Educational Objectives:
1. Review the differential diagnosis of interstitial lung disease.
2. Develop a standard approach for an initial outpatient visit for interstitial lung disease.
3. Identify interstitial lung diseases with clear pathognomonic findings.

Scenario:
Mrs. F is a 75-year-old woman with a history of hypothyroidism who presents for a second opinion regarding interstitial lung disease. She reports that she first noted dyspnea about 2 years ago, which was attributed to issues with her thyroid medications. She never had a chest x-ray. Her shortness of breath was mildly progressive, but a few months ago, she got a respiratory infection, and her breathing worsened significantly. She went to a local pulmonologist, who ordered a CT scan (representative images below). Before proceeding with care locally, she wanted a second opinion and has come to see you.

Question 1: What is a systematic approach when considering the broad differential diagnosis of interstitial lung disease?

Multiple ways exist to classify interstitial lung diseases (AKA diffuse parenchymal lung disease). The chart below is a suggested method to help take an initial history of sending initial testing.
Adapted from King TE. Idiopathic interstitial pneumonias: progress in classification, diagnosis, pathogenesis and management. Trans Am Clin Climatol Assoc 2004; 115: 43-78.

**IPF= idiopathic pulmonary fibrosis, NSIP= non-specific interstitial pneumonitis, DIP= desquamative interstitial pneumonia, RB-ILD= respiratory bronchiolitis-ILD, AIP= acute interstitial pneumonia, COP= cryptogenic organizing pneumonia, LIP= lymphocytic interstitial pneumonia, HP= hypersensitivity pneumonitis, LAM= lymphangioleiomyomatosis, PLCH= pulmonary Langerhan’s cell histiocytosis, PAP= pulmonary alveolar proteinosis.

Question 2: What historical facts would help narrow this list down?

a. Symptom duration
   - i. Acute: Drug-induced, HP, IPF exacerbation, AIP
   - ii. Episodic: HP, COP, Chronic eosinophilic pneumonia

b. History of autoimmune diseases or symptoms
   - i. Common diseases include rheumatoid arthritis, polymyositis/dermatomyositis, anti-synthetase syndrome, lupus, scleroderma, and Sjogren’s
   - ii. Symptoms include arthritis/arthralgias, Raynaud’s, dysphagia, characteristic rashes, and sicca symptoms.
   - iii. Some patients have interstitial lung disease and symptoms or serologic results suggesting rheumatologic disease but do not meet the criteria for any specific autoimmune diagnosis. Such patients are considered to have interstitial pneumonia with autoimmune features (IPAF)

c. Medications/Drugs
   - i. MANY. The British Thoracic Society guidelines have an online summary. See Wells AU et. al. (full reference below).

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Nitrofurantoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-modifying antirheumatic drugs</td>
<td>Sulfasalazine, methotrexate, gold penicillamine, leflunomide, etanercept</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Amiodarone, ACE inhibitors, statins</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>Bleomycin, cyclophosphamide, selective EGFR-inhibitors</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>Heroin, methadone, talc</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Oxygen, radiation, aspirin, interferons</td>
</tr>
</tbody>
</table>
d. Occupational and other exposures:

<table>
<thead>
<tr>
<th>Type of Antigen</th>
<th>Examples of Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mushrooms, fungi, yeasts</td>
<td>Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Dairy barns (farmer's lung)</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Metalworking fluids, sauna, hot tub</td>
</tr>
<tr>
<td>Bird proteins</td>
<td>Pigeons, dove feathers, ducks, parakeets</td>
</tr>
<tr>
<td>Chemicals</td>
<td>Isocyanates (auto painters), zinc, dyes</td>
</tr>
</tbody>
</table>

Figure borrowed from Lacasse Y, Girard M, Cormier Y. Recent advances in hypersensitivity pneumonitis. Chest. 2012;142:208-217.

e. Smoking history: There are a few interstitial lung diseases associated with cigarette smoking:

i. Desquamative Interstitial Pneumonia (DIP)
ii. Respiratory Bronchiolitis – Interstitial Lung Disease (RB-ILD)
iii. Pulmonary Langerhans Cell Histiocytosis (PLCH)
iv. Combined pulmonary fibrosis/emphysema (CPFE)

Scenario continued:
Mrs. F notes 2 years of symptoms with recent dramatic worsening. She notes lower back and knee pain, but no other joint symptoms. She thinks her fingers get cold and sometimes numb in the cold, but she hasn’t noted color changes. Other than occasional over-the-counter medicines, she has only ever taken levothyroxine. She has never smoked. She is from Mexico and spends about six months per year there still. There is no known mold or water damage in her homes. She previously owned a pet bird several years ago and does not have a hot tub.

