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Granulomatous Lung Disease

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- Clinical focus: Interstitial Lung Disease
- Research focus: interstitial lung disease utilizing high dimensional multimodal longitudinal data

DISCLOSURES

None



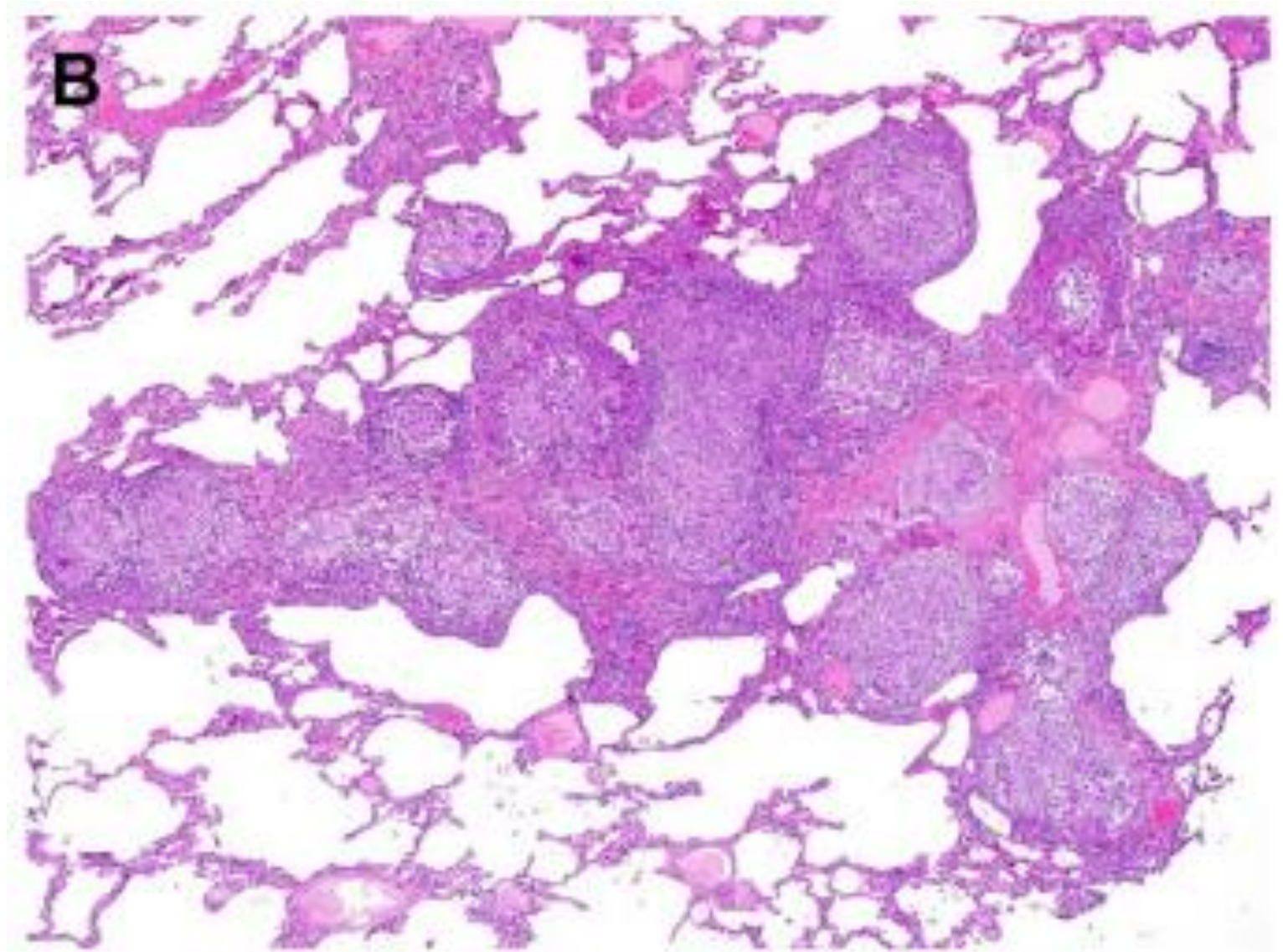
OBJECTIVES

- Describe the differential diagnoses for granulomatous lung disease
- Describe management options for hypersensitivity pneumonitis and pulmonary sarcoidosis



Granuloma

- Collection of epithelioid histiocytes (activated macrophages, typically tightly joined and cohesive appearing)
 - With or without multinucleated giant cells (fusion of multiple macrophages with single cell and multiple nuclei)
- Granulomas are the most common nonneoplastic finding in lung biopsies (TBBx, wedge)



“(B) The nodules comprise multiple well-formed, non-necrotizing granulomas, often surrounded by lamellar fibrosis.”

