Welcome!
PFF CARE CENTER NETWORK EXPANSION

Pulmonary Fibrosis
FOUNDATION
Occupational and Environmental Exposures and Pulmonary Fibrosis

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PFF Care Center Network site
Disclosures

- Advisory board: Intermune, Boehringer-Ingelheim
- Faculty: France Foundation
Overview

- What is Pulmonary Fibrosis?

- What are the *known* occupational and environmental causes of Pulmonary Fibrosis?

- What is *Idiopathic* Pulmonary Fibrosis (IPF)?
  - Is Idiopathic Pulmonary Fibrosis actually caused by occupational and environmental exposures?
What is Pulmonary Fibrosis?
“The word "pulmonary" means ‘lung’ and the word "fibrosis" means **scar tissue** – similar to scars that you may have on your skin from an old injury or surgery. So, in its simplest sense, *pulmonary fibrosis (PF) means scarring in the lungs*. But, pulmonary fibrosis is more serious than just having a scar in your lung. In PF, the scar tissue builds up in the walls of the air sacs of the lungs, and eventually the **scar tissue makes it hard for oxygen to get into your blood**. Low oxygen levels (and the stiff scar tissue itself) can cause you to feel short of breath, particularly when walking and exercising.”

http://www.pulmonaryfibrosis.org/life-with-pf/about-pf
Pulmonary Fibrosis....

- “isn’t just one disease. It is a family of **more than 200** different lung diseases”

- “falls into even **larger group of interstitial lung diseases**” (ILD)

  - “When an interstitial lung disease includes scar in the lung, we call it pulmonary fibrosis.”

http://www.pulmonaryfibrosis.org/life-with-pf/about-pf
Asthma

Abnormal Airway

Normal lung interstitium

Pulmonary Fibrosis

Abnormal interstitium
Interstitial Lung Disease

Idiopathic

Idiopathic Pulmonary Fibrosis
AIP
NSIP

Connective Tissue Disease/Autoimmune

Scleroderma
Systemic Lupus Erythematosis
Rheumatoid Arthritis
Polymyositis/Dermatomyositis

Occupational and Environmental

Inorganic dust
Organic dust
Gases/Fumes
Radiation

Drug Induced

Chemotherapeutic agents
Radiation
Antiarrhythmics
Antibiotics
Anticonvulsants

Genetic Inherited

Familial pulmonary fibrosis
Hermansky-Pudlak syndrome
What are the *known* occupational and environmental causes of Pulmonary Fibrosis?
Known Occupational and Environmental Causes

- Pneumoconioses
  - Asbestosis
  - Silicosis
  - Coal workers pneumoconiosis
- Hypersensitivity pneumonitis
- Chronic beryllium disease
- Other:
  - Metals: (i.e. Cobalt, indium, aluminum)
  - Flock worker’s lung

- NOT considered Idiopathic Pulmonary Fibrosis (IPF)
- Each entity has a distinct pattern that differs from IPF
Known Occupational and Environmental Causes

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ASBESTOSIS
What is Asbestos?

- Heterogeneous group
- Naturally occurring fiber
- Hydrated magnesium silicates

Properties

- Tensile strength
- Flexible
- Resistant to chemical and thermal degradation
- High electrical resistance
- Can be woven
Amphibole vs. serpentine

**AMPHIBOLE**: (long straight)
- crocidolite, amosite, tremolite
- Considered *more* toxic

**SERPENTINE**: (curved)
- chrysotile (mostly)
- 90% of all asbestos chrysotile
- Considered *less* toxic
Asbestos: Occupations/Industries

<table>
<thead>
<tr>
<th>OCCUPATIONS</th>
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<tbody>
<tr>
<td>Plumbers</td>
</tr>
<tr>
<td>Pipefitters</td>
</tr>
<tr>
<td>Steamfitters</td>
</tr>
<tr>
<td>Electricians</td>
</tr>
<tr>
<td>Insulation workers</td>
</tr>
<tr>
<td>Carpenters</td>
</tr>
<tr>
<td>Boilermakers</td>
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<tr>
<td>Welders and cutters</td>
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<td>Janitors</td>
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<tr>
<th>INDUSTRIES</th>
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<tbody>
<tr>
<td>Construction</td>
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<tr>
<td>Shipbuilding &amp; Repair</td>
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<tr>
<td>Chemicals</td>
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<tr>
<td>Nonmetallic mineral stone</td>
</tr>
<tr>
<td>Railways</td>
</tr>
<tr>
<td>Yarn, thread, fabric mills</td>
</tr>
<tr>
<td>Trucking</td>
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<tr>
<td>Plastic and rubber</td>
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Asbestosis

