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Sarcoidosis and Hypersensitivity Pneumonitis

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Disclosures

- UpToDate – authorship royalties
- Genetech – clinical endpoint committee

Hypersensitivity Pneumonitis

- Inflammation in the lungs caused by breathing certain triggers, including chemicals, molds, dust, fungi, and bacteria
- Imaging classically with upper lobe predominant changes including ground glass opacities and centrilobular nodules, more chronic changes including fibrosis and traction bronchiectasis can also be present depending on the duration of disease
- Pathology classically demonstrates loosely formed granulomas that are centered around the airways

Cormier Y, Lacasse Y. Clin Pulm Med. 1996; 3:72.

Epidemiology

- Prevalence varies by climate, occupational and environmental exposures
- Estimates from available studies: 0.3-0.9 per 100,000 individuals
- Higher incidence in high-risk populations – one study reported that among bird breeders the incidence is 54.6 per 100,000 people
- Insurance claim data show a 1-year prevalence of 1.67-2.71 per 100,000 people in the US
- ILD registry data varies greatly – reported prevalence of ILD cases ranges from 2% to 47%

Raghu G, Remy-Jardin M, Reyerson CJ, et al. Am J of Resp Crit Care Med 2020; 202(3):e36-e69.

Methods of Categorization

1. Old System: Based on the frequency, duration, and intensity of exposure, along with the duration of illness
   - Suggests an evolution of disease
2. Two categories: Nonfibrotic (inflammatory) and Fibrotic (can be mixed inflammatory and fibrotic)
   - Updated in the 2020 ATS/JRS/ALAT guidelines

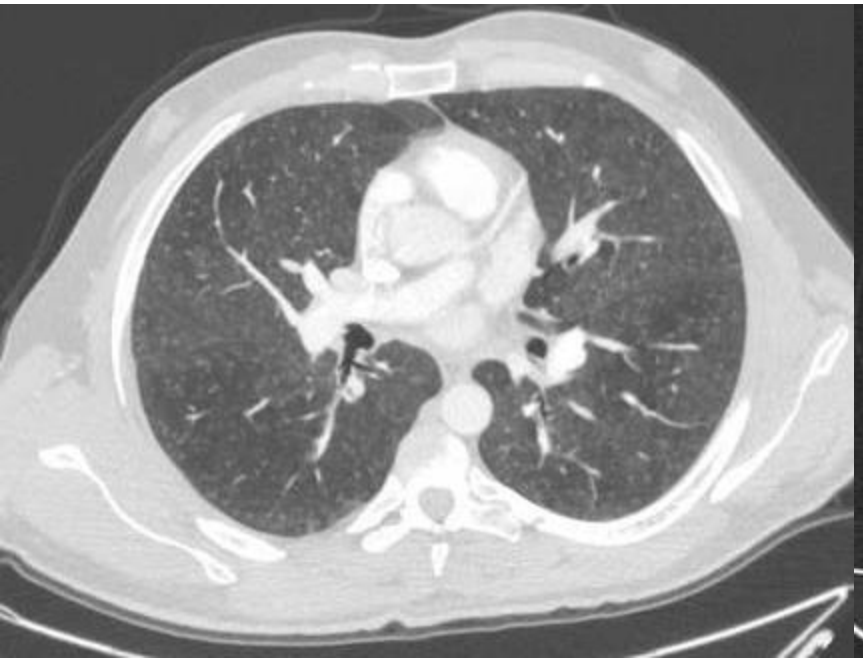
Classical Classification

- Acute – often confused with infection, characterized by acute onset (4-6 hours after exposure), improves with removal of exposure
  - Classic board question is “hot tub lung” which occurs due to exposure to nontuberculous mycobacteria
- Subacute – gradual development of symptoms
- Chronic – insidious onset, may lack the history of the acute episodes, imaging characterized by upper lobe predominant ground glass and possible fibrosis (depending on the time course)
  - Classic examples: Bird Fancier’s Disease, Farmer’s Lung

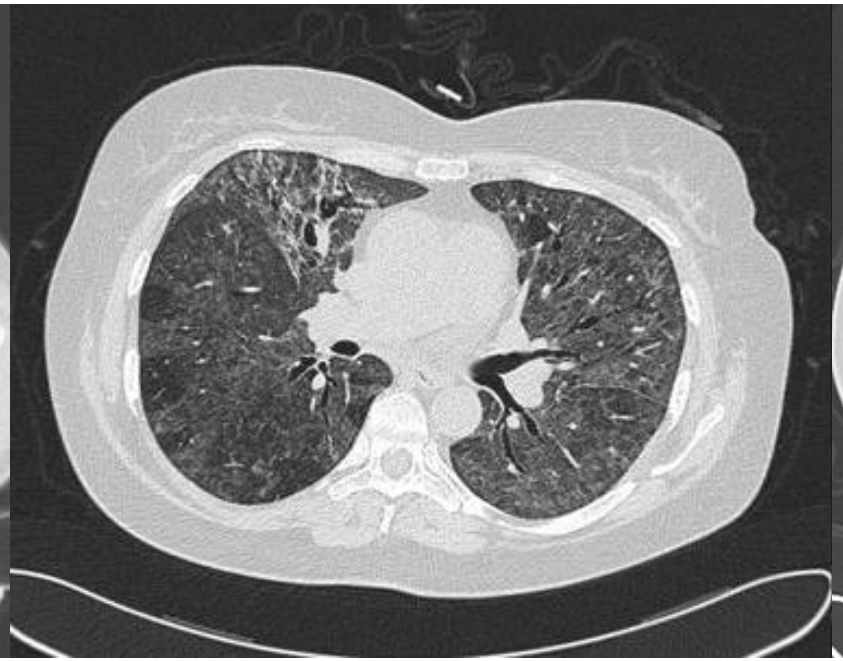
Richerson HB, Bernstein IL, Fink JN, et al. J Allergy Clin Immunol 1989; 84:839.