Granulomatous Lung Disease Differential Diagnosis

Non-Infectious

- Sarcoidosis
- Hypersensitivity pneumonitis
- Chronic beryllium disease
- Hot tub lung
- Vasculitis
- Aspiration pneumonia
- Talc granulomatosis
- Rheumatoid nodule
- Bronchocentric granulomatosis
- Malignancy
- Drug induced
- Granulomatous and lymphocytic interstitial lung disease (GLILD)

Infectious

- Mycobacteria – tuberculosis and nontuberculous mycobacteria
- Endemic fungi – histoplasma, cryptococcus, coccidioides, Blastomyces
- Pneumocystis
- Aspergillus
- Parasites - Dirofilaria

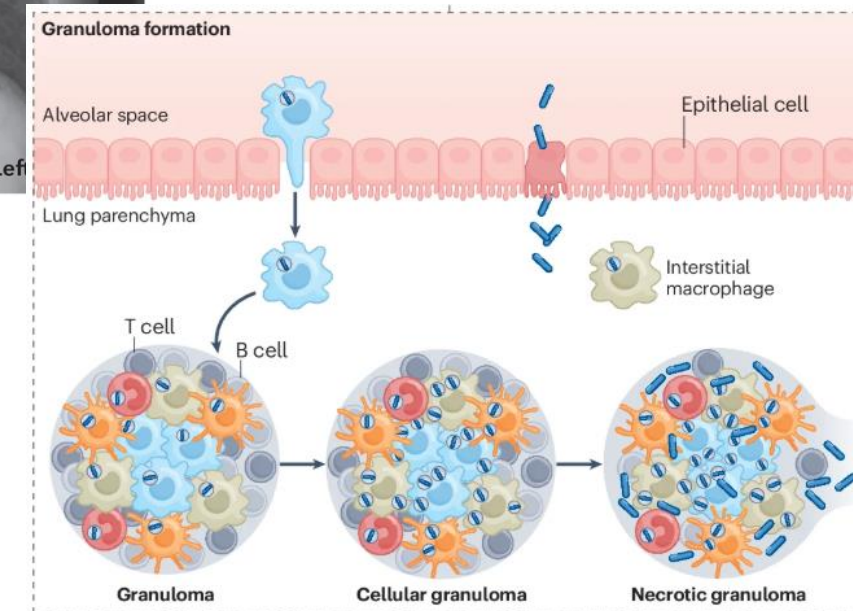
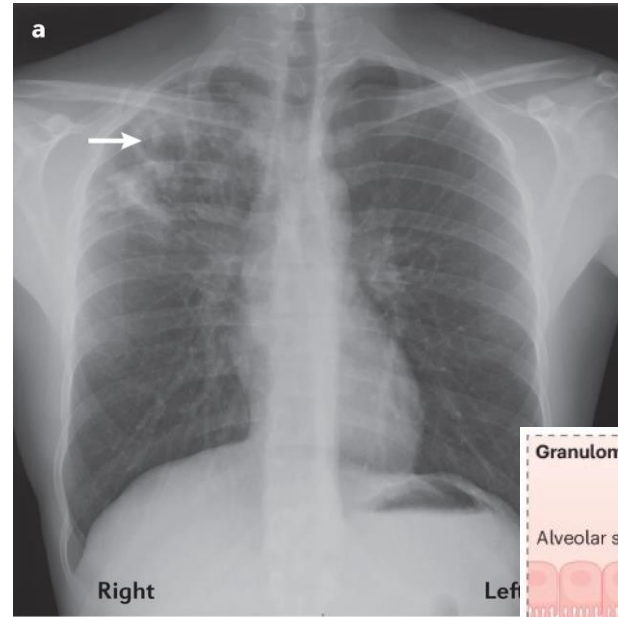


Infectious Etiologies



Tuberculous Mycobacterial Disease

- Lungs are the major site of infection (tubercle bacillus obligate aerobic slow growing bacterium)
- Pulmonary complications include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis
- Radiographic findings
 - Hilar lymphadenopathy – 65% of cases
 - Pleural effusions – 33% (1/3) of cases
 - Pulmonary infiltrates – 27% of cases



Poulsen A. Acta Tuberc Scand. 1957;33(1-2):37.

Pai, M. et al. Tuberculosis. Nat Rev Dis Primers 2, 16076 (2016). 8

Warner, D.F., et al. Nat Rev Microbiol 23, 788–804 (2025)



Nontuberculous Mycobacterial Disease

- Pulmonary disease usually caused by *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii*
 - Geography plays a role in the epidemiology of NTM
- Symptoms vary based on underlying lung disease – cough, fatigue, malaise, weakness, dyspnea, chest pain, and hemoptysis

TABLE 1] Examples of Clinically Relevant Slow-Growing and Rapid-Growing NTM Species¹

Slow-Growing NTM Species	Rapid-Growing NTM Species
<i>M avium</i> complex, comprising:	<i>M abscessus</i> complex, comprising:
<i>M avium</i>	<i>M abscessus</i> subspecies <i>abscessus</i>
<i>M intracellulare</i>	<i>M abscessus</i> subspecies <i>massiliense</i>
<i>M chimaera</i>	<i>M abscessus</i> subspecies <i>bolletii</i>
<i>M kansasii</i>	<i>M chelonae</i>
<i>M malmoense</i>	<i>M fortuitum</i>
<i>M xenopi</i>	

Table 2 Host factors associated with nontuberculous mycobacteria–lung disease (NTM-LD).