- Usually chronic exposure necessary (10+ years); but high intense brief exposure for as little as 1 month
- Long latency (20-30 years)
- Symptoms: Insidious onset of dyspnea, cough
- Smokers at risk
- Examination: inspiratory crackles, clubbing, cor pulmonale
- PFT’s: Restriction; Reduced DLCO
  - Obstruction reflects concomitant smoking
Who is at risk?: 1.3 million US Workers

Historical legacy of older workers
- Workers in occupations managing remaining hazard
- Asbestos abatement
- Renovation and demolition of structures
- New products:
  - Friction surface (brake pads)
  - Roofing materials
  - Vinyl tile
  - Imported cement pipe and sheeting
- Passive exposure (carrying home asbestos on clothes)
- Developing countries
Diagnosis

- Evidence of structural change by
  - Imaging OR Histology
- Evidence of plausible causation by
  - History OR Markers of exposure (plaques) OR Recovery of asbestos bodies
- Exclusion of alternative diagnoses
- Evidence of functional impairment by
  - Signs and symptoms OR
  - PFT’s (Restriction or reduced DLCO) OR
  - Inflammation (BAL) OR
  - Exercise testing
Asbestosis HRCT

Figure 1a HRCT lung windows demonstrate lower lobe predominant disease with evidence of reticular markings and honeycombing. Figure 1b: Mediastinal windows reveal evidence of pleural thickening and calcifications. Courtesy of Jonathan Killam, MD and Ami Rubinowitz, MD.

Gulati M. Curr Opin Pulm Med. 2015
Pathology: Examining for Asbestos Fibers

- Lung Tissue
  - Bronchoscopy
    - Bronchoalveolar lavage fluid (BAL) for asbestos bodies
    - Transbronchial biopsy

- Pathology
  - Light microscopy
  - Scanning/Transmission electron microscopy
  - Energy-dispersive X-ray analysis

**Light Microscopy with Iron Stains**
- Ferruginous bodies are fibers surrounded by a coating of iron and protein
- Coating may also surround talc, glass, iron, carbon
- Asbestos body if surrounds asbestos

Courtesy Robert Homer, MD PhD
Hypersensitivity Pneumonitis
Hypersensitivity Pneumonitis

• Also known as Extrinsic Allergic Alveolitis
  • Heterogeneous group of diseases from inhalational exposure to organic particles

• Forms:
  • Acute (4-8 hours)—flulike symptoms after intense/intermittent exposure
  • Subacute (weeks to months)
  • Chronic (months to years)—Repeated acute episodes or low level chronic exposure

• Outbreaks reported water sources

• Smoking protective
<table>
<thead>
<tr>
<th>Disease</th>
<th>Agent</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer’s Lung</td>
<td>Microbes&lt;br&gt;Thermophilic actinomycetes&lt;br&gt;Saccharopolyspora rectivirgula&lt;br&gt;Thermactinomyces vulgaris</td>
<td>Moldy hay, straw</td>
</tr>
<tr>
<td>Woodworker’s Lung</td>
<td>Alternaria species&lt;br&gt;Penicillium chrysogenum</td>
<td>Moldy wood dust</td>
</tr>
<tr>
<td>Hot tub lung</td>
<td>Mycobacterium avium complex</td>
<td>Contaminated water</td>
</tr>
<tr>
<td>Humidifier lung</td>
<td>Bacteria---Thermoactinomyces candidus, Bacillus sp, Thermophilic actinomycetes&lt;br&gt;Fungi ---Aureobasidium pullulans&lt;br&gt;Amoebae---Naegleria gruberti</td>
<td>Contaminated water</td>
</tr>
<tr>
<td>Metal workers’ lung</td>
<td>Mycobacterium avium complex</td>
<td>Contaminated metal working fluids</td>
</tr>
<tr>
<td>Bird---fancier’s lung</td>
<td>Animals&lt;br&gt;Avian protein</td>
<td>Bird excreta, blood or feather</td>
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<tr>
<td>Pigeon breeder lung</td>
<td></td>
<td></td>
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<tr>
<td>Feather duvet lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woodworker’s lung</td>
<td>Alternaria, Penicillium spp</td>
<td>Wood pulp, dust</td>
</tr>
<tr>
<td>Paint refiner’s lung</td>
<td>Isocyanates</td>
<td>Plastics, resins, paints</td>
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</table>
Hypersensitivity Pneumonitis--Diagnosis

