Diffuse parenchymal lung disease from sarcoidosis to alphabet soup

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Cleveland Clinic
Disclosures

- Consulting/advisory
  
  Boehringer-Ingelheim
  Genentech
  Gilead
  Celgene
  Araim
  Mitsubishi-Tanabe

- Research support
  
  Boehringer-Ingelheim
  Mallinkrodt
  Gilead
  Araim
  NHLBI

- No medication is FDA-approved for the other ILDs
A 59 year-old man presents with progressive dyspnea on exertion over the past one year. He reports a dry cough but no wheezes, sputum production, fevers or hemoptysis. He smoked 1 ppd for 20 years but quit 10 years ago. He works as a lawyer. PFTs are as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Actual</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>1.28</td>
<td>38</td>
</tr>
<tr>
<td>FVC</td>
<td>1.57</td>
<td>35</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>2.70</td>
<td>42</td>
</tr>
<tr>
<td>DLCO</td>
<td>5.06</td>
<td>16</td>
</tr>
</tbody>
</table>
Is all UIP IPF?
What is CPFE? LAM?
Objectives

- Review the diagnostic approach and classification of ILD
- Update the pathogenesis and treatment of IPF
- Recognize the diagnostic dilemma encountered with IIPs
- Discuss sarcoidosis
Interstitial lung disease

Known cause
- Occupational
- Medications
- Radiation
- Connective tissue disease

Idiopathic interstitial pneumonias

Smoking-related
- Respiratory-bronchiolitis-ILD
- Desquamative interstitial pneumonia
- Langerhan’s cell histiocytosis

Granulomatous
- Sarcoidosis
- Hypersensitivity pneumonitis
- CVID and other causes

Other ILD
- Lymphangioleiomyomatosis
- Eosinophilic pneumonia
- Alveolar proteinosis

Idiopathic pulmonary fibrosis

Nonspecific interstitial pneumonia

Cryptogenic organizing pneumonia

Acute interstitial pneumonia

Classifying ILD

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, Moises Selman, Athol U. Wells, Jurgen Behr, Demosthenes Bouras, Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo Cordeiro, Vincent Cottin, Bruno Crestani, Marjolein Drent, Rosalind F. Duddden, Jim Egan, Kevin Flaherty, Cory Hogaboam, Yoshikazu Inoue, Takeshi Jokoh, Dong-Sooon Kim, Masanori Kitaichi, James Loyd, Fernando J. Martinez, Jeffrey Myers, Shandra Protzko, Ganesh Raghur, 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
Drug reactions are frequently missed
Which may be associated with obstruction as well as restriction?

- Idiopathic pulmonary fibrosis
- Sarcoidosis
- Asbestosis
- Combined pulmonary fibrosis-emphysema
- Scleroderma-ILD
- Lymphangioleiomyomatosis (LAM)
- Hypersensitivity pneumonitis
- Amiodarone lung
Which may be associated with obstruction as well as restriction?

- Idiopathic pulmonary fibrosis
- Sarcoidosis
- Asbestosis
- Combined pulmonary fibrosis-emphysema
- Scleroderma-ILD
- Lymphangioleiomyomatosis (LAM)
- Hypersensitivity pneumonitis
- Amiodarone lung
Which are more likely to have exaggerated ↓FVC% < ↓DLCO%?

- Sarcoidosis
- IPF
- Hypersensitivity pneumonitis
- Rheumatoid lung
- Asbestosis
- Smoking-related ILD
Physical exam

- Non-specific
- Rales, squeaks, wheezes
- Connective tissue disease signs
- Lymph nodes
- Clubbing
- Cor pulmonale
Interstitial Lung Abnormalities are present in 8-13%
ILAs associate with pulmonary restriction
Weekly multidisciplinary conference
Interstitial lung disease

Known cause
- Occupational
- Medications
- Radiation
- Connective tissue disease

Idiopathic interstitial pneumonias

Idiopathic interstitial pneumonias

Smoking-related
- Respiratory-bronchiolitis-ILD
- Desquamative interstitial pneumonia
- Langerhan’s cell histiocytosis

Granulomatous
- Sarcoidosis
- Hypersensitivity pneumonitis
- CVID and other causes

Other ILD
- Lymphangioleiomyomatosis
- Eosinophilic pneumonia
- Alveolar proteinosis

Idiopathic pulmonary fibrosis

Nonspecific interstitial pneumonia

Cryptogenic organizing pneumonia

Acute interstitial pneumonia

Lymphocytic Interstitial pneumonia

Idiopathic pneumonia with autoimmune features (IPAF)

Combined pulmonary fibrosis and emphysema (CPFE)

Smoking related interstitial fibrosis (SRIF)

Pleuroparenchymal fibroelastosis (PPFE)
Practical approach for diagnosis of IPF

Diagnostic Algorithm for IPF

SuspectedILD

History
Physical Exam
Spirometry

Autoimmune panel
Exposures
Medications

Identifiable causes for ILD?