Categories of Hypersensitivity Pneumonitis

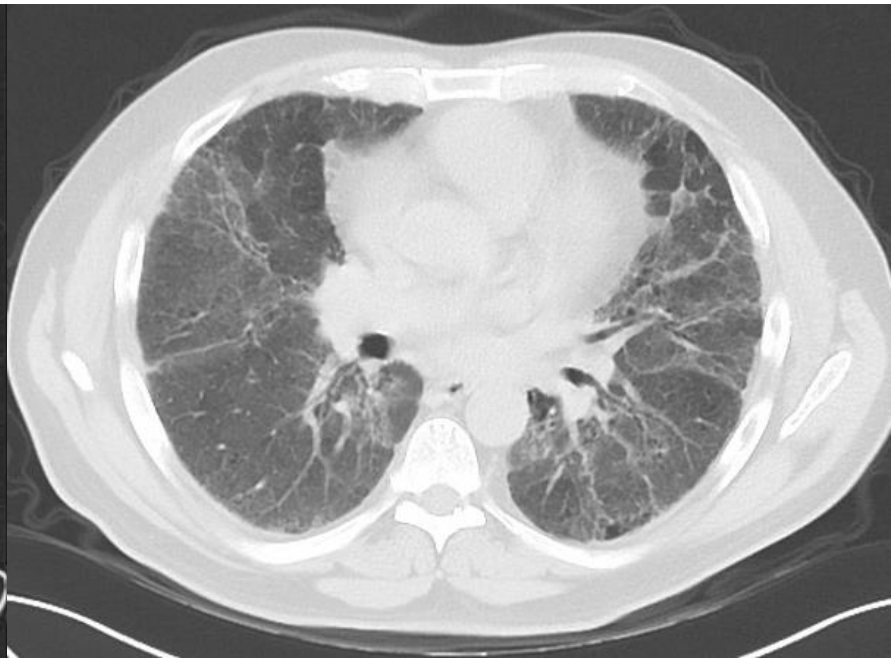
Acute



Subacute



Chronic



Nonfibrotic vs Fibrotic Hypersensitivity Pneumonitis

- Nonfibrotic/Purely Inflammatory: defined by the presence of predominantly inflammatory changes on imaging and/or pathology
  - Patients with this pattern who can avoid ongoing exposure likely have a better prognosis, with either recovery or stability

- Fibrotic: evidence of fibrosis on imaging and/or pathology, can also have an inflammatory component
  - Associated with poor prognosis, especially in the following groups: those with a UIP pattern, persistent exposure or inability to identify the exposure, cigarette smoking, lower baseline vital capacity, lack of BAL lymphocytosis

Raghu G, Remy-Jardin M, Reyerson CJ, et al. Am J of Resp Crit Care Med 2020; 202(3):e36-e69.

Evaluation and Diagnosis

- Detailed Exposure History:
  - Pets – especially birds, cleaning outdoor bird feeders
  - Hobbies – involving feathers, fur, plants, wood or metal workings
  - Other feather exposures: comforters, duvets, sleeping bags, jackets
  - Water damage to home or place of work
  - Hot tub, jacuzzi, sauna, or swimming pool use
  - Air conditioning units, humidifiers
  - Workplace Exposures (examples) – lab animals, veterinary work, barns/stables, farming, mushroom growing/processing, brewery, winery, metalworking, plastic manufacturing, spray painting, wood working

Lab Testing

- Serologic Assays for specific IgG antibodies – these include precipitin tests, ELISA assays, and automated detection by ImmunoCAP
- Controversial – sensitivity and specificity vary by the antigen being tested, duration and frequency of exposure, smoking history, and stage of disease
  - *Positive tests are evidence of exposure, not disease as they are often positive in asymptomatic individuals
- Recommended with very low confidence in recent ATS/ALAT/JRS guidelines

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Bronchoscopy and Biopsy

- Bronchoalveolar lavage (BAL) – marked lymphocytosis, greater than 20% but often over 50%
  - Can be less than 20% in patients with fibrotic HP
- Transbronchial biopsy – yield is lower in more advanced/fibrotic disease, most studies report a diagnostic yield of 10-40%. Using with BAL increased rate of diagnosis from 27% to 53%
- Cryobiopsy – larger piece of tissue, limited data in HP, but in other diffuse parenchymal lung diseases, diagnostic accuracy is similar to surgical lung biopsy
- Surgical Lung Biopsy – only when a diagnosis cannot be made based on imaging, history, and/or bronchoscopy results

Raghu G, Remy-Jardin M, Ryerson C, et al. Am J of Resp Crit Care Med 2020; 202(3):e36.

Histopathology

- Nonfibrotic: chronic cellular bronchiolitis with peribronchial lymphocytic inflammation, with small poorly-formed noncaseating granulomas near the respiratory and/or terminal bronchioles, chronic cellular pneumonitis