Chronic Hypersensitivity Pneumonitis

- Differs from Idiopathic Pulmonary Fibrosis CT Scans
  - Upper and mid lung zones involved (versus lower lobe)
  - Mosaic attenuation and/or air trapping
  - Centrilobular nodules and ground glass may be present

Courtesy Ami Rubinowitz, MD
Hypersensitivity Pneumonitis: Diagnosis

- Poorly formed granuloma—hallmark of hypersensitivity pneumonitis

Courtesy Robert Homer, MD PhD
Hypersensitivity Pneumonitis--Diagnosis

- Evidence of exposure
  - Acute symptoms with exposure
  - Improvement upon removal from exposures
- Positive specific precipitating antibodies
- High resolution chest CT Scan
- Bronchoscopy (lymphocytosis, low CD4/CD8 ratio)
- Surgical lung biopsy
Treatment

- Removal from exposure
- Corticosteroid therapy
What is *idiopathic* Pulmonary Fibrosis (IPF)?
Interstitial Lung Disease

Idiopathic

Idiopathic Pulmonary Fibrosis
AIP
NSIP

Connective Tissue Disease/Autoimmune

Scleroderma
Systemic Lupus Erythematosus
Rheumatoid Arthritis
Polymyositis/Dermatomyositis

Occupational and Environmental

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Chemotherapeutic agents
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Antiarrhythmics
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Anticonvulsants

Genetic Inherited

Familial pulmonary fibrosis
Hermansky-Pudlak syndrome
“IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP”

- Idiopathic=Unknown Cause
UIP Pattern on HRCT

- UIP
  - Peripheral, subpleural and bibasilar reticulonodular opacities associated with reduced lung volumes
  - Honeycombing changes
  - Traction bronchiectasis
  - Lower lobe predominant

Courtesy of Dr. Ami Rubinowitz
Biopsy: Usual Interstitial Pneumonia

- Patchy collagen fibrosis
- Temporality: Variegated
- Fibroblastic foci:
- Scant inflammation
- Honeycombing

Courtesy of Robert Homer, MD PhD
Diagnosis of Idiopathic Pulmonary Fibrosis

Usual Interstitial Pneumonia Pattern = Idiopathic Pulmonary Fibrosis (IPF)

Diagnosis
• Exclusion of other known causes of UIP
• Presence of UIP on HRCT
• HRCT pattern of *definite/possible* UIP with a surgical lung biopsy showing *definite/probable* UIP
Is Idiopathic Pulmonary Fibrosis actually caused by occupational and environmental exposures?
Is Idiopathic Pulmonary Fibrosis an Environmental Disease?

Varsha S. Taskar and David B. Coultas

Department of Medicine, The University of Texas Health Center at Tyler, Tyler, Texas
Proposed Pathogenesis—Risk Factors

- Exposures
  - Occupational and Environmental Exposures (including tobacco smoke)
- Microbial agents
- Gastroesophageal reflux
- Genetic factors

Modified from Selman et al, Expert Opin Emerging Drugs 2011
Challenges

- Rare disease
  - Case Control studies

- Exposure misclassification
  - Past exposures
    - Recall bias
    - Long latency period

- Variation in susceptibility
Genetic Variation

- Common variation in the promoter of the gene encoding mucin 5b associated with familial interstitial pneumonia and IPF
- Impaired host defense that allows for excessive lung injury from inhaled cigarette smoke can enhance expression