Yes
Definite UIP
Evaluate HRCT

No
Definite UIP

MDD*

Yes
Surgical Lung Biopsy or Cryobiopsy
Probable UIP
Possible UIP
Unclassifiable fibrosis
Other

No
Diagnostic Uncertainty

MDD*

IPF

Yes
No
Not IPF

IPF is worse than others
5-Year Survival Rate of IPF is Poor
Clinical prognostic factors per ATS

**TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS**

<table>
<thead>
<tr>
<th>Baseline factors*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of dyspnea†</td>
<td></td>
</tr>
<tr>
<td>$D_{LCO}$ &lt; 40% predicted</td>
<td></td>
</tr>
<tr>
<td>Desaturation ≤ 88% during 6MWT</td>
<td></td>
</tr>
<tr>
<td>Extent of honeycombing on HRCT†</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Longitudinal factors</td>
<td></td>
</tr>
<tr>
<td>Increase in level of dyspnea†</td>
<td></td>
</tr>
<tr>
<td>Decrease in Forced Vital Capacity by ≥ 10% absolute value</td>
<td></td>
</tr>
<tr>
<td>Decrease in $D_{LCO}$ by ≥ 15% absolute value</td>
<td></td>
</tr>
<tr>
<td>Worsening of fibrosis on HRCT†</td>
<td></td>
</tr>
</tbody>
</table>

Others include:

- Age
- Smoking
- Low BMI

Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, AJRCCM 2011
Variable course of IPF

- Approximately 40,000 new cases per year in the U.S.
- 50,000/yr die from IPF
IPF Begins With an Initial Epithelial Injury

- Injury of alveolar epithelial cells
- Initiation of normal repair mechanisms
- Release of profibrotic mediators into the alveolar space
- Wound clot formation with inadequate epithelial repair

Pathogenesis of IPF

Epithelial Injury

Epithelial Remodeling

Disruption of Basement Membrane

Formation of Provisional Matrix

“Feed-Forward” Progression

Recruitment of Pro-Fibrotic Mediators

Fibroblastic Foci Formation
Genetic influencers of fibrosis

- Trafficking defects
  - IT3T SFTP C
  - ABCA3 mutations
  - HPS

- ER stress
  - Surfactant protein mutations
  - Tobacco smoke
  - Herpes viruses
  - Hypoxia

- Increased DNA damage
  - Short telomeres
  - Tobacco smoke
  - Toxic exposures
  - Impaired DNA repair

- Proliferative defects
  - TERT or TERC mutations
  - Dyskerin regulation abnormalities
  - Short telomeres

- Senescence
  - Short telomeres
  - Aging

Secondary environmental stimuli
- Respiratory viruses
- Inhaled particulates
- Tobacco smoke
- Aspiration

Activation of stress response pathways
- Enhanced AEC apoptosis
- Aberrant activation of developmental programs and profibrotic mediator production

EMT

Fibroblast

Collagen deposition
MUC5B promoter polymorphism and risk of UIP pattern in ILAs

Putman RK. Eur Respir J 2017
ASCEND trial: pirfenidone for IPF

King TE. N Engl J Med 2014
INPULSIS trials: nintedanib
Is possible UIP just occult definite UIP?

Figure 3. Change from baseline in FVC over time by subgroup. SLB = surgical lung biopsy; UIP = usual interstitial pneumonia.
IPF therapy

Good ideas

• Pulmonary rehabilitation
• Oxygen supplementation
• Find comorbidities
  – OSA
  – GER
  – Depression
• “The lungs can’t take a joke”—hygiene and vaccines

Bad ideas

• Prednisone
• Immunosuppressants
• PAH treatment?
• High Vt ventilation
Interim summary: IPF

• Most common and most devastating ILD
• Think of it in older males, especially with exposures
• Acute exacerbations may be idiopathic or not
• 5-10% FVC decline, 10-15% DLCO decline, worsened oxygenation are tip-offs for poor outcomes
• More pulmonary rehab
• “Interstitial lung abnormalities”…
Etiology and histopathology both influence the outcome.