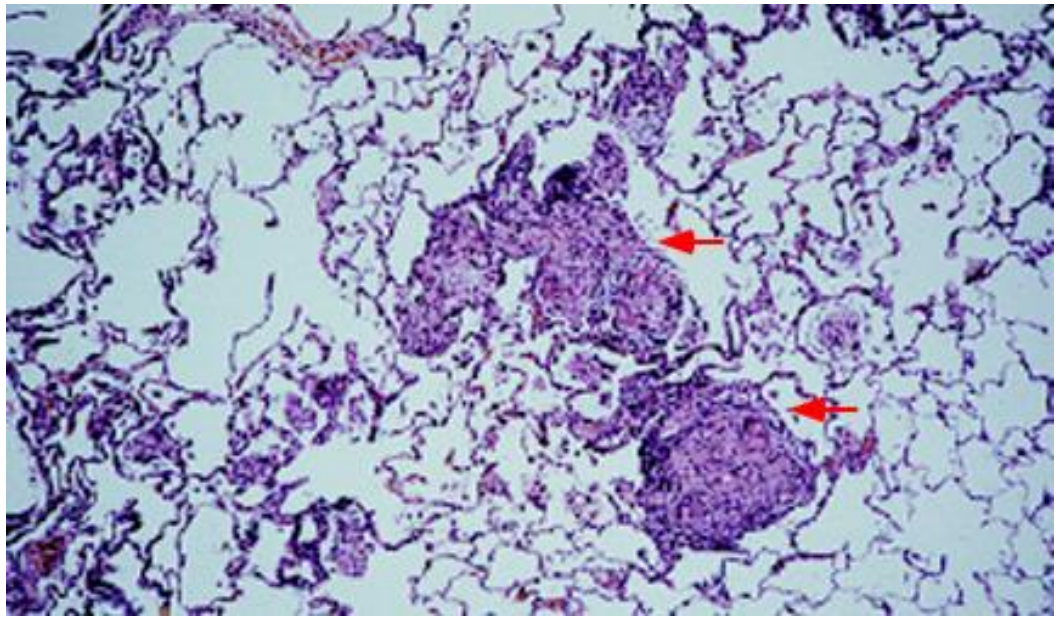
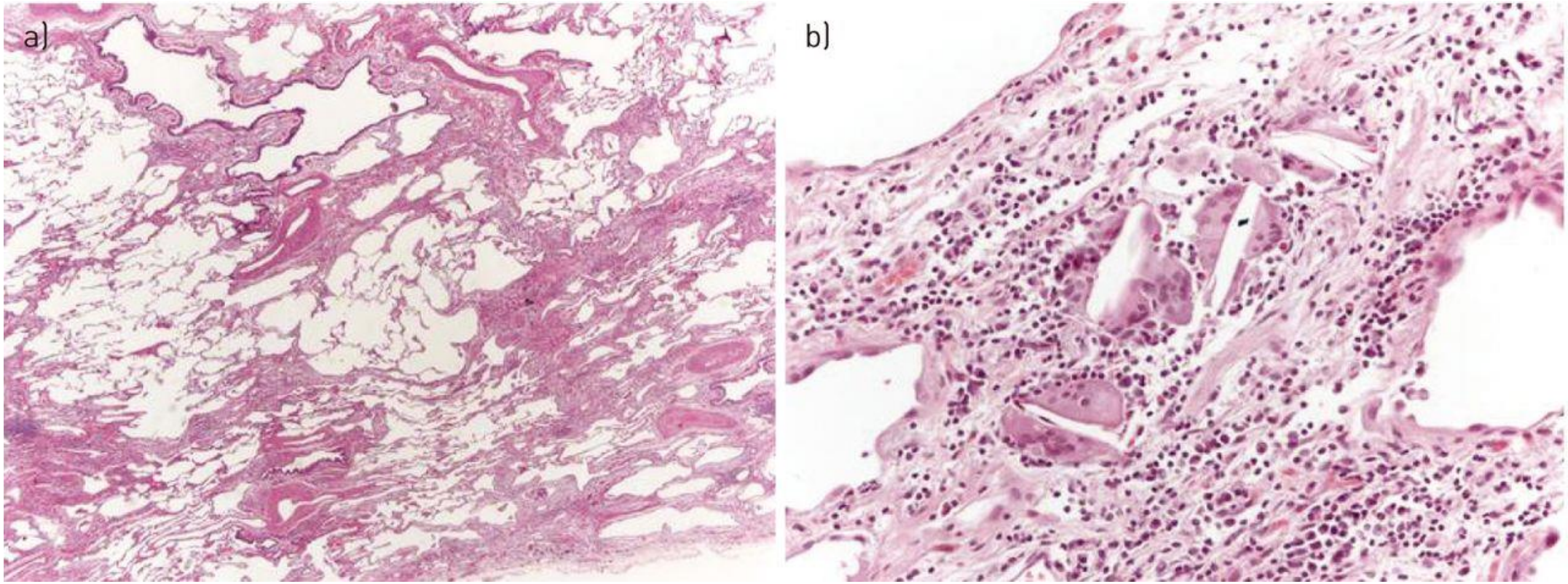


Image from UptoDate, Courtesy of Dr. T. King

Histopathology

- Chronic / Fibrotic: can have features of UIP or fibrotic NSIP and often include poorly or loosely formed granulomas; there can also be areas of organizing pneumonia



Wuyts W, Cavazza A, Rossi G, et al. Eur Resp Rev. 2014; 23: 308-319.

Treatment

Inflammatory HP:

- Acute HP with mild symptoms – antigen avoidance
- Persistent symptoms – antigen avoidance and corticosteroids
  - Steroid dose is usually prednisone 0.5mg/kg a day x 1 month then a - month taper, no change in long term outcomes

Fibrotic HP:

- Chronic HP – antigen avoidance, treatment with corticosteroids or steroid sparing agent (mycophenolate or azathioprine). Progressive fibrosis would qualify for initiation of nintedanib