Question 3: You plan to obtain updated pulmonary function tests, a six-minute walk test, review the CT scan with the radiologist and see her again in a month to discuss the results. What, if any, laboratory testing would you order?

There is no clear consensus on what laboratory tests need to be ordered. The BTS guidelines provide the following “memory card” for initial ILD visits:
Because ILD can be the first manifestation of any of the above connective tissue diseases, consider also sending the following tests:

- ANA
- RF, CCP
- Anti-Jo-1
- Anti-MDA5
- Anti-SCL-70
- RNA polymerase III
- SSA/SSB
- ANCA with reflex MPO/PR3
- CK, aldolase
- Serum precipitins – only serve as markers of exposure; false negatives are common.

To help you narrow the differential diagnosis based on radiology, a table from the ATS IPF guideline describing the expected radiologic pattern of abnormality for UIP and alternative diagnosis is included below.
Table borrowed from Raghu et al. American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5. 2018. PMID 30168753

**Scenario continued:**
You review Mrs. F’s scan with the radiologist. There are clear peripheral reticular interstitial changes, but there is a significant amount of upper lobe involvement, making this less consistent with a UIP pattern. The primary radiographic differential diagnosis is NSIP versus Fibrotic HP. Her labs return with an elevated ANA (1:640) and RF (96), but are otherwise normal, including the serum HP panel. PFTs show moderately severe restriction with a moderate diffusion defect, and her walk test demonstrated the lowest SpO2 at 92% with a distance of 880 feet. You suspect a diagnosis of interstitial pneumonia with autoimmune features (IPAF), but feel that fibrotic HP has not been excluded, given her exposure history. She presents for follow-up.
**Question 4: What is the most appropriate next diagnostic step?**

Options include:
- Empiric treatment
- Bronchoscopy with BAL/TBBx
- Bronchoscopy with cryobiopsy
- Referral for surgical lung biopsy

There is no definite answer, but the adjacent algorithm from the 2008 BTS guidelines and the recently updated ATS guidelines can help us make the decision. Because the HRCT did not provide us with a diagnosis that can be made with a “high degree of confidence,” we should consider proceeding with another diagnostic step. Additionally, for this patient, we should review the list of diagnoses for which a BAL/TBBx and cryobiopsy might increase the diagnostic confidence.

Question 5: If you were to proceed with bronchoscopy and BAL, what BAL cellular profile would be most consistent with hypersensitivity pneumonitis?

<table>
<thead>
<tr>
<th>BAL finding</th>
<th>Consistent interpretation/suggested diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils &gt; 25%</td>
<td>Eosinophilic pneumonitis</td>
</tr>
<tr>
<td>Lymphocytes &gt; 26%</td>
<td>Sarcoidosis, HP, cellular NSIP, drug reaction, CBO, UIP, lymphoproliferative disorder</td>
</tr>
<tr>
<td>Neutrophils &gt; 50%</td>
<td>AIP, DAD, AEPF, pulmonary infection</td>
</tr>
<tr>
<td>Bloody fluid</td>
<td>Pulmonary haemorrhage, DAD</td>
</tr>
<tr>
<td>High haemosiderin score</td>
<td>DAA, DMD</td>
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<tr>
<td>CD1a+ cells &gt; 4%</td>
<td>PLCH</td>
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<tr>
<td>Milky BAL fluid with PAS-positive amorphous debris</td>
<td>PAP</td>
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<tr>
<td>Monotypic lymphocytes</td>
<td>Pulmonary lymphomatous malignancy</td>
</tr>
<tr>
<td>Malignant cells</td>
<td>Pulmonary malignancy</td>
</tr>
<tr>
<td>Squamous epithelial cells &gt; 5%</td>
<td>Unsuitable sample due to upper airway secretion contamination</td>
</tr>
<tr>
<td>Bronchiolar epithelial cells &gt; 5%</td>
<td>BAL sample may be unsuitable for cell analysis</td>
</tr>
</tbody>
</table>

Figure borrowed from Meyer KC, Raghu G. Bronchoalveolar lavage for the evaluation of interstitial lung disease: is it clinically useful? Eur Respir J. 2011;38:761-769.

Scenario continued:
Because the differential includes fibrotic HP and NSIP/IPAF, the case is discussed at a Multi Disciplinary Case conference. Options of treating with steroids for a short period are discussed as is the option of a biopsy. After extensive discussion with the patient about the recommendations, decision is made to pursue a lung biopsy (considerations are patient preference to know exactly what she is dealing with vs the potential harm from a biopsy). You decide that BAL will not increase your ability to distinguish between the leading diagnoses. She undergoes a surgical lung biopsy without complication.