Mooney JJ. Chest 2013
Park JH. Am J Respir Crit Care Med 2007
HP is a common cause of occupational lung disease

“Almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach old age.”

-Morbis Artificum Diatriba
Hypersensitivity pneumonitis syndrome

Usually due to inhaled antigens (≤ 5µm)

- Animal proteins
- Micro-organisms
- Hydrocarbons (e.g. isocyanates)

Organ involvement in a US sarcoidosis clinic

Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012
Frequency of treatment requirement

Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012
Sarcoidosis in US military personnel during WWII
Sarcoidosis more common in the Southeast

Baughman RP. Ann Am Thorac Soc 2016
Sarcoidosis in the US

2010-2013 Optum Database

Incidence

- Asian: 3.2
- African-American: 17.8
- Caucasian: 8.1
- Hispanic: 4.3

Prevalence

- Asian: 18.94
- African-American: 141.36
- Caucasian: 49.80
- Hispanic: 21.66

Baughman RP. Ann Am Thorac Soc 2016
Upward age shift

Tukey MH. Sarcoidosis Vasc Diffuse Lung Dis 2013
Many individuals resolve their CXR
Rising sarcoidosis mortality in the US

Non-hispanic Males: Numbers of Deaths and Age-adjusted Mortality Rates per 1,000,000 Men

- Deaths: Non-hispanic White Males
- Deaths: Non-hispanic Black Males
- Mortality Rates: Non-hispanic White Males
- Mortality Rates: Non-hispanic Black Males

Swigris JJ. AJRCCM 2011
Multifaceted dyspnea of sarcoidosis

- Deconditioning
- Airways stenosis Bronchospasm
- Cardiac sarcoidosis
- Pulmonary HTN
- Anemia
- Myopathy -diaphragm -appendicular
- Obesity
- Airways stenosis Bronchospasm
Cardiac sarcoidosis

DE-MRI

DE-MRI/PET Fusion
Sarcoidosis therapy: MICO

Masterful Inactivity with Cat-like Observation
The decision to treat

Symptomatic
- Organ function impaired
- Organ endangered
- Progressive disease
- Clear-cut activity
- Low likelihood of remission

Minimal symptoms
- Good organ function
- Low risk of danger
- Inactive disease
- Higher likelihood of remission

Treatment favored

Patient preferences

Observation favored

Wijsenbeek MS, Clin Chest Med 2015
Sarcoidosis patients respond to multiple mycobacterial antigens

Oswald-Richter KA. Respir Res. In press
Effects of 8 weeks of CLEAR therapy in pulmonary sarcoidosis

Drake WP. SVDLD 2014
Major sarcoidosis trends

• Emerging diagnostic technology
  – FDG-PET
  – EBUS-TBNA
  – Cardiac sarcoidosis

• Move away from steroids

• Demographic shift

• Focus on non-inflammatory aspects
  – Pulmonary hypertension
  – Fatigue, neuropathy, comorbidities

• Collaboration
Conclusions

• Interstitial lung diseases ≈ 200 types
• History, exam, PFTs and radiology diagnose most ILDs
• PFTs are crucial for assessment and longitudinal care
• UIP ≠ IPF
• Pulmonary fibrosis ≠ IPF
Sarcoidosis misconceptions

- Affects younger adults
- Cardiac disease is rare
- Usefulness of ACE level
- Most commonly treated with prednisone
THANK YOU FOR THE INVITATION!
*Current options include - methotrexate, azathioprine, leflunomide, and mycophenolate.*
One size does not fit all

Steroids

Good prognosis
Responsive organs
Comorbidities
Recent onset

Steroid-sparing

Poor prognostic factors
Challenging organs
Comorbidities
Chronicity
Cumulative risk of steroid complications

Hazard ratio: 2.37  (1.34-4.17)

Other covariates
Age/yr 1.021  (1.001-1.041)
Pre-existing disease 2.27  (1.33-3.89)

Duration of steroids (mos) 1.023  (1.013-1.033)
Cumulative dose (grams) 1.038  (1.019-1.056)
Concordance