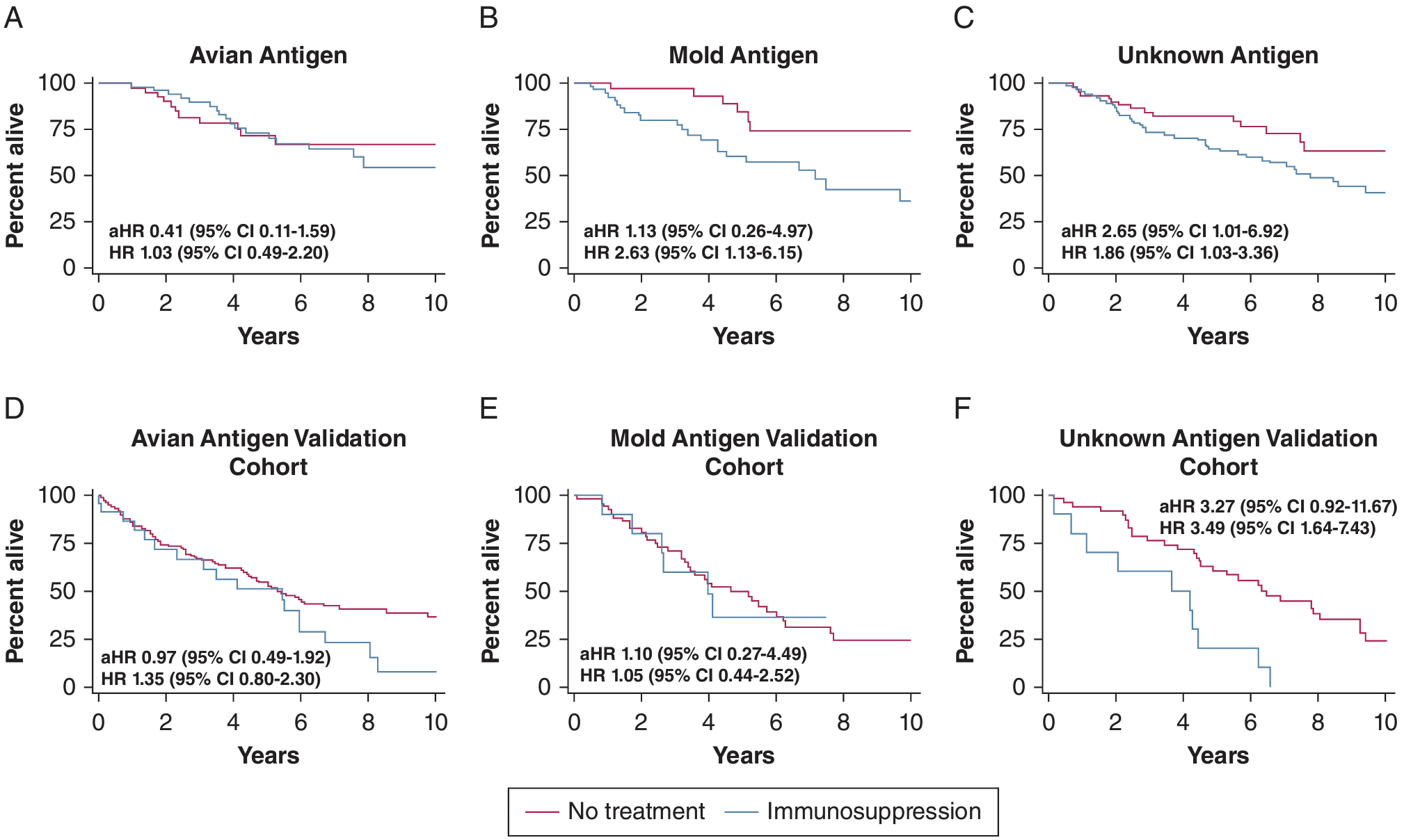
Salisbury ML, Myers JL, Belloli EA, et al. Am J Respir Crit Care. 2017; 196(6):690.
Morriset J, Johannson KA, Vittinghoff E, et al. Chest. 2017; 151(3):619.
Flaherty K, Wells A, Cottin V, et al. NEJM. 2019; 381:1718-1727.
Raghu G, Remy-Jardin M, Ryerson C, et al. Am J of Resp Crit Care Med 2020; 202(3):e36.

Treatment

Fibrotic HP:

- Retrospective data from the Canadian Registry for Pulmonary Fibrosis that response to immune suppression varied by antigen exposure
- No groups had an improvement in symptoms or PFTs
- Some groups, including those with no antigen identified, had worse survival on immune suppression

Mullin ML, Fernandez G, Marinescu D-C, et al. Chest. 2024; 165(6):1435-1443.

