ILD: Objectives

• Understand the basic classification of ILD
• Understand the basic nomenclature of ILD
• Describe the etiologies of subsets of ILD
• Describe the basic work-up for ILD.
• Understand when bronchoscopy is useful vs when not useful
• Describe the basic management strategy for ILD, Understand when specific treatment is indicated
ILD: Outline

• Review Basic Classification and Pathology
• Diagnostic Work-up of ILD
• Specific Disease Entities
• General Treatment Strategies
• Disease Management Issues
ILD Definitions/Terminology

• ILD “Interstitial Lung Disease”
  – Heterogeneous Group of Diffuse Parenchymal Lung
diseases (Non infectious) affecting the pulmonary
interstitial space (but also the alveolar space).
  – Clinical/pathologic/radiologic classification
    • Descriptive

• Idiopathic Interstitial Pneumonias (IIP)
  – Subset of ILD, that tend to me more chronic and have
  specific patterns.
  – Classification is more pathologic pattern on biopsy
    • Pathologic
# Diffuse Parenchymal Lung Disease

<table>
<thead>
<tr>
<th>“Idiopathic Interstitial Pneumonias”</th>
<th>“Other ILD”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UIP</strong></td>
<td>Cryptogenic Organizing Pneumonia - COP (BOOP)</td>
</tr>
<tr>
<td>- Usual Interstitial Pneumonia</td>
<td></td>
</tr>
<tr>
<td><strong>NSIP</strong> (cellular &amp; fibrotic)</td>
<td>Eosinophilic Pneumonia</td>
</tr>
<tr>
<td>- Nonspecific IP</td>
<td></td>
</tr>
<tr>
<td><strong>LIP</strong></td>
<td>Hypersensitivity Pneumonitis (HSP)</td>
</tr>
<tr>
<td>- Lymphocytic IP</td>
<td></td>
</tr>
<tr>
<td><strong>RB-ILD</strong></td>
<td>Vasculitis/Pulmonary Hemorrhage syndromes</td>
</tr>
<tr>
<td>- Respiratory Bronchiolitis-ILD</td>
<td></td>
</tr>
<tr>
<td><strong>DIP</strong></td>
<td>Sarcoid</td>
</tr>
<tr>
<td>- Desquamative IP</td>
<td></td>
</tr>
<tr>
<td><strong>AIP</strong> (Hamman-Rich Syndrome)</td>
<td>Pulmonary Langerhans Cell Histiocytosis (“EG”, smokers)</td>
</tr>
<tr>
<td>- Acute IP</td>
<td></td>
</tr>
<tr>
<td><strong>LAM</strong></td>
<td>LAM</td>
</tr>
</tbody>
</table>
Idiopathic Interstitial Pneumonias

UIP

NSIP

(RB-ILD & DIP)

• Pathologic Patterns seen on Lung Biopsy
• These pathologic patterns also have CT correlates
• Both the pathology and the CT scan have associated diseases
• All IPF is UIP
• Some UIP is not IPF
ILD Pathologic Classification

**TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES**

<table>
<thead>
<tr>
<th>Major idiopathic interstitial pneumonias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>Idiopathic nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>Respiratory bronchiolitis–interstitial lung disease</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia</td>
</tr>
<tr>
<td>Acute interstitial pneumonia</td>
</tr>
<tr>
<td>Rare idiopathic interstitial pneumonias</td>
</tr>
<tr>
<td>Idiopathic lymphoid interstitial pneumonia</td>
</tr>
<tr>
<td>Idiopathic pleuroparenchymal fibroelastosis</td>
</tr>
<tr>
<td>Unclassifiable idiopathic interstitial pneumonias</td>
</tr>
</tbody>
</table>

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### TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical–Radiologic–Pathologic Diagnoses</th>
<th>Associated Radiologic and/or Pathologic–Morphologic Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic fibrosing IP</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Usual interstitial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Idiopathic nonspecific interstitial pneumonia</td>
<td>Nonspecific interstitial pneumonia</td>
</tr>
<tr>
<td>Smoking-related IP*</td>
<td>Respiratory bronchiolitis-interstitial lung disease</td>
<td>Respiratory bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Desquamative interstitial pneumonia</td>
<td>Desquamative interstitial pneumonia</td>
</tr>
<tr>
<td>Acute/subacute IP</td>
<td>Cryptogenic organizing pneumonia</td>
<td>Organizing pneumonia</td>
</tr>
<tr>
<td></td>
<td>Acute interstitial pneumonia</td>
<td>Diffuse alveolar damage</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: IP = interstitial pneumonia.