DE-MRI

DE-MRI/PET Fusion
Rising number of sarcoidosis hospitalizations in the US

Gerke AK. BMC Pulm Med 2012
Clinical outcome after 5 years

<table>
<thead>
<tr>
<th>Clinical outcome score</th>
<th>Therapy</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved</td>
<td>Never</td>
<td>59 (12%)</td>
</tr>
<tr>
<td>Resolved</td>
<td>Not within 1 year</td>
<td>44 (9%)</td>
</tr>
<tr>
<td>Minimal (&lt;25% of peak disease)</td>
<td>Never</td>
<td>47 (9%)</td>
</tr>
<tr>
<td>Minimal (&lt;25% of peak disease)</td>
<td>Not within 1 year</td>
<td>38 (8%)</td>
</tr>
<tr>
<td>Persistent, no current therapy</td>
<td>Never</td>
<td>41 (8%)</td>
</tr>
<tr>
<td>Persistent, no current therapy</td>
<td>Not within 1 year</td>
<td>54 (11%)</td>
</tr>
<tr>
<td>Current therapy, asymptomatic</td>
<td></td>
<td>57 (11%)</td>
</tr>
<tr>
<td>Current therapy, symptomatic</td>
<td></td>
<td>115 (23%)</td>
</tr>
<tr>
<td>Current therapy, worsening</td>
<td></td>
<td>45 (9%)</td>
</tr>
</tbody>
</table>

32%
## Prognosis versus clinical features

<table>
<thead>
<tr>
<th>Characteristics Associated with Worse Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 at onset</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Requirement for steroids</td>
</tr>
<tr>
<td><strong>Extrapulmonary involvement</strong></td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Neurologic (except isolated CN palsy)</td>
</tr>
<tr>
<td>Lupus pernio</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Osseous disease</td>
</tr>
</tbody>
</table>

**Pulmonary Involvement**
- Stage 3-4 chest radiograph
- Pulmonary hypertension
- Significant lung function impairment
- Moderate to severe dyspnea on presentation
- BAL neutrophilia at presentation
**Effect of prolonged corticosteroids**

Effects of 2 years steroid treatment in Stage 2/3 patients

<table>
<thead>
<tr>
<th>Unchanged</th>
<th>FVC</th>
<th></th>
<th>DLCO</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>Placebo</td>
<td>CS</td>
<td>Placebo</td>
</tr>
<tr>
<td>Unchanged</td>
<td>11 (37%)</td>
<td>8 (40%)</td>
<td>9 (36%)</td>
<td>6 (37%)</td>
</tr>
<tr>
<td>Improved</td>
<td>13 (43%)</td>
<td>6 (30%)</td>
<td>13 (52%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>Worsened</td>
<td>6 (20%)</td>
<td>6 (30%)</td>
<td>3 (12%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>20</td>
<td>25</td>
<td>16</td>
</tr>
</tbody>
</table>
Treated patients typically require ongoing treatment

337 enrolled

118 untreated
  118 spontaneous remission
    10 relapsed 108 sustained

219 treated
  103 induced remission
    76 relapsed 27 sustained
  116 recalcitrant disease

Gottlieb JE. Chest 1997
Medications in FSR registry population

[Bar chart showing the prevalence of various medications taken by patients in the FSR registry population.]

- NO MEDICATIONS TAKEN
- Prednisone, Dexamethasone
- Methylprednisolone (Medrol)
- Inhaled Steroids (Advair, ...)
- Hydroxychloroquine (Plaquenil)
- Chloroquine (Aralen)
- Methotrexate (Rheumatrex)
- Azathioprine (Azasan, Imuran)
- Lefunomide (Arava)
- Mycophenolate Mofetil
- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab (Cimzia)
- Golimumab (Simponi)
- Etanercept (Enbrel)
- Rituximab (MabThera, Rituxane)
- Cyclophosphamide (Cytoxan)
- Pentoxifylline (Pentoxil, Trenil)
- IVIG (Carimune, Fleboimmune)
- Thalidomide (Thalomid)
- Adrenocorticotropic (Acthar)
- Unsure
- Other medication not listed

1652 people provided 3084 response(s)
RESULTS: Metabolic Complications among 154 new sarcoidosis patients seen at CCF

76 patients developed or had worsening average of 1.9 ± 1 conditions per patient

Rate of Metabolic Complications

- Obesity
- HTN
- Ocular
- Bone density
- Lipids
- Diabetes
Quality of life and use of steroids are opposite

Table 3—Differences in Predicted HRQL Scores Between Patient Groups Based on Oral Corticosteroid Treatment*