Question 6: When her biopsy results return, what is the best way to determine a final diagnosis?

To more confidently make a final diagnosis, it is important to have a multidisciplinary discussion involving pulmonologists, radiologists, and pathologists. Flaherty et al. conducted a study to assess the utility of the multidisciplinary discussion. The study consisted of several steps, from pulmonologists and radiologists reviewing the HRCT individually to a consensus discussion including pulmonologists, radiologists, and pathologist.

Though there is no way to know if the final diagnoses were “correct,” the researchers measured inter-observer agreement at each stage:

<table>
<thead>
<tr>
<th>Table 3. Interobserver Agreement at Each Diagnostic Step</th>
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<tbody>
<tr>
<td>Step</td>
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<tr>
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<tr>
<td>1</td>
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<td>4</td>
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<td>5</td>
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</table>

Importantly, the final diagnosis was more influenced by pathologists in cases of non-IPF idiopathic interstitial pneumonias compared to IPF.

Here is a schematic of how a multidisciplinary discussion can help make confident diagnoses of IPF or consider alternative diagnoses.

![Schematic](image)

Figure borrowed from Raghu et al Am J Respir Crit Care Med 205e18-e47. DOI: 10.1164/rccm.202202-0399ST

**Scenario continued:**
Mrs. F’s biopsy demonstrated patchy fibrosis with marked lymphoid aggregates and moderate to severe interstitial chronic inflammatory infiltrates, suggesting an underlying collagen vascular disease. A multidisciplinary discussion was held, and given the positive autoimmune serologies, atypical CT pattern for IPF, and pathology findings not consistent with fibrotic hypersensitivity pneumonitis, the consensus diagnosis was connective tissue disease-associated interstitial lung disease/IPAF. Mrs. F was started on mycophenolate mofetil and her PFTs have remained stable while on therapy.

**Question 7: Is there a role for antifibrotic therapy in this patient? What other therapies could be considered in the future?**

With recent data from the SENSCIS trial\(^{(10)}\) and INBUILD trial\(^{(9)}\) there is data to suggest that nintedanib therapy could slow the rate of lung decline in patients with systemic sclerosis-associated ILD and patients with progressive fibrosing lung disease with and without a UIP pattern of fibrosis. Additionally, there was recent FDA approval for the inhaled pulmonary vasodilator treprostinil for patients with ILD and documented secondary pulmonary hypertension by RHC based on data from the INCREASE trial. Serial monitoring with pulmonary function tests evaluating the DLCO and screening with transthoracic echocardiogram may provide helpful information in patients with ILD in whom right heart dysfunction is suspected. Given the relatively advanced nature of Mrs. F’s ILD, obtaining an echocardiogram at this juncture would be reasonable.
References:


Pre/Post-Test Questions:

1. Which of the following ILDs is NOT most commonly seen in smokers?
   a. Pulmonary Langerhan’s Cell Histiocytosis
   b. Respiratory Bronchiolitis Interstitial Lung Disease
   c. Lymphangiolyomyomatosis
   d. Desquamative Interstitial Pneumonia

2. A 35-year-old female presents to the office for new onset dyspnea and possible interstitial changes on her CXR. She has a CT scan and ultimately undergoes a bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy as part of her evaluation. The BAL fluid reveals the presence of CD1a+ cells. Which of the following is the most likely diagnosis based on the BAL fluid findings alone?
   a. Pulmonary Alveolar Proteinosis
   b. Hypersensitivity Pneumonitis
   c. Lymphocytic Interstitial Pneumonia
   d. Pulmonary Langerhan’s Cell Histiocytosis

3. A 65-year-old male with a history only notable for hypertension presents to the clinic for evaluation of ILD. He has no clear systemic symptoms to suggest connective tissue disease, and the remainder of the clinical history is largely unrevealing. He has a high-resolution CT chest that reveals findings concerning either idiopathic pulmonary fibrosis or non-specific interstitial pneumonitis. However, at this point, you remain uncertain about his underlying diagnosis and decide to consider additional testing with tissue biopsy. He has a history of hypertension treated with lisinopril 5 mg daily and no other significant co-morbidities. His PFTs reveal an FEV1 of 50% predicted (declined from 65% one year prior). He does not desaturate with ambulation. His 6MWT distance is normal for his age. Which of the following would be the best approach to his management moving forward according to established BTS guidelines?
   a. Bronchoscopy with bronchoalveolar lavage
   b. Bronchoscopy with bronchoalveolar lavage and transbrochial lung biopsy
   c. Surgical lung biopsy
   d. Initiate empiric treatment for the most likely cause of his ILD and monitor with serial PFTs and six-minute walk tests