Mechanism	Dysfunction type	Disease representative	Population size, general	Population size, Taiwan	Association with NTM-LD	Treatable/controllable?
Defense defect of pulmonary physiology and clearance	Ciliary defect	Primary ciliary dyskinesia	12,000 to 17,000 in Norway and Japan ^{39,40} ; 3% in bronchiectasis in the the United States ⁴¹	Rare	NTM isolation has been reported as 1.1–1.9% ^{41,43}	No
		Bronchiectasis	Prevalence 94.8 per 100,000 population ⁴⁴	Prevalence 130 per 100,000 population ⁴⁵	1.7%–8.3% with NTM isolation and 0.48%–2.3% met microbiologically defined NTM-LD, ^{42,48} OR of 2.14 ⁴⁷	Controllable for the cause and secondary infection
	Inspissated secretion	Cystic fibrosis	30,000 people in the United States ⁴⁹	Very rare	3%–13% NTM-LD No has been reported in patients with CF ^{53,54}	No
	Structural lung change	Cartilage and elastin deficiency in airway	Rare	Rare	No adequate data	No
		Bronchiectasis COPD	As above Common. Prevalence 9.9% in United Kingdom, ⁶⁴ 6.1% in and 14.3% in Latin America. ⁶⁵	Common. Prevalence 6.1% in Taiwan ⁶³	Coexistence of 14% –39% ^{15,30} ; OR = 1.17 –15.7 ^{62,66,67}	Controllable
		Alpha-1 antitrypsin deficiency	3–5 in 1500 individuals with European ancestry	Rare	No large study. Might be compatible with COPD	Controllable
Immune suppression	Macrophage dysfunction	Pulmonary alveolar proteinosis	40 cases per million ⁷³	Rare	MAC has been isolated from 8 among 19 patients with PAP79	Controllable
	Immune deficiency in lung	ICS	Common drug	Common drug	OR = 1.86 –2.74 ^{84,85}	Controllable
	Systemic immune deficiency	Anti-TNF- α therapy	Not uncommon; approximately 0.4% ^{87,88}	Not uncommon	OR = 2.19 ⁸⁹	Controllable

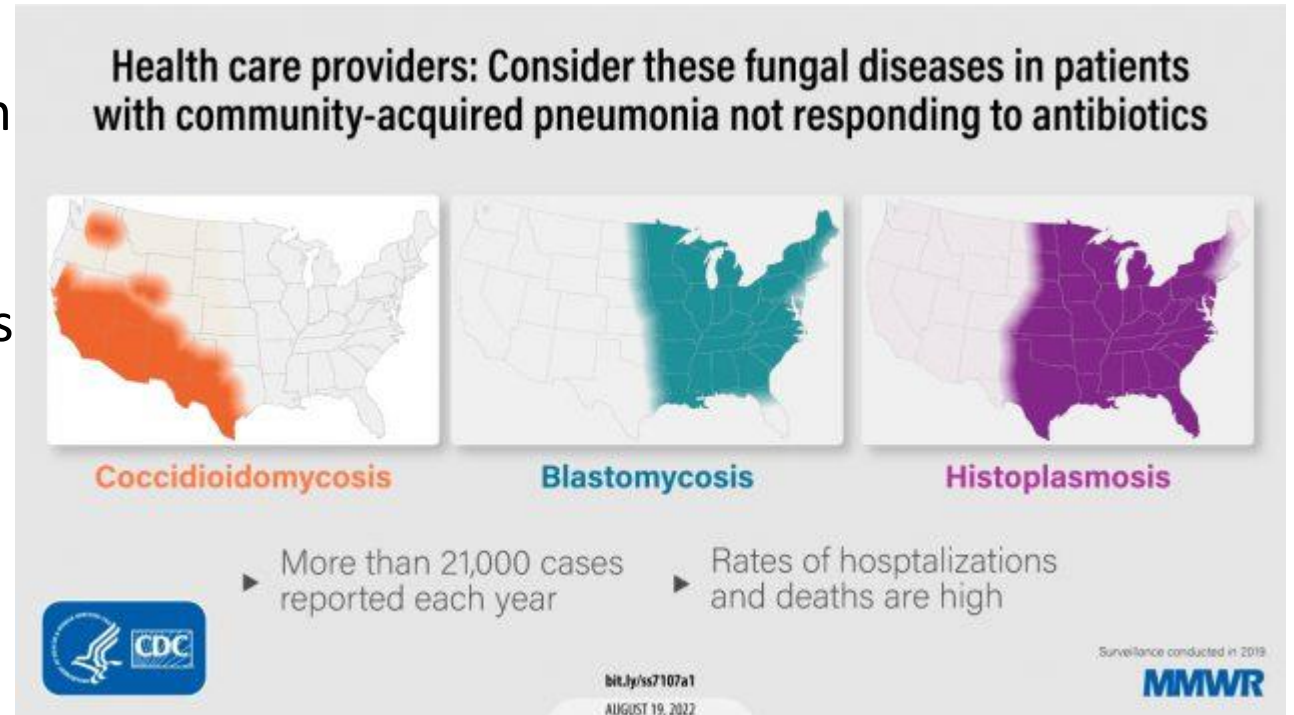
Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; NTM, nontuberculous mycobacteria; LD, lung disease; OR, odds ratio; TNF- α , tumor necrosis factor-alpha.

Teirstein AS, et al. Mt Sinai J Med. 1990;57(4):209.
 Reich JM, Johnson RE. Chest. 1992;101(6):165.
 Kumar K, Loebinger MR. Chest. 2022 Mar;161(3):637-646.
 Shu CC, et al. J Formos Med Assoc. 2020 Jun;119



Endemic Fungi

- Often present with mediastinal/hilar lymphadenopathy and pneumonia
- Histoplasma – most common in Midwestern states in the Ohio and Mississippi River Valleys
- Blastomycosis – systemic pyogranulomatous infection, primarily in south-central and upper midwestern United States
- Cryptococcus – worldwide distribution, most common in immune compromised hosts
- Coccidioides – most common in the southwestern United States, especially Arizona and the San Joaquin Valley of California



Non-Infectious Etiologies

Hypersensitivity Pneumonitis and Pulmonary Sarcoidosis



Hypersensitivity Pneumonitis

- Inflammation in the lungs caused by inhalation of 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 (peribronchiolar)
- A clinical diagnosis?