<table>
<thead>
<tr>
<th>Group</th>
<th>Unadjusted Score</th>
<th>p Value</th>
<th>Adjusted Score†</th>
<th>p Value</th>
<th>Adjusted Score‡</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid users (n = 56)</td>
<td>52 (45–58)</td>
<td>&lt;0.0001</td>
<td>49 (43–56)§</td>
<td>0.031</td>
<td>48 (44–53)‖</td>
<td>0.011</td>
</tr>
<tr>
<td>No steroids (n = 55)</td>
<td>37 (31–43)</td>
<td></td>
<td>39 (33–44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF36-PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid users (n = 56)</td>
<td>31 (28–34)</td>
<td>0.011</td>
<td>32 (29–35)†</td>
<td>0.048</td>
<td>32 (29–35)‡</td>
<td>0.044</td>
</tr>
<tr>
<td>No steroids (n = 55)</td>
<td>37 (34–40)</td>
<td></td>
<td>37 (34–40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF36-MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid users (n = 56)</td>
<td>42 (39–46)</td>
<td>0.055</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No steroids (n = 55)</td>
<td>47 (44–50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1812 people provided 3430 response(s)
Main immunosuppressive options

- Corticosteroids
- Cyclophosphamide
- Azathioprine
- Methotrexate
- Leflunomide
- Mycophenolate
- Chlorambucil

Options from 1869:
- Colchicum
- Arsenic
- Acid iron
- Potassium iodide
- Lead/mercury ointment

Options from 2016:
- Antimalarials
- Methotrexate
- Leflunomide
- Mycophenolate
- Thalidomide
- Pentoxifylline
- Rituximab
- Adalimumab
- Infliximab
- Golimumab
Explant granuloma burden

**New diagnosis**

**Explant**

**Average Percent Surface Area of Granulomas**

- **Number of Patients**
  - 0 to 0.05
  - 0.05 to 0.1
  - 0.1 to 0.5
  - 0.5 to 1
  - 1 to 2
  - 2 to 3
  - 3 to 4
  - 4 to 5
  - 5 to 6
  - 6 to 7

- **Percent Surface Area Granulomas**
  - 0 to 0.05
  - 0.05 to 0.1
  - 0.1 to 0.5
  - 0.5 to 1
  - 1 to 2
  - 2 to 3
  - 3 to 4
  - 4 to 5
  - 5 to 6
  - 6 to 7
Challenges for pathophysiologic research

Sarcoidosis vs “sarcoidoses”

Genetic (? Etiologic) variability between populations

When is the disease studied?

Where is the disease studied?

Absence of a robust animal model
STAT1 plays a central role in sarcoidosis
Stat1-downstream genes in blood microarray
IFN-gamma producing Th17

Table 1: T effector cell subset phenotypes

<table>
<thead>
<tr>
<th>CCR4-/CXCR3+</th>
<th>CCR4+/CXCR3-</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR6-</td>
<td>Th1</td>
</tr>
<tr>
<td>CCR6+</td>
<td>Th17.1</td>
</tr>
<tr>
<td></td>
<td>Th17</td>
</tr>
</tbody>
</table>

Ramstein J. AM J Respir Crit Care Med. In press.
IL-10 antagonism of TNF
Treatment-requiring patients versus STAT3
Enhanced STAT3 phosphorylation in resolving sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>Non-severe</th>
<th>Severe</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

![Image of Western blot analysis](image.png)

**SOCS3**

**IL10 receptor alpha**

**IL-6**

**IL10 dose (ng/mL)**

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Non-severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.2</td>
<td>2</td>
</tr>
</tbody>
</table>

![Image of bar graphs](image.png)
Treatment-requiring patients versus STAT3

<table>
<thead>
<tr>
<th>IL10 dose (ng/mL)</th>
<th>Severe</th>
<th>Non-severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

- **P-STAT3**
- **STAT3**

Percent of LPS-stimulated TNF expression

- Non-severe
- Severe
Physicochemical similarity of the Kveim reagent and amyloid protein

Chen ES. Am J Respir Crit Care Med 2010
Amyloid A staining in non-sarcoidosis granulomas
Serum amyloid A hypothesis

1. Innate response induces expression of systemic and intracellular SAA
2. Induces hyperpolarized $T_h1$ response to pathogenic microbial antigens and misfolding and/or aggregation of SAA
3. Misfolded and/or aggregated SAA ‘seeds’ further SAA accumulation and release of soluble SAA peptides
4. SAA induces feed-forward amplification of local antigen-specific $T_h1$ responses to trapped antigens

Inability to clear SAA and antigens leads to chronic inflammation and fibrosis

Clearance of SAA and antigens enables remission

Chen ES. Nat Rev Rheumatol 2011
Effects of 8 weeks of CLEAR therapy in pulmonary sarcoidosis