*Desquamative interstitial pneumonia can occasionally occur in nonsmokers.
Interstitial Lung Disease

• Cough, shortness of breath
• Reticulations on CXR, multifocal opacities
• Ground glass and/or reticulations on CT
• Restrictive Lung Disease (usually)
  – LAM, Sarcoid, pulmonary Langerhans cell histiocytosis may have obstructive pattern
• Reduced DLCO & hypoxemia
ILD Behavior

• **Acute (days to weeks)**
  - Eosinophilic pneumonia
  - Hypersensitivity Pneumonitis (HSP)
  - COP/BOOP
  - Pulmonary hemorrhage syndromes (vasculitis)

• **Subacute (weeks to months)**
  - Collagen Vascular Associated (NSIP, ANCA/Vasculitis)
  - Drug induced
  - HSP
  - Sarcoid
  - COP/BOOP

• **Chronic (years)**
  - IPF
  - Collagen Vascular Associated (NSIP)
  - Drug Induced
  - Chronic HSP
  - Sarcoid
Diagnosis of ILD

• VATS Lung biopsy- GOLD standard
• Bronchoscopy for Select Cases
• Radiographic Appearance
  – Pattern on HRCT extremely useful
• Consultation with multidisciplinary team
  – Radiology
  – Pulmonary
  – Rheumatology
  – Renal
CT Patterns

• Ground Glass
  – Acute → Blood, Puss, Water
  – Chronic → Cellular inflammation

• Reticulations
  – Chronic Process -> fibrosis formation
    • Histopathology → Dense cellular inflammation and/or Fibrosis

• Honey Combing → Chronic fibrosis

• Architectural Distortion (chronic or severe acute fibrotic reaction)
  – “traction bronchiectasis”
Ground Glass CT
Reticulations & Honeycombing
Traction bronchiectasis
Case

• 66 year old with DOE, crackles and recurrent admission for “CHF”. Dry cough for 5 years
• ECHO with mild diastolic dysfunction
• CTPA shows “diffuse fibrosis”
• Sent to pulmonary for further eval
• VATS lung biopsy shows “usual interstitial pneumonia” and “honeycombing”

• What is the diagnosis and management?
IPF
Question

• What is the pathology of Idiopathic Pulmonary Fibrosis?
• What is the natural history of pulmonary fibrosis?
• What are the physiologic complications of IPF?
UIP

• Usual Interstitial Pneumonia
  – Fibrosis, honey combing and some ground glass
  – “temporal and geographic heterogeneity”
  – ALWAYS involved the bases
  – Honeycombing
  – Poor prognosis (in general)
  – High risk for lung cancer (peripheral adenocarcinoma)
UIP – when its not IPF

• Asbestosis
• Collagen vascular disease
• Chronic Hypersensitivity pneumonitis
• Drug toxicity (some)
Histopathologic

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UIP Natural History

- Progressive Dyspnea
- Progressive Hypoxemia
- Secondary Pulmonary HTN
- Cor pulmonale
- At risk for lung cancer
- Poor Long Prognosis
Work-up

- Serologic Evaluation
- Extensive history to exclude chronic hypersensitivity pneumonitis
- Detailed drug and chemotherapy history
- “HRCT” with definitive findings
- Appropriate age etc
- Rheumatology referral if needed
IPF Standard of Care

• Diagnosis
  – Clinical-Radiographic may be sufficient in many cases
• Home Oxygen
• Pulmonary Rehab
• Consideration for Anti-Fibrotic Agent
  – Nintedanib, Pirfenidone
• Referral to University Center (SELECT CASES)
• End of life counseling
55 year old female with “recurrent pneumonia” referred to pulmonary

- 55 year old female with “recurrent” pneumonias for 6 months, smoker
- Treated with antibiotics and steroids during 3 admissions, 3 months in a row
- Myalgias and rough finger tips
- Weight loss, dry cough, no fevers
- Extreme fatigue during steroid tapers
- Then developed rash and myalgias

Diagnosis?
NSIP
Non-Specific Interstitial Pneumonia
CT - NSIP
NSIP Pathology

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NSIP

- Nonspecific Interstitial Pneumonia
  - Ground glass and fibrosis
  - “temporal and geographic homogeneity”
  - Spares the costophrenic angle
  - Lack of honeycombing
  - Favorable prognosis (in general)
  - Less clear association with cancer (unlike IPF/UIP)
  - Can have “cellular” vs “fibrotic” pattern, fibrosis outcomes worse
NSIP- Disease Associations