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 HP among ILD cases ranges from 2% to 47%



Methods of Categorization

1. 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



Categories of Hypersensitivity Pneumonitis

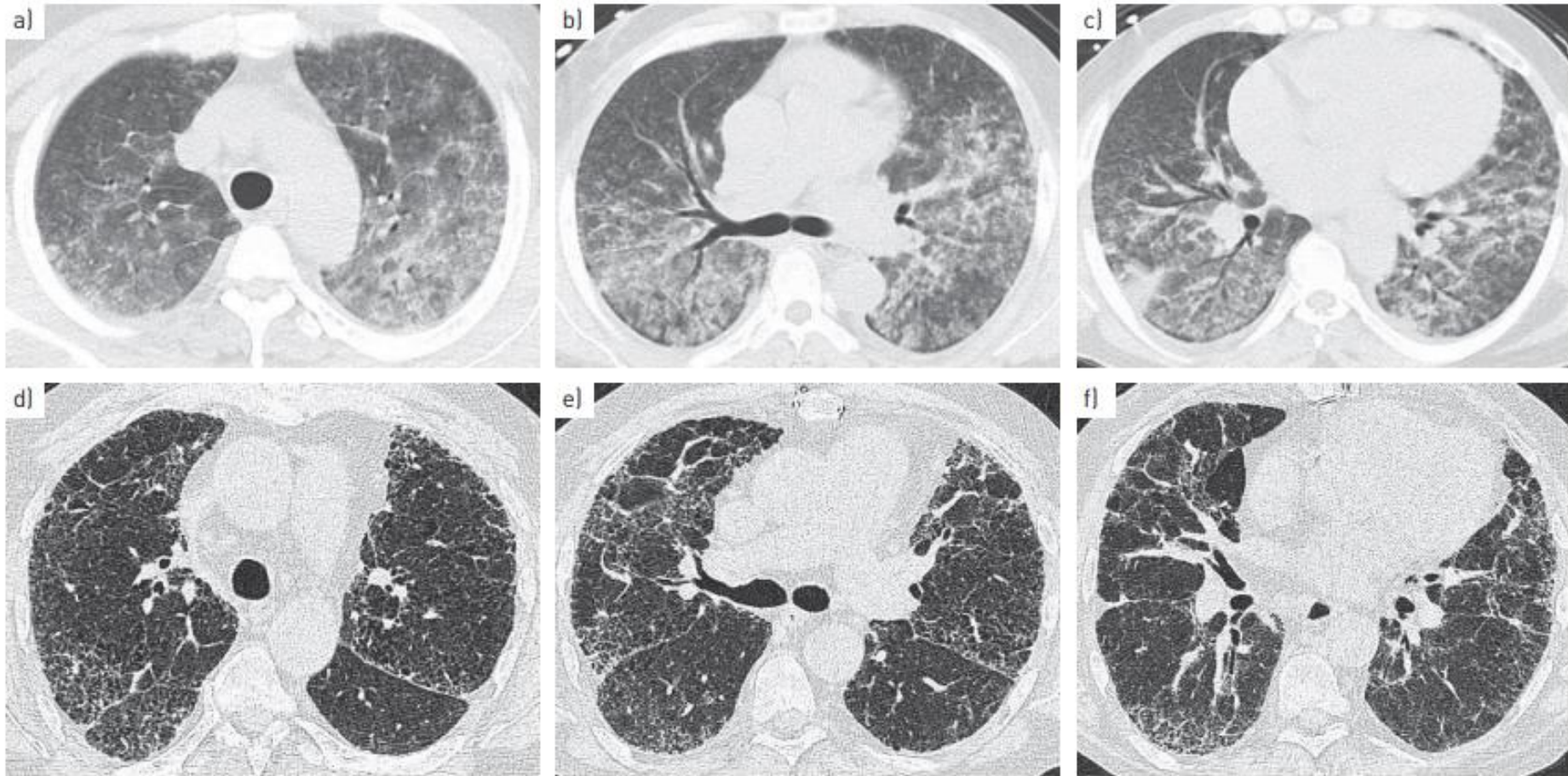


FIGURE 1 Chest high-resolution computed tomography (HRCT) of a-c) acute hypersensitivity pneumonitis and d-f) chronic hypersensitivity pneumonitis. Chest HRCT of acute hypersensitivity pneumonitis shows bilateral ground-glass densities with centrilobular micronodular accentuation and minor consolidation. Chest HRCT of chronic hypersensitivity pneumonitis shows bilateral reticular shadowing, traction bronchiectasis and minor mosaic perfusion along with some micronodules.