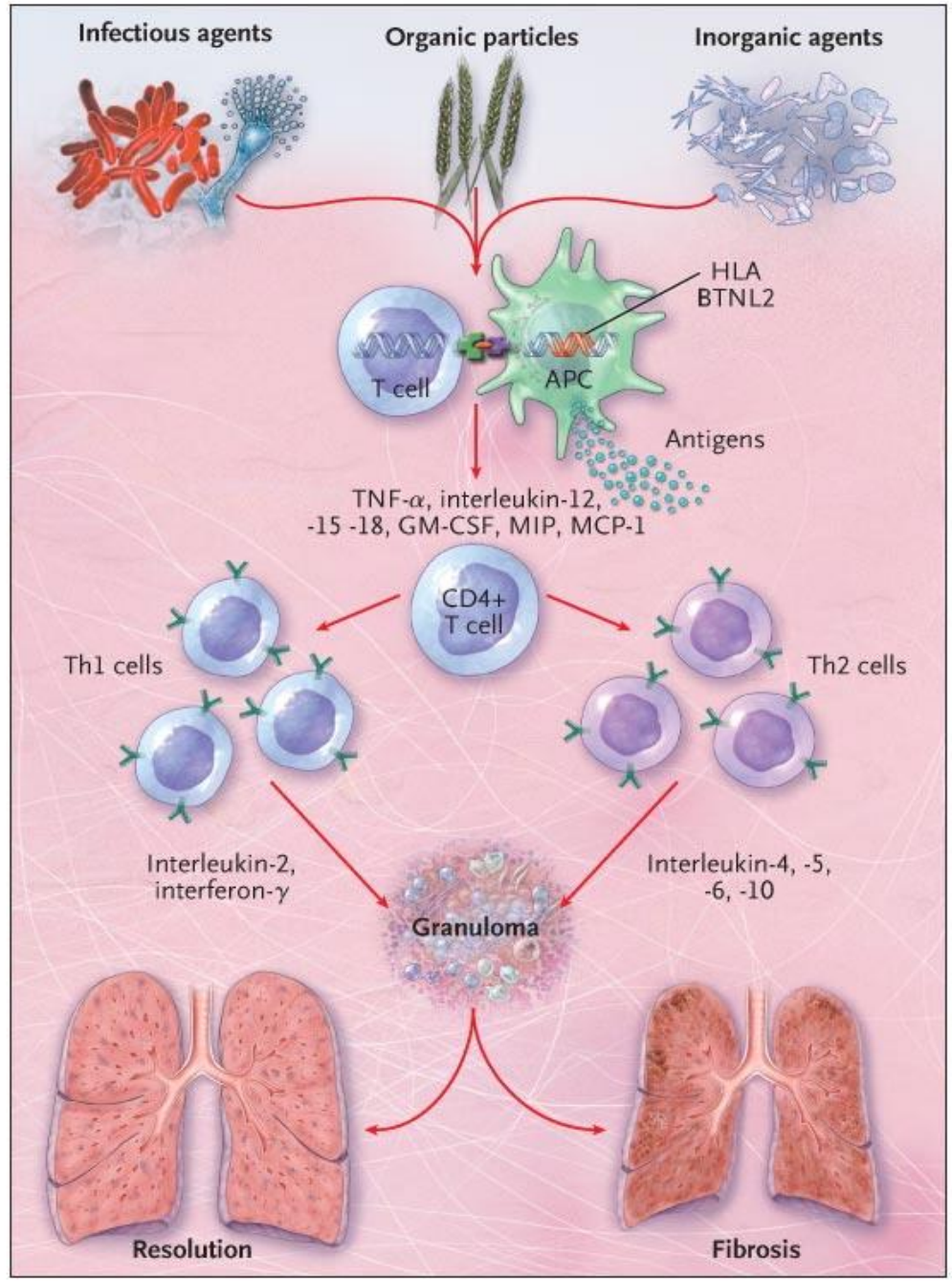


Mullin ML, Fernandez G, Marinescu D-C, et al. Chest. 2024; 165(6):1435-1443.

Sarcoidosis

- Multisystem granulomatous disorder that primarily involves:
  - Lung – 95% of cases
  - Skin – 16% of cases
  - Lymph nodes – 15% of cases
  - Eye – 12% of cases
  - Cardiac – registries note it occurs in about 5% of cases
    - Autopsy studies report a prevalence between 20-60% of cases

Baughman RP et al. Am J Respir Crit Care Med. 2001: 164; 1885-9.
Bernstien M et al. Arch Intern Med. 1999: 44: 721-34.
Tadamura E et al. AJR Am J Roentgenol. 2005: 185(1) 110-5.



Iannuzzi MC et al. N Engl J Med 2007;357:2153-2165.

Epidemiology

- Prevalence 10 to 20 per 100,000 people
- More common in certain ethnic groups
    - Black Americans ~3-fold greater risk
    - Incidence ratio between 2:1 and 7:1
    - Prevalence ratio between 3:1 and 5:1

- In the US it is more common in women (1.5:1)
- Black Americans – peak prevalence rates 30-39 years of age
- White Americans – flat incidence rates through adulthood

Culver, DA. et al. BMJ. 2019;367:l5553.
Rybicki BA. et al. Am J Epidemiol. 1997: 145(3): 234-41.

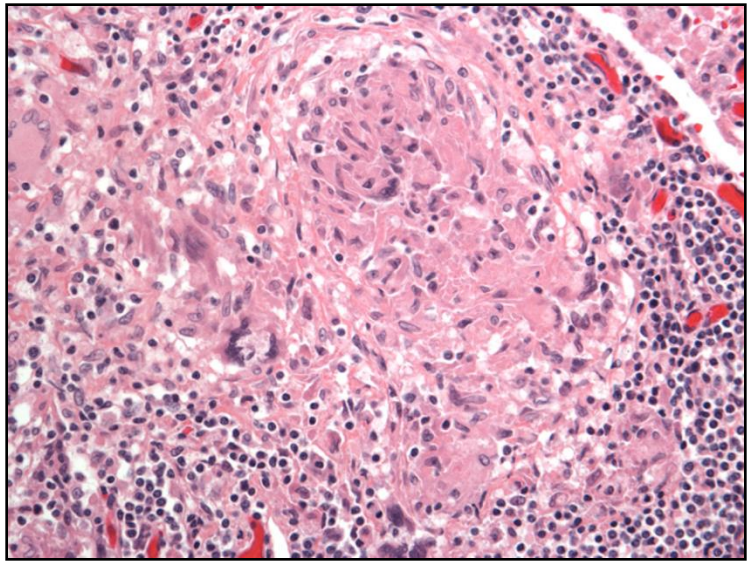
Environmental Risk Factors

- Commonly agreed that there is not one single environmental cause of sarcoidosis
- Fungal Exposure: Higher levels of NAHA (marker of fungal cell biomass) in homes of newly diagnosed sarcoid cases compared to controls
- Mycobacterial antigens – (mKatG) identified more commonly in the serum and tissue of patients with sarcoidosis
- Silicate dust exposure (high levels)

Tercelj M. et al. Environ Health 2011: 10(1): 8.
Izbicki G et al. Chest. 2007: 131(5); 1414-23.
Drake WP et al. JAMA Dermatol. 2013: 149(9); 1040-9.
Loupasakis K. et al. J Clin Rheumatol. 2015: 21(1): 19-23.