Drake WP. SVDLD 2014
# Sarcoidosis trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target</th>
<th>Site</th>
<th>Endpoint</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR</td>
<td>Non-tuberculous mycobacteria</td>
<td>Pulmonary</td>
<td>FVC</td>
<td>138</td>
</tr>
<tr>
<td>Nicotine</td>
<td>T-regs</td>
<td>Pulmonary</td>
<td>CT scan</td>
<td>50</td>
</tr>
<tr>
<td>ACTHAR gel</td>
<td>Melanocortin receptors</td>
<td>Pulmonary</td>
<td>Steroid toxicity</td>
<td>20</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>GR</td>
<td>All</td>
<td>HRQOL</td>
<td>76</td>
</tr>
<tr>
<td>Ustekinumab/Golimumab</td>
<td>p40 subunit of IL12 and IL23</td>
<td>Pulmonary Cutaneous</td>
<td>FVC Global skin</td>
<td>173</td>
</tr>
</tbody>
</table>
What is the magnitude of expected change in real life?

- n=53 patients treated with prednisone for 3-8 weeks
- Median FVC improvement 5.4%
- Median DLCO improvement was 10.3%
- >5% improvement of FVC was highly associated with improved MRC dyspnea and with patient global impression of benefit
Magnitude of infliximab benefit on FVC

Clinical trials

Cleveland Clinic experience

Effect on FVC with variable study design
Sample size needed for various study durations in CWP

No. of subjects per arm

Spirometry measured every 6 months

Annual change in FEV1 (mL) between treatments

Wang M. Am J Respir Crit Care Med 2000
PET Scan Predicting Response to Therapy in Sarcoidosis: FVC Change

Keijzers RG Sarcoidosis Vasc Diffuse Lung Dis. 2011
Clinical study considerations

• Population
  – Population likely to progress
  – Equipoise about placebo versus treatment
  – Enrich for activity

• Endpoint
  – FVC—compare placebo versus drug—two sided
  – Need for therapy escalation
  – Composite of clinical deterioration (TTCW)
  – Surrogate (biologic, PET)
  – PRO
Steroid dose in practice

- Chronic dosing in Johns Hopkins cohort\(^1\)
  - 91% ≤ 15 mg
  - 65% ≤ 10 mg

- Infliximab trial (n=122/138)\(^2\)
  - median dose 10 mg/d (2-50 mg/d)

- Golimumab/ustekinumab trial (n=131/173)\(^2\)
  - median dose 10 mg/d (2-30 mg/d)

---

2. Rosemary Watt, personal communication
Steroids are associated with impaired QOL
Lymphocyte trafficking in the CNS
*Interact to promote IFN responses but do not bind each other.
Louis Siltzbach and the Kveim-Siltzbach test

- Recapitulated granulomatous reaction after intradermal injection of spleen or LN
- Clonal T-cell population in granulomas
- Insoluble and resistant to heat, acid, nucleases and proteases
Evidence for a transmissible etiology

- Analogy with granulomatous lung diseases
- Reproducibility with Kveim reagent
- Case-clustering (nurses, Naval personnel)
- Epidemiologic data (Isle of Man)
- Transmission by transplant (heart, lung, bone marrow)
Geographic variance: hospitalization for sarcoidosis
Multiple attempts to isolate mycobacterial DNA

Gupta D. Eur Respir J 2007
Identification of humoral immunity against sarcoidosis protein extracts

Pooled IgG from sarcoidosis patients only binds unidentified proteins in extracts of sarcoidosis tissues. The protein fraction is poorly soluble and protease resistant, consistent with known properties of the Kveim-Siltzbach reagent.
Peptide signature

Mycobacterial catalase-peroxidase in 5/9 sarcoid tissues
CD4 responses to mycobacterial antigens in sarcoidosis BAL cells
CD4+ responses in 2/3 of subjects
Sarcoidosis patients respond to multiple antigens

Oswald-Richter KA. Respir Res. In press
T-cell response depend on HLA type

Chen ES. J Immunol 2008
Sarcoidosis Murine Lung Granuloma Model Using *Mycobacterium* Superoxide Dismutase A Peptide