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



Evaluation and Diagnosis

Detailed Exposure History

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

Bronchoscopy and Biopsy



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

Table 2. Sources of Antigens Known to Cause Hypersensitivity Pneumonitis

Matter	Typical Sources	HP Disease
Organic particulate matter		
I. Microbes		
Fungi/molds*		
<i>Aspergillus</i> spp., <i>Alternaria alternata</i> , <i>Aureobasidium</i> spp., <i>Botrytis cinerea</i> , <i>Cephalosporium</i> spp., <i>Cladosporium</i> spp., <i>Cryptococcus</i> spp., <i>Fusarium</i> spp., <i>Graphium</i> spp., <i>Mucor</i> spp., <i>Penicillium</i> spp., <i>Rhizopus</i> spp., <i>Trichoderma</i> spp., phytase (enzyme from <i>Aspergillus</i> or <i>Trichoderma</i>)	Moldy hay Contaminated water Contaminated plant material Contaminated sawdust, moldy wood Contaminated houses (flooded), domestic ventilation and cooling systems, upholstered furniture, potted flowers Compost Contaminated stucco Moldy cork <i>Aspergillus</i> enzyme in baking agents Organic wastes Contaminated water, moldy wood Mold on grapes Contaminated wind instruments Contaminated wood Peat Cheese casings Moldy surface of salami Potted flowers, greenhouses	Farmer's lung Humidifier lung Malt worker's lung Woodworker's lung Indoor air alveolitis (domestic HP) Compost lung Stucco worker's lung Suberosis Baker's lung Waste sorter's lung Sauna taker's lung Wine grower's lung Wind instrument alveolitis Sequoiosis Peat worker's lung Cheese washer's lung Salami producer's lung Greenhouse HP
Yeasts*		
<i>Candida</i> spp., <i>Geotrichum candidum</i> , <i>Saccharomyces cerevisiae</i> , <i>Saccharomonospora viridis</i> , <i>Saccharopolyspora rectivirgula</i> , <i>Torulopsis glabrata</i> , <i>Trichosporon</i> spp.	Contaminated misting fountains and humidifiers Moldy hay Contaminated swimming pools Contaminated wind instruments Contaminated houses, damp and decayed wood, old mats Human intestine, fingernails, and skin Baker's yeast, brewer's yeast, wine yeasts Moldy thatched roof Mushrooms Compost	Humidifier lung Farmer's lung Footcare alveolitis Wind instrument lung Summer-type HP (<i>Trichosporon</i> spp.)†, indoor air alveolitis Candida alveolitis Yeast powder alveolitis Thatched roof lung Mushroom grower's lung Compost lung
Edible mushrooms		
Mushrooms (shiitake, bunashimeji, <i>Pleurotus</i> , <i>Pholiota</i> , <i>Lyophyllum</i> , <i>Agaricus</i>)	Mushrooms growing	Mushrooms grower's lung
Bacteria*		
<i>Acinetobacter</i> spp., <i>Bacillus</i> spp., <i>Klebsiella</i> spp., nontuberculous mycobacteria, <i>Phoma</i> spp., <i>Pseudomonas</i> spp., <i>Stenotrophomonas</i> spp., <i>Staphylococcus</i> spp., <i>Streptomyces</i> spp., <i>Thermoactinomyces</i> spp., endotoxin from pool water sprays and fountains, <i>Bacillus subtilis</i> enzymes (subtilisin)	Contaminated water Whirlpools Contaminated machine fluid Sewage treatment plants Sawdust Detergents, washing powders, biological cleaning agents Moldy hay Contaminated water, moldy wood Contaminated wind instruments Moldy shower curtains Contaminated water Compost Edible mushroom manure Moldy thatched roofs Moldy molasses, bagasse dust	Humidifier lung Whirlpool alveolitis Machine operator's lung Sewage worker's pneumonitis Woodworker's lung Detergent workers alveolitis, indoor air alveolitis Farmer's lung Sauna taker's lung Wind instrument alveolitis Indoor air alveolitis Steam iron alveolitis Compost lung Mushroom grower's lung Thatched roof disease Bagassosis
Protozoa		
Amoebae	Contaminated humidifiers and air conditioning systems	Humidifier lung



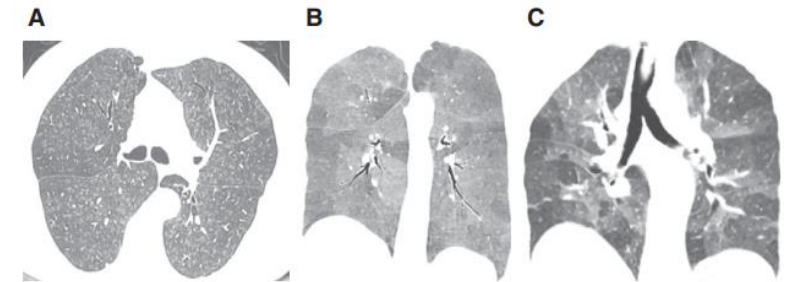
Treatment

Inflammatory HP:

Acute HP with mild symptoms – antigen avoidance

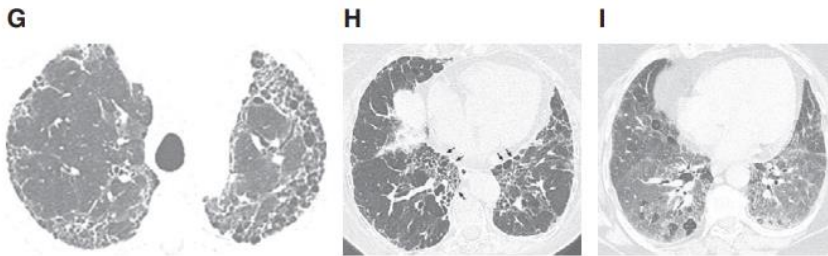
Persistent symptoms – antigen avoidance and corticosteroids

- Steroid dose is usually prednisone 0.5mg/kg a day x 1 month then a 3 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 antifibrotics



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(27):1718-1727.