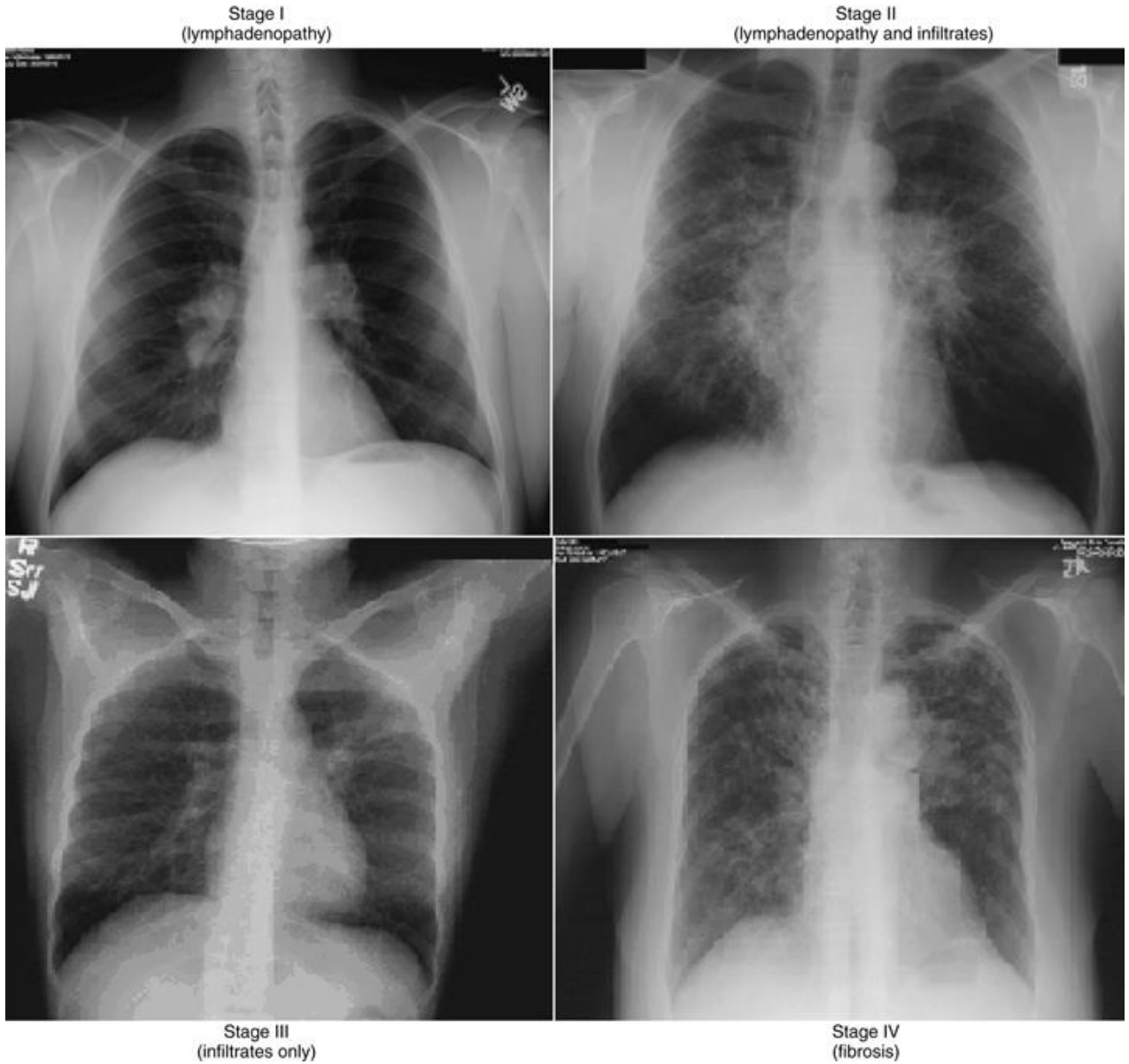
Diagnosis

- Compatible clinical and radiological manifestations
- Exclusion of other disease that present similarly
- Histopathologic detection of noncaseating granulomas
- ACE level – should not be used for diagnosis
  - Elevated in ~75% of patients with sarcoidosis
  - Nonspecific
- Transbronchial Lung Biopsy vs. EBUS
  - Diagnostic yield
    - 53% for transbronchial biopsy
    - 80% for EBUS



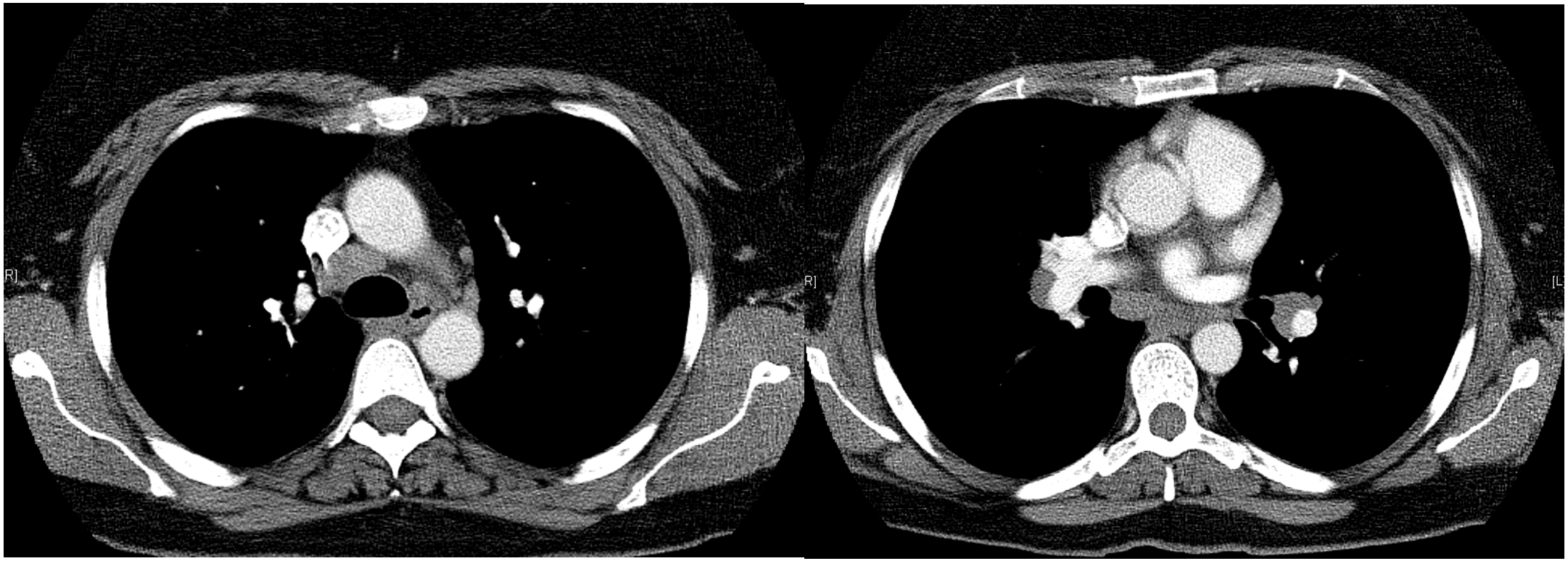
Statement on Sarcoidosis. Am J Respir Crit Care Med. 1999: 160(2); 736-55.