## Risk Factors--Exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>England/Wales Scott et al</th>
<th>Trent, UK Hubbard et al</th>
<th>United States, Mullen et al</th>
<th>United States Baumgartner</th>
<th>Japan Iwai et al</th>
<th>Japan Miyake et al</th>
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<tbody>
<tr>
<td>Agriculture/farming</td>
<td></td>
<td></td>
<td>1.60 (1.0-2.5)</td>
<td>3.01 (1.29-7.43)</td>
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<tr>
<td>Livestock</td>
<td>10.89 (1.24-96.0)</td>
<td></td>
<td>2.70 (1.30-5.50)</td>
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<tr>
<td>Wood dust</td>
<td>2.94 (0.87-9.9)</td>
<td>1.71 (1.01-2.92)</td>
<td>3.3 (0.42-25.8)</td>
<td>1.60 (0.80) 3.30</td>
<td>6.71 (0.37-123.59)</td>
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<tr>
<td>Textile dust</td>
<td>0.9 (0.24-3.44)</td>
<td>1.80 (1.10-2.96)</td>
<td>1.90 (0.80-4.40)</td>
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<tr>
<td>Mold</td>
<td></td>
<td></td>
<td>16.0 (1.62-158)</td>
<td></td>
<td>0.98 (0.48-2.01)</td>
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</tr>
<tr>
<td><strong>Metal dust</strong></td>
<td><strong>10.97 (2.34-52.4)</strong></td>
<td><strong>1.68 (1.07-2.65)</strong></td>
<td><strong>2.00 (1.00-4.00)</strong></td>
<td><strong>1.34 (1.14-1.59)</strong></td>
<td><strong>9.55 (1.68-181.12)</strong></td>
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<tr>
<td>Stones/sand/silica</td>
<td>1.59 (0.52-4.79)</td>
<td>1.76 (1.01-3.07)</td>
<td>11.01 (1.05-115)</td>
<td>3.90 (1.20-12.70)</td>
<td></td>
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<tr>
<td>Wood fires</td>
<td>12.55 (1.40-114.0)</td>
<td></td>
<td>0.80 (0.40-1.60)</td>
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<tr>
<td><strong>Smoking</strong></td>
<td><strong>1.11 (0.13-1.40)</strong></td>
<td><strong>1.57 (1.01-3.43)</strong></td>
<td><strong>1.60 (1.10-2.40)</strong></td>
<td><strong>2.94 (1.37-6.3)</strong></td>
<td><strong>3.23 (1.01-10.84)</strong></td>
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</tr>
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Epidemiologic Evidence

- Population attributable risk for IPF (Taskas, Clin Chest Med 208)
  - Smoking 49%
  - Farming 21%
  - Livestock 4%
  - Wood dust 5%
  - Metal dust 3.4 %
  - Stone /sand/silica 3.5%

Lung Tissue Analysis (Few studies)
- ie Silica/silicates (Monso, Envir Health 1990)
Implications

- Clinical course?

- Exposure management
  - Reduction versus cessation
  - Public health implications

- Medical management?

- Worker’s compensation
  - “Black” lung benefits for Coal Workers
Key Points

- There are known causes of pulmonary fibrosis not referred to as Idiopathic Pulmonary Fibrosis
  - ie. Chronic hypersensitivity pneumonitis, Asbestosis

- There may be occupational and environmental risk factors for Idiopathic Pulmonary Fibrosis (IPF)

- Future study is needed to better understand the prognostic and treatment implications of pulmonary fibrosis related to exposures
Q + A
• If I have cHP with a UIP pattern seen on a CT scan, can I take either of the newly approved medications for IPF?

• Could exposure to asbestos on a U.S. Navy ship almost 50 years ago be a precursor to IPF?

• My husband passed away from IPF in 2013. He served overseas in the Middle East, could the dust, oil, gas fires, etc. contribute to his IPF?

• My mother worked in an electronics assembly line for years, doing lead soldering no vent hoods and I wonder if there is a connection between PF and this work?
Wednesday March 11, 2015
“Pulmonary Hypertension & Pulmonary Fibrosis”
Presented by: Steven Nathan, MD
Inova Fairfax Hospital

Wednesday March 18, 2015
“Ask a Doc”
The PFF Medical Team will answer your questions during this hour-long Q+A session.
Thank you.