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



Considerations of new updates – BIP – bronchiolocentric interstitial pneumonia

facilitates discussion and improves the ability to arrive at a final diagnosis ([supplementary table S3](#)). For example, the committee suggests that a radiological or pathological pattern of BIP be reported as “BIP pattern, favour HP but with differential diagnosis including CTD-ILD and drug-associated ILD”, or “BIP pattern, favour HP”, depending on the extent to which ancillary features suggest different clinical diagnoses. Such information would then be integrated with clinical data to support a multidisciplinary diagnosis with confidence that should similarly be documented in a standardised and explicit manner [15].

cases that are not HP and support further studies related to the provisional clinical entity of idiopathic BIP. This new terminology has potential to be confusing given the change from recent HP guidelines [25, 33]; however, updating terminology will encourage more precise classification of HP, support greater recognition of non-HP disorders that can have overlapping clinical features, imaging, and pathology, and provide a framework for future research to define the features of BIP in patients with diagnoses other than HP [54, 67–74]. The summaries for clinical, CT, and pathology features of BIP provided herein are primarily drawn from existing HP literature, including the previous guidelines on the diagnosis of HP [25, 33], as well as other causes of airway-centred interstitial pneumonia that have been referred to using a variety of terms. Importantly, although some cases previously labelled as HP will now be classified as idiopathic BIP, the proposed change in terminology does not alter the diagnostic approaches taken in recent HP guidelines.