Swaisgood CM. Am J Respir Cell Mol Biol 2011
### Association with rural exposures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Exposure profile</th>
<th>% cases (n = 44)*</th>
<th>% controls (n = 88)*</th>
<th>Unadjusted OR with 95% CI</th>
<th>Adjusted ORb with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of a coal stove</td>
<td>Yes</td>
<td>22.7</td>
<td>4.5</td>
<td>6.2 [1.7, 22.7]</td>
<td>3.3 [0.9, 12.8]</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>77.3</td>
<td>95.5</td>
<td></td>
<td></td>
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<tr>
<td>Use of a wood stove</td>
<td>Yes</td>
<td>63.6</td>
<td>27.3</td>
<td>4.1 [1.9, 9.0]</td>
<td>3.7 [1.5, 8.8]</td>
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<tr>
<td></td>
<td>No</td>
<td>34.1</td>
<td>72.7</td>
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<td></td>
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<tr>
<td>Use of a fireplace</td>
<td>Yes</td>
<td>54.5</td>
<td>26.1</td>
<td>5.5 [2.0, 14.9]</td>
<td>6.8 [2.1, 21.8]</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>43.2</td>
<td>73.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of or exposure to insecticides and/or herbicides other than for home extermination</td>
<td>Yes</td>
<td>31.8</td>
<td>17.0</td>
<td>2.1 [0.9, 4.7]</td>
<td>2.0 [0.8, 5.1]</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>68.2</td>
<td>83.0</td>
<td></td>
<td></td>
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<tr>
<td>Use of well or spring water</td>
<td>Yes</td>
<td>50.0</td>
<td>29.5</td>
<td>2.2 [1.1, 4.7]</td>
<td>2.4 [1.0, 5.6]</td>
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<tr>
<td></td>
<td>No</td>
<td>47.7</td>
<td>70.5</td>
<td></td>
<td></td>
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<tr>
<td>Living or working on a farm</td>
<td>Yes</td>
<td>27.3</td>
<td>10.2</td>
<td>3.4 [1.2, 9.1]</td>
<td>3.1 [1.1, 8.9]</td>
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<tr>
<td></td>
<td>No</td>
<td>70.5</td>
<td>89.8</td>
<td></td>
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</table>

Kajdasz DK. Ann Epidemiol 2001
Sarcoidosis-like disease in fire-fighters

"Sarcoid-like" Granulomatous Pneumonitis
FDNY: Pre & Post WTC
## Photocopier use and risk of sarcoidosis

<table>
<thead>
<tr>
<th>PHOTOCOPIER USE</th>
<th>TERTILE</th>
<th>ODDS RATIO (95% CONFIDENCE INTERVAL)</th>
<th>P VALUE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of use (years)</td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0.234</td>
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<tr>
<td>1 – 7</td>
<td>1.37</td>
<td>(0.82, 2.31)</td>
<td>0.010</td>
<td></td>
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<tr>
<td>&gt; 7</td>
<td>2.01</td>
<td>(1.18, 3.42)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Overall trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of use (times per Week)</td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0.746</td>
</tr>
<tr>
<td>1 – 3</td>
<td>1.10</td>
<td>(0.63, 1.91)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>&gt; 3</td>
<td>2.19</td>
<td>(1.31, 3.65)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Overall trend</td>
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</tr>
<tr>
<td>Duration of use (min per episode)</td>
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<td></td>
<td></td>
<td>Reference</td>
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<tr>
<td>0</td>
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<td>1</td>
<td>0.415</td>
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<td>1 – 2</td>
<td>1.26</td>
<td>(0.72, 2.20)</td>
<td>0.018</td>
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<td>&gt; 2</td>
<td>1.83</td>
<td>(1.11, 3.02)</td>
<td>0.018</td>
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</tr>
<tr>
<td>Overall trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total lifetime exposure (hours)</td>
<td></td>
<td></td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
<td>0.824</td>
</tr>
<tr>
<td>1 – 60</td>
<td>1.07</td>
<td>(0.61, 1.88)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1.98</td>
<td>(1.18, 3.35)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Overall trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 adjusted for age, sex, method of data collection and history of clerical work
ACE versus other prognostic markers in pulmonary sarcoidosis