Scadding Stages



http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

Chest CT Characteristics



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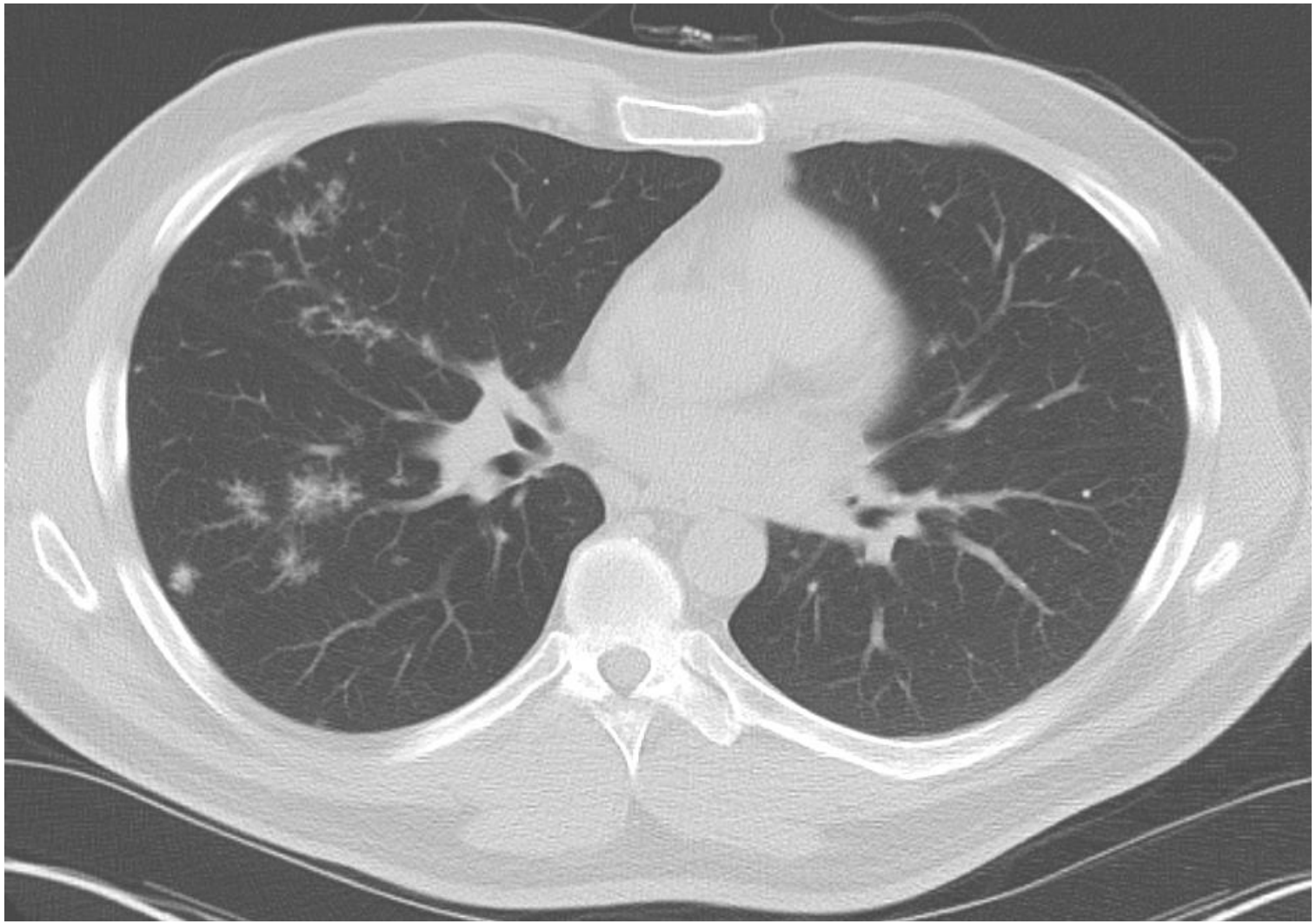


Prognosis

- 452 sarcoid patients from the University of Cincinnati
  - Median age 50 (25-78)
  - Mortality 4% and 9% at 5 and 10 years respectively

- Predictors of Increased Mortality
  - Age
  - Pulmonary Fibrosis
  - Pulmonary Hypertension

Kirkil G., et al. Chest 2018 Jan;153(1):105-113.

Who do we treat?

- Predominantly based on symptoms or evidence of disease progression
  - Limited evidence for disease modifying effect of therapy
  - Declining lung function - no consensus definition

Paramothayan NS. Cochrane Database Syst Rev. 2005: 2: CD002994.
Paramothayan NS. Cochrane Database Syst Rev. 2006: 3: CD03535.

Treatment Options

- Corticosteroids – first line therapy; recommended dose 20-40mg/day
- Steroid refractory, steroid intolerant or unable to taper
  - Methotrexate (15mg/week) with folic acid
  - Azathioprine (2mg/kg daily)
  - Leflunomide (20mg daily)
  - Mycophenolate mofetil

- Refractory Disease
  - Infliximab (3-5mg/kg every 4-6 weeks after loading)
  - Adalimumab (40mg every two weeks)

Baughman RP et al, Am J Respir Crit Care Med. 2011: 183(5): 573-81.

Clinical Monitoring in Sarcoidosis

- Reasonable Approach Asymptomatic– Every 12-18 months, for at least two years
  - Physical Exam and ROS
  - Labs including calcium, renal and liver function, complete blood count
  - 1,25 dihydroxy vitamin D
  - Pulmonary Function Testing
  - Eye exam
  - EKG
    - ATS suggests that the need for ocular and cardiac examinations be based on symptoms if the baseline exam is normal

Clinical Monitoring in Sarcoidosis

- **Active Disease**
- Every 3-4 Months:
  - Physical Exam and ROS
  - Labs based on disease activity and therapy
- Every 6 Months:
  - Eye exam – if on hydroxychloroquine
- Every 12 Months:
  - Labs including calcium, renal and liver function, complete blood count
  - 1,25 dihydroxy and 25 hydroxy vitamin D
  - Pulmonary Function Testing
  - Eye exam
  - EKG
  - Chest X-ray