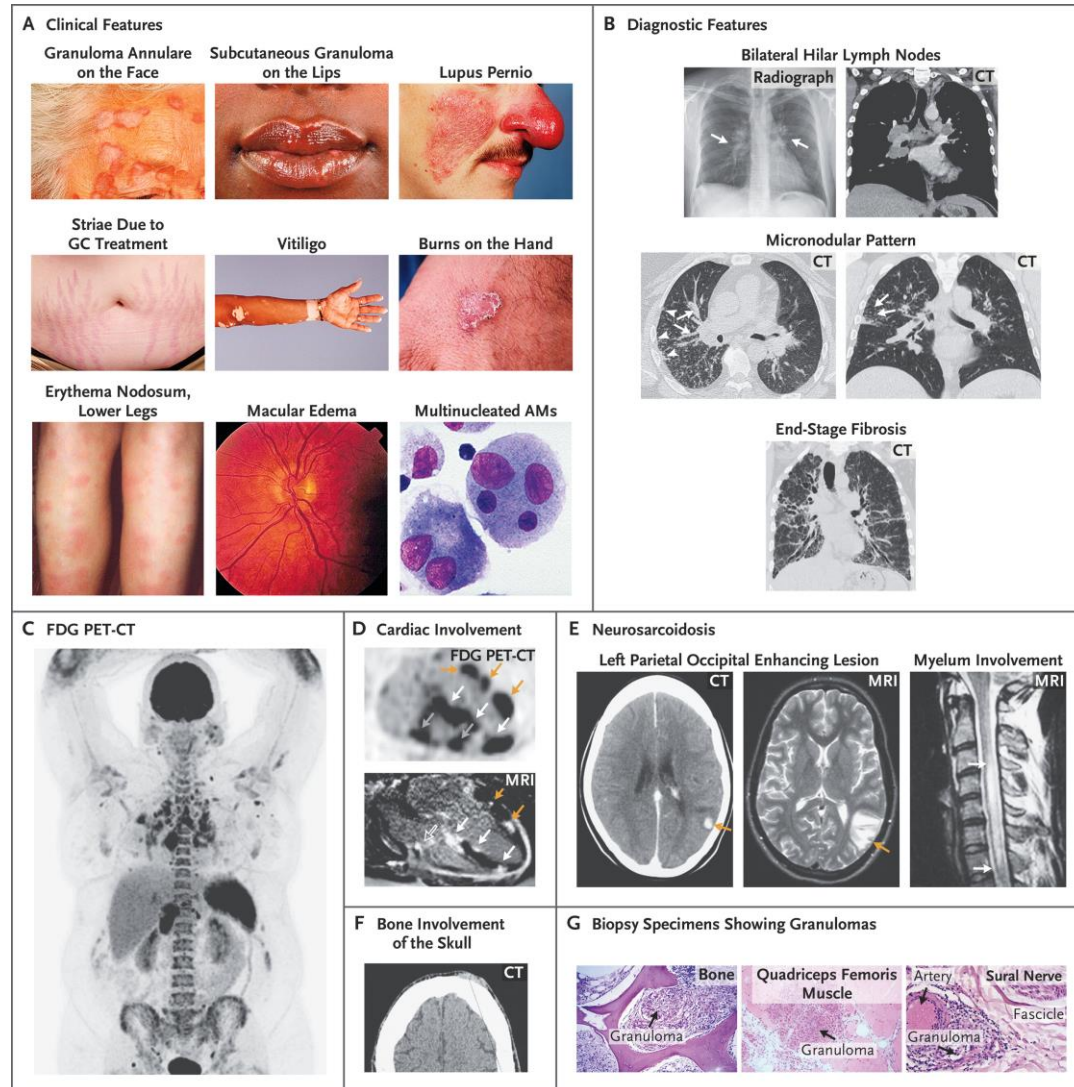


Considerations of new updates - BIP

BIP	Presentation Non-fibrotic BIP: acute/subacute onset frequently with respiratory and systemic symptoms Fibrotic BIP: chronic onset but with variable risk of progression. Potential for rapid worsening, especially with ongoing exposure Risk factors No clear age or sex predilection. Positive exposure history for HP- associated antigens	Non-fibrotic BIP: centrilobular ground-glass nodules, mosaic attenuation, and/or lobular air trapping Fibrotic BIP: peribronchovascular ground-glass, traction bronchiectasis, mosaic attenuation, lobular air trapping, and three-density sign. Features can overlap with non- fibrotic BIP	Non-fibrotic BIP: bronchiolocentric chronic inflammation ± non- necrotising granulomatous inflammation Fibrotic BIP: bronchiolocentric fibrosis often with peribronchiolar metaplasia ± bronchiolocentric inflammation
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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

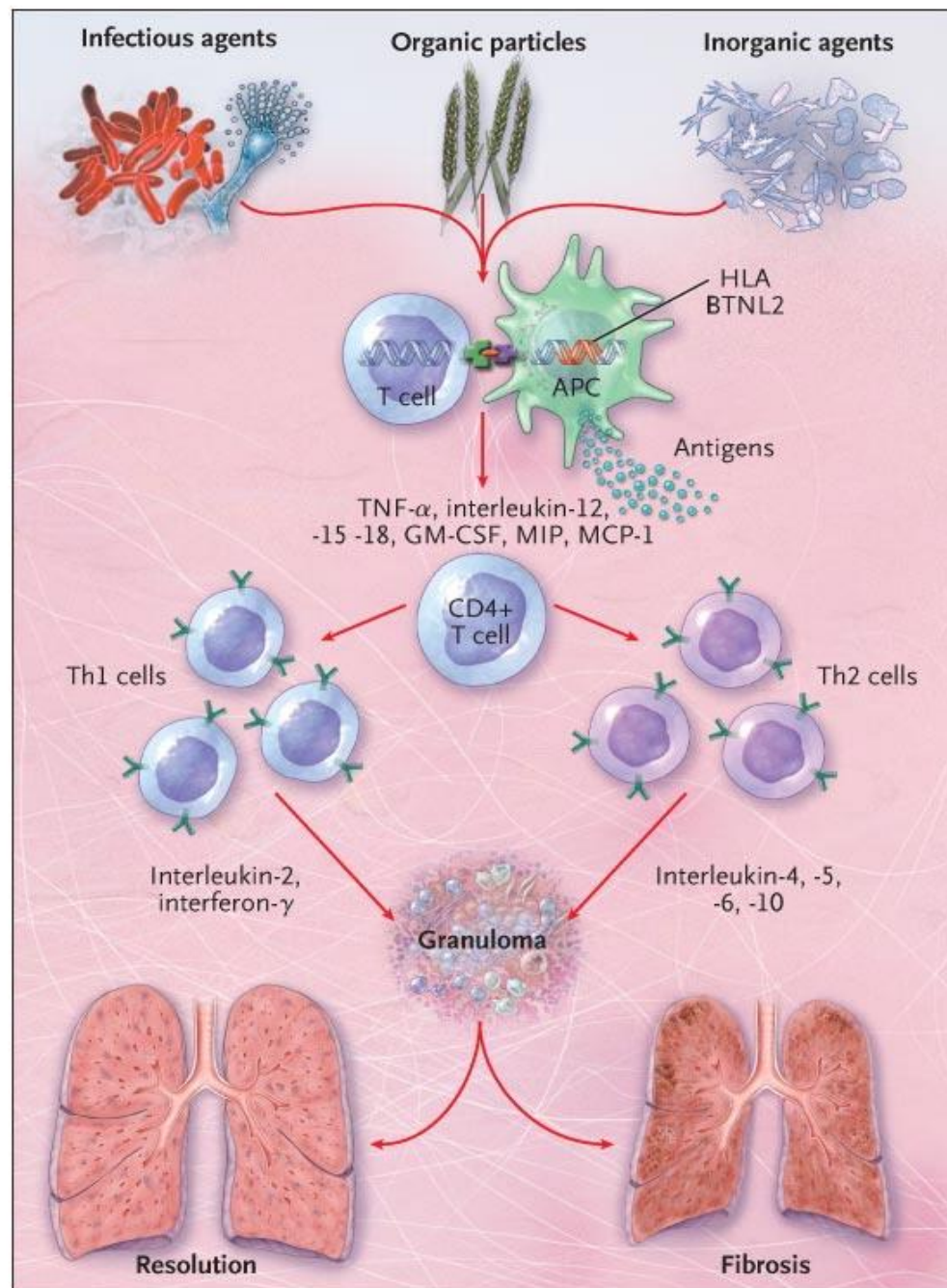
Baughman RP et al. Am J Respir Crit Care Med. 2001; 164: 1885-9.

Bernstien M et al. Arch Intern Med. 1999; 44: 721-34.

Tadamura E et al. AJR Am J Roentgenol. 2005; 185(1):110-5.

Drent M, et al. N Engl J Med. 2021 Sep 9;385(11):1018-1032.