Risk of increasing infiltrates

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>Cut-Off Level</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Discriminative Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA</td>
<td>0.444</td>
<td>9.3</td>
<td>38.5</td>
<td>73.3</td>
<td>62.8</td>
</tr>
<tr>
<td>sIL-2R</td>
<td>0.758</td>
<td>1,195</td>
<td>61.5</td>
<td>73.3</td>
<td>69.8</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>0.692</td>
<td>11.25</td>
<td>76.9</td>
<td>66.7</td>
<td>69.8</td>
</tr>
<tr>
<td>ACE</td>
<td>0.613</td>
<td>17.95</td>
<td>76.9</td>
<td>50</td>
<td>58.1</td>
</tr>
<tr>
<td>KL-6</td>
<td>0.836</td>
<td>354</td>
<td>76.9</td>
<td>70</td>
<td>72.1</td>
</tr>
<tr>
<td>Total cells</td>
<td>0.633</td>
<td>1.80</td>
<td>76.9</td>
<td>56.7</td>
<td>62.8</td>
</tr>
<tr>
<td>AM</td>
<td>0.574</td>
<td>1.73</td>
<td>46.2</td>
<td>73.3</td>
<td>65.1</td>
</tr>
<tr>
<td>Ly</td>
<td>0.669</td>
<td>0.52</td>
<td>69.2</td>
<td>70</td>
<td>69.8</td>
</tr>
<tr>
<td>Neu</td>
<td>0.456</td>
<td>0.01</td>
<td>76.9</td>
<td>36.7</td>
<td>48.8</td>
</tr>
<tr>
<td>Eo</td>
<td>0.435</td>
<td>0.01</td>
<td>30.8</td>
<td>76.7</td>
<td>62.8</td>
</tr>
</tbody>
</table>

Miyoshi S. Chest 2010
Rate of eight complications in individuals using GC > 60 days

n=2167 patients

Curtis JR. Arthritis Rheum 2006
HRQL in 114 sarcoidosis patients versus steroid dose

< 500 mg vs. > 500 mg of prednisone over the prior year

<table>
<thead>
<tr>
<th>PRO module</th>
<th>&gt;500 mg prednisone/year</th>
<th>&lt;=500 mg prednisone/year</th>
<th>Minimum important difference**</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHQ total [+ ]</td>
<td>4.18 (0.37)</td>
<td>4.17 (0.33)</td>
<td>N/A</td>
<td>0.88</td>
</tr>
<tr>
<td>SHQ physical [+ ]</td>
<td>4.73 (0.70)</td>
<td>4.46 (0.69)</td>
<td>N/A</td>
<td>0.05</td>
</tr>
<tr>
<td>SHQ daily [+ ]</td>
<td>4.01 (0.41)</td>
<td>4.17 (0.48)</td>
<td>N/A</td>
<td>0.08</td>
</tr>
<tr>
<td>SHQ emotional [+ ]</td>
<td>3.79 (0.51)</td>
<td>3.81 (0.45)</td>
<td>N/A</td>
<td>0.35</td>
</tr>
<tr>
<td>SAT pain [- ]</td>
<td>54.5 (10.0)</td>
<td>51.8 (10.1)</td>
<td>3.2</td>
<td>0.18</td>
</tr>
<tr>
<td>SAT fatigue [- ]</td>
<td>54.8 (114)</td>
<td>48.9 (10.6)</td>
<td>3.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAT satisfaction [+ ]</td>
<td>46.5 (10.7)</td>
<td>51.5 (11.8)</td>
<td>3.0</td>
<td>0.03</td>
</tr>
<tr>
<td>SAT daily activities [+ ]</td>
<td>42.1 (7.5)</td>
<td>45.8 (9.5)</td>
<td>3.0</td>
<td>0.03</td>
</tr>
<tr>
<td>SAT lung [- ]</td>
<td>45.7 (9.1)</td>
<td>42.7 (9.5)</td>
<td>2.7</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Judson MA. Respir Med 2015
Impact of higher steroid use on health care encounters

• Adjusted OR for more than 50% median (2.9 grams) CS exposure
  – Visit related to sarcoidosis 3.09 (1.99-4.80)
  – Infection visits 1.74 (1.16-2.62)
  – Visits for CV or DM 1.49 (0.96-2.32)
  – Non-sarcoidosis ED 2.19 (1.46-3.30)

Rising number of sarcoidosis hospitalizations in the US

Gerke AK. BMC Pulm Med 2012
Rising sarcoidosis mortality in the US

Non-hispanic Males: Numbers of Deaths and Age-adjusted Mortality Rates per 1,000,000 Men


- Sarcoidosis 58.8%
- Other causes 25.1%
- Ischemic heart disease 7.2%
- COPD 2.3%
- Cardiomyopathy 1.7%
- Lung cancer 1.4%
- Stroke 1.4%
- Pneumonia 1.1%
- Cirrhosis/Liver cancer* 1.0%