• Drug Toxicity
  – Amiodarone
  – Chemotherapy

• Collagen Vascular Disease
  – RA, Dermatomyositis, Scleroderma, Lupus etc

• Hypersensitivity may look like this

• Idiopathic
  – Biopsy shows NSIP
  – Drug, rheumatologic and other etiologies excluded
  – These are difficult cases that often need referral
Smoking Related ILD

- RB-ILD (respiratory bronchiolitis ILD)
- DIP (Desquamative interstitial pneumonia)
- Pulmonary Langerhans cell histiocytosis (Eosinophillic Granuloma “EG”)

(Eosinophillic pneumonia common in smokers)
These all have fairly classic CT findings and coupled with history easy diagnosis to make
Practical Classification when history taking and evaluating

• Extrinsic
  – Environment (humidifier, birds, hot tub etc)
  – Drug (amio etc)
  – Smoking

• Intrinsic - medical condition

• Idiopathic
Practical Treatment

• **Steroid/Immunosuppressant Response**
  – NSIP (in theory)
  – Sarcoid, Eosinophilic pneumonia
  – Drug Induced (in theory)
  – Hypersensitivity (HSP) in theory

• **Non-steroid responsive**
  – UIP
  – IPF
  – ?Fibrotic NSIP
<table>
<thead>
<tr>
<th>Clinical Behavior</th>
<th>Treatment Goal</th>
<th>Monitoring Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible and self-limited (e.g., many cases of RB-ILD)</td>
<td>Remove possible cause</td>
<td>Short-term (3- to 6-mo) observation to confirm disease regression</td>
</tr>
<tr>
<td>Reversible disease with risk of progression (e.g., cellular NSIP and some fibrotic NSIP, DIP, COP)</td>
<td>Initially achieve response and then rationalize longer term therapy</td>
<td>Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved</td>
</tr>
<tr>
<td>Stable with residual disease (e.g., some fibrotic NSIP)</td>
<td>Maintain status</td>
<td>Long-term observation to assess disease course</td>
</tr>
<tr>
<td>Progressive, irreversible disease with potential for stabilization (e.g., some fibrotic NSIP)</td>
<td>Stabilize</td>
<td>Long-term observation to assess disease course</td>
</tr>
<tr>
<td>Progressive, irreversible disease despite therapy (e.g., IPF, some fibrotic NSIP)</td>
<td>Slow progression</td>
<td>Long-term observation to assess disease course and need for transplant or effective palliation</td>
</tr>
</tbody>
</table>
Bronchoscopy

- For acute/subacute process (eosinophilic pneumonia, acute HP, Pulmonary Hemorrhage)
- Generally not helpful in diagnosing specific ILD
  - May be helpful in sarcoid and HSP
  - Useful to rule out hemorrhage
- Useful to rule out infection
- Useful when “stuck” after have started therapy (eg rule out infection vs progression of disease)
- Consider in patients too high risk for VATS
Case

- 62 year old female, cough, dyspnea & wheeze during summer fires. Worse over 2 weeks
- SaO2 85%
- HTN, Nonsmoker, otherwise healthy
- Maybe some mild DOE over 12 months when you really pin her down
Ground Glass
Ground Glass CT
Differential Diagnosis

• Acute (blood, pus, water)
  – Acute HP, Acute Eosinophilic Pneumonia

• Chronic ?
  – ? Eosinophilic Pneumonia
  – ?HP
  – ?NSIP

• Serologic negative

• ECHO normal, BNP normal

• Bronch no eos
Diagnosis, Hypersensitivity Pneumonitis

- Further discussions revealed daily hottub exposure
- Bronch grew MAI
- “Hottub Lung”
- Treated with steroids
  - (and brief 3 drug therapy for MAI)
- Rapid improvement, so MAI therapy stopped
HP Post Steroids
Drug Therapy for “steroid responsive diseases”

• Usually corticosteroids in the 1mg/kg dose range (Bactrim Prophylaxis!)
• Treatment of underlying disease
  – eg Rheumatologic agent
• Addition of steroid sparing agent if >6months of therapy needed
• “Lung friendly drugs”
  – Azathioprine, Mycophenolate, prednisone
  – vs Methotrexate, Cytoxan
Management: Monitoring Disease Course