Epidemiology

Prevalence 10 to 20 per 100,000 people

More common in certain ethnic groups

- Black/African American ~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/African American – peak prevalence rates 30-39 years of age

White Americans – flat incidence rates through adulthood



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

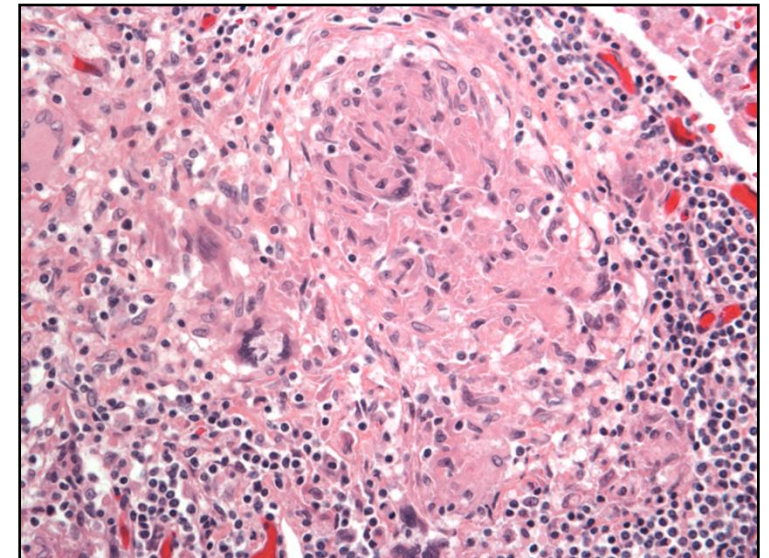
Compatible clinical and radiological manifestations

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



Scadding Stages

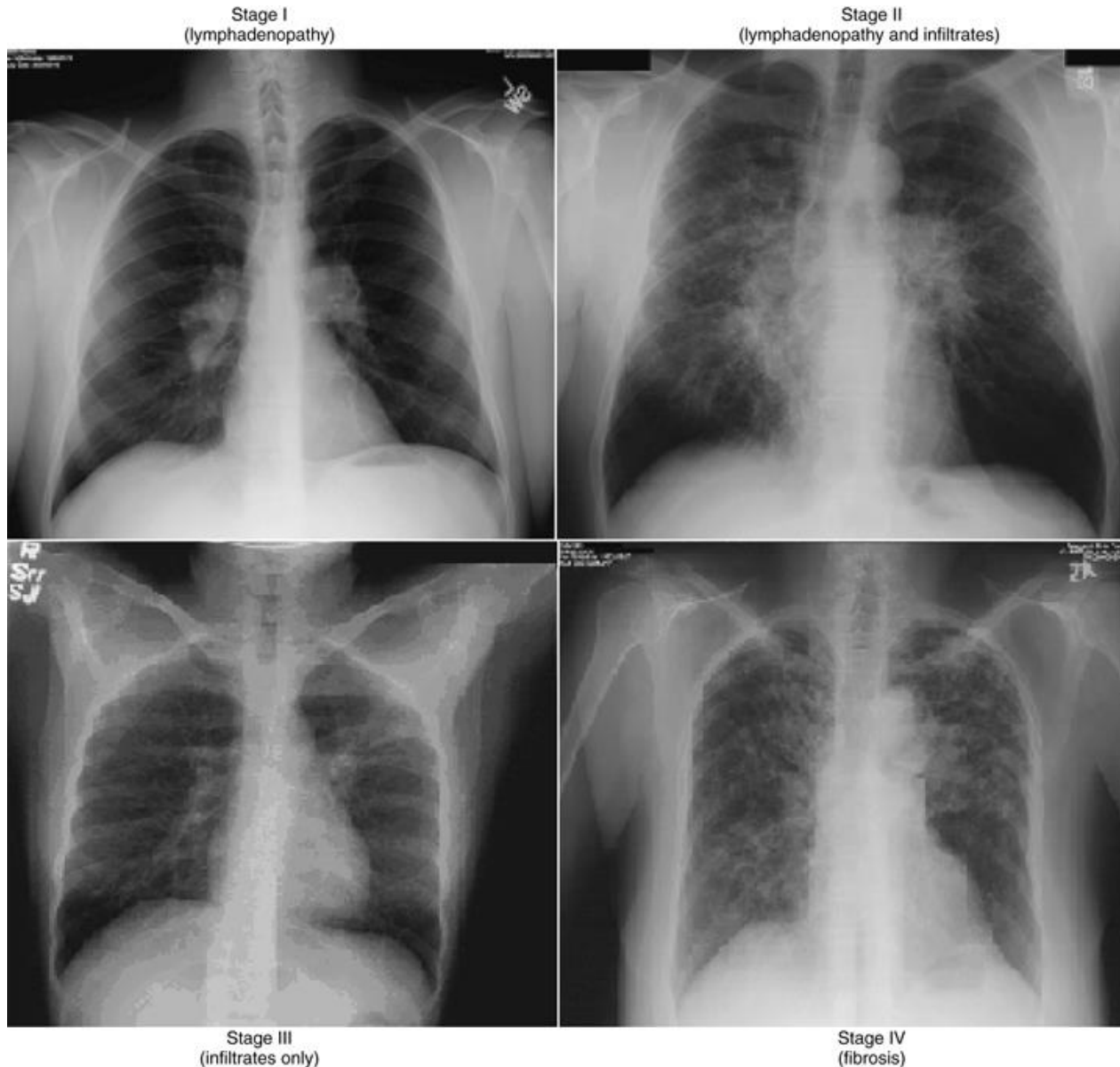


Table 1 | Radiographic types of sarcoidosis

Radiographic type	Radