Dyspnea, hypoxemia
- Fever
- Cough
- Flu symptoms
- GGO
AE-ILD

- Lung biopsy contraindicated in most cases
- Only a consideration when UIP not prior diagnosed
Radiology AE-IPF

A

B

First Annual Symposium: Successful Management of Lung Disease
Treatment

- No evidenced based management strategy as no treatment with demonstrated efficacy
- Weak recommendation for high dose steroids (ATS/ERS)
- Immunosuppressive therapy
- Broad spectrum antibiotics (difficult to exclude infection)
  - PCT guidance with decreased antibiotic exposure
- Polymyxin B perfusion
  - Absorption of inflammatory, fibrogenic and angiogenic cytokines
- Studies ongoing
Corticosteroids in AE-IPF

• No controlled studies
• Varying degrees of improvement
• Retrospective reviews hampered by lack of standardized definition of AE-IPF
• Do not prevent exacerbations
• Potentially lower AE rates in studies not allowing immunosuppression in IPF
Other Immunosuppression

- Cyclosporin plus steroids
- Tacrolimus
- IV cytoxan
- Sivelestat (neutrophil elastase inhibitor)
- Imuran
- Rituxan and plasma exchange being studied
  - AJRCCM2013;187; A5712
Hemoperfusion with Polymyxin B-Immobilized fiber Column

- Absorb endotoxin and ROS
- Removal activated neutrophils
- Significant reduction in cytokines
- Improved oxygenation
- 3 month survival 72\%(14 patients) vs 48\%(18 patients)
  - ARRDCCM 2014;189:A1419
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge et al, ASCEND Study Group
NEJM 2014;370:2083

- 127 study sites
- Ages 40-80, UIP definite on HRCT or Surgical biopsy
- FVC 50-90%, DICO 30-90%, 6 min walk 150m or more
- Pirfenidone 2403 mg/day or placebo for 52 weeks
- 278 pirfenidone and 277 placebo
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge et al ASCEND Study Group
NEJM 2014;370:2083

- Baseline FVC 67% predicted
- Death or Decline in FVC of 10% reduced by 47% in pirfenidone group
- Percent with no decline in FVC increased in pirfenidone group
  - 22.7% vs 9.7%
- Treatment effect seen at week 13
- Mean decline in FVC 428cc vs 235cc
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge et ASCEND Study Group
NEJM 2014;370:2083

• Increase in 6 minute walk
• Decrease in death or disease progression reduced by 43%
• No difference in dyspnea at week 52
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge et ASCEND Study Group
NEJM 2014;370:2083

- Fewer deaths in Pirfenidone group, but not significant (4% vs 7.2%)
- Pooled Ascend and Capacity trials (1247 patients) death reduced by 48%
  – IPF deaths reduced by 68%
- GI and Skin side effects
- Increased LFTs 2.9%
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
Talmadge et ASCEND Study Group
NEJM 2014;370:2083
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
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NEJM 2014;370:2083
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis
INPULSIS Trial Investigators

- Targets multiple tyrosine kinases including VEGF, FGF and PDGF
- 205 sites in 24 countries
- Age ≥40
- IPF within 5 years
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis
INPULSIS Trial Investigators

• FVC $\geq$ 50% and DlCO 30-79%
• Prednisone $\leq$ 15mg/day permitted
• Nintedanib 150mg bid or placebo for 52 weeks
• 1066 patients randomized
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

INPULSIS Trial Investigators

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

INPULSIS Trial Investigators

- Higher incidence diarrhea 4.5%
- Higher incidence increased LFT 4.5%
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

INPULSIS Trial Investigators

- Inpulsis 2 significantly increased time to first exacerbation
  - 3.6% vs 9.6% exacerbated
- Inpulsis 1 no significant difference in time to first exacerbation
- No significant difference in death rate
  5.9% nintedanib vs 7.8% placebo
Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

INPULSIS Trial Investigators
Preventive Strategies AE-IPF

- Nintedanib in a pooled prespecified sensitivity analysis increases time to first confirmed or suspected exacerbation
- Pirfenidone did not reduce exacerbation rates in phase 3 trials
- **Active treatment of reflux**
  - AE-IPF 0/24 vs 9/114 (0 vs 7.6%)
  - With GERD Dx 89% vs 25%
Perioperative Pirfenidone for Lung Cancer Surgery in IPF
Iwata et al Surgery Today Sept 2014

- 28 patients with IPF undergoing lung cancer surgery
- 12 pirfenidone, 16 controls
- 30 day exacerbations 37% control, 0% pirfenidone
Recombinant Human Thrombomodulin in Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Kensuke Kataoka, MD, PhD; Hiroyuki Taniguchi, MD, PhD; Yasuhiro Kondoh, MD, PhD; Osamu Nishiyama, MD, PhD; Tomoki Kimura, MD, PhD; Toshiaki Matsuda, MD; Toshiki Yokoyama, MD, PhD; Koji Sakamoto, MD, PhD; and Masahiko Ando, MD, PhD

CHEST 2015; 148(2): 436 - 443