Lofgren's Syndrome

- Present in less than 5-10% of patients with sarcoidosis
- Combination of erythema nodosum (EN), hilar lymphadenopathy, migratory polyarthralgias, and fever – more common in women
  - Men often present with bilateral ankle arthritis and *without* erythema nodosum
- The presence of this constellation of symptoms is 95% specific for the diagnosis of sarcoidosis
- Associated with a good prognosis and spontaneous remission

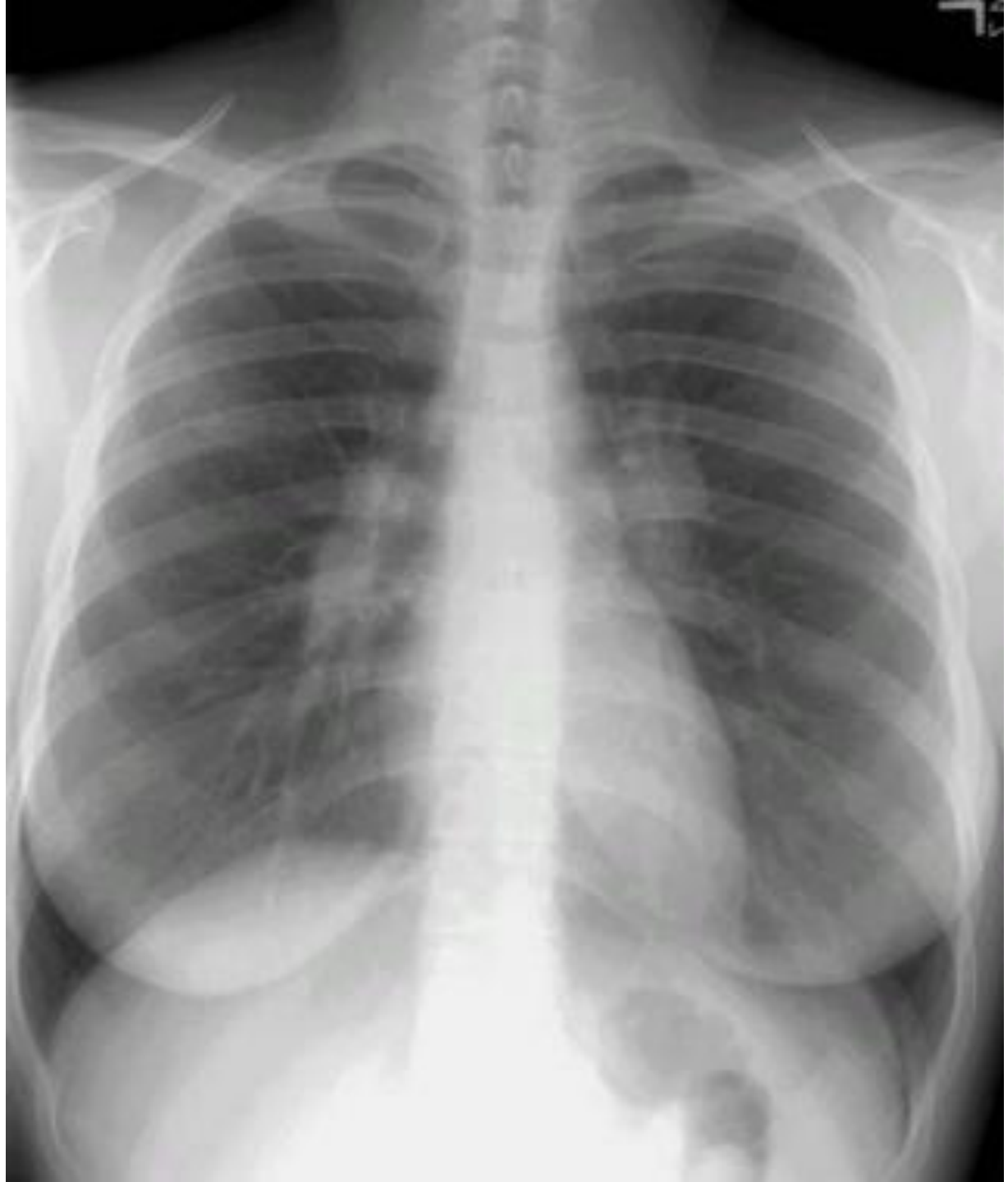
Grunewald J, Eklund A. Am J Respir Crit Care Med. 2007;175(1):40.

Summary / Conclusions

- Hypersensitivity pneumonitis and sarcoidosis are both granulomatous diseases, however hypersensitivity is limited to the lungs
- Hypersensitivity pneumonitis is classified into two categories: nonfibrotic and fibrotic; in both categories antigen identification and avoidance leads to a better prognosis
- Sarcoidosis is multisystem granulomatous disease, that commonly affects the lungs but can affect almost any organ system. The severity classification system is based on the degree of pulmonary involvement on imaging
- Corticosteroids are first line treatment for both conditions

Question 1

- A 24-year-old woman presents for follow up. Six weeks ago, she fell and had a chest x-ray done in the ER for evaluation of pleuritic chest pain. The chest pain has resolved, she denies any shortness of breath, cough, fever/chills, night sweats or weight loss. No joint pain or swelling. Her vital signs and physical exam are within normal limits. Chest x-ray is shown on the next slide.



Question 1

- Which of the following is the most appropriate management?

A. Endobronchial ultrasound and biopsy
B. High-resolution CT scan of the chest
C. Prednisone
D. Observation

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Question 2

- A 22-year-old man presents with fever, chills, dyspnea, and nonproductive cough. He is a college student and spends his summers working on a farm. His symptoms worsen during the week to the point that he will miss a few days of work. When he is away from work his symptoms improve, the cycle begins again when he returns to work. On exam his temperature is 100.1, blood pressure is 120/80, heart rate is 98, and respiratory rate is 22. Oxygen saturation is 94% on RA. His lungs have crackles throughout. Chest x-ray has upper-lobe ground glass opacities.

Question 2

- Which of the following is the most appropriate treatment?

A. Counsel the patient not to return to work
B. Mycophenolate
C. Nintedanib
D. Prednisone

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References

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