• Weigh risk/benefits of therapy
  – Obesity, heart failure, diabetes
• Short term follow-up during observation period
  – eg monitor for spontaneous remission in sarcoid
• Withdrawal of offending agent, and monitor
• Close monitoring and counseling for deteriorating IPF patients
Monitoring Response to Treatment

• Follow CT scan, PFTs, FiO2 needs
• PFTs and CT 3 months after therapy
• Frequent (eg 1-3month) clinic follow-up initially to closely monitor
• Annual to bi-annual follow-up for stable disease/not changing therapy
“I am more short of breath” does not equal “My ILD is Worse”

- ILD worse
- Drug side effect/toxicity
- Infectious complication
- Non-Pulmonary Disease
  - Cardiac
  - Pulmonary Vascular
  - Other chronic medical condition
Managing Disease

Decline in Lung Function or CT worse

- Disease Progression
- Treatment Toxicity
- Infectious Complications
Monitoring Complications of Treatment

• PCP prophylaxis

• Drug side effects (eg LFTs, CBC, renal function)

• May need Infectious Disease assistance

• Involve Rheum and Renal when appropriate
Infections

• Remember when on immunosuppressant, Fever, productive cough and elevated WBC will rarely all be present
• Malaise, poor appetite, increased DOE, increase oxygen, tachycardia are more likely
• Other collagen vascular disease is “great” yet patient is clinically deteriorating-> ?infection
Established ILD: when to bronch

• New worsening of CT or lung function, and on immunosuppression
• Failed standard “CAP” or “HCAP” therapy
• Concern for flare of disease but adding immunosuppressant is next step, and no recent investigation (eg bronch or VATS) that shows no infection
• Patient who won’t tolerate VATS and need lower risk attempt at diagnosis
• Concern for infection
SUMMARY: ILD Diagnosis

• **History, history, history**
  – Age of patient
  – Pace of disease
  – HSP or Drug risks (amiodarone, nitrofurantoin, certain chemotherapy agents etc)
  – Occupational risks
  – Infectious risks (eg Sarcoid Mimics)

• **CT scan**
  – Pattern is VERY helpful with clear, good history

• **SeroLogic evaluation**
ILD – Evaluation Made Easy

• **No infection/Infectious syndrome**
• **CT read and pattern**
• **Rule out Drugs**
• **Acute/Sub-acute**
  – Eosinophillic Pna, ANCA vasculitis, acute HP ?, COP, ?Sarcoid
• **Chronic > 1 year**
  – Smoker ? (?RBILD, DIP on CT)
  – HSP risk stratification/history (birds, humidifiers, steamers, hot-tubs)
  – Rheumatologic symptoms (?NSIP pattern, ?Serologies)
  – UIP or NSIP pattern on CT
Diffuse Parenchymal Lung Disease

Known Etiology
Drugs, Collagen Vascular Disease, Exposure

Smoking Related
RB-ILD
DIP
PLCH

Smoking Cessation +/- Steroids

Remove offending agent
Treat Underlying Disease +/- Immunosuppression

Idiopathic Interstitial Pneumonias

Acute/Subacute COP/BOOP

Chronic UIP/IPF

Less Clear therapy

Steroids

Sarcoid
NSIP
HSP
ILD: When to Refer

- Would strongly consider Pulmonary Consultation if suspecting ILD
- Jump start work up: CT Scan, PFTs, (ANA panel, ANCA panel)
- Don’t start steroids unless you know what you are treating*
- More “Urgent referral”:
  - Subacute process (< 6 months)
  - New significant hypoxemia with ILD on CT
  - Concern for pulmonary hemorrhage
  - Acute syndrome and unclear if infection or acute ILD (eg eosinophillic pneumonia, pulmonary hemorrhage, autoimmune) and bronchoscopy needed to help evaluate.

* We all may be forced to start “empiric steroids” is certain cases, but exhaustive work-up should at least be initiated and infection ruled out and/or clear risk benefits considered.
T/F: All UIP is equivalent to IPF
T/F: NSIP has the worst prognosis of all ILD
T/F: All New ILD patients should undergo bronchoscopy as part of the initial work-up
T/F: IPF can be diagnosed by history, exam and HRCT alone
T/F: Bronchoscopy is useful for assessing for infection
T/F: Corticosteroids are first line agents for steroid responsive ILD
T/F: VATS lung biopsy should strongly considered in any disease being considered for immunosuppression
Resources and Citations


• IPF: Challenges and Opportunities for the Clinician and Investigator. Swigris et al. CHEST 2005 127(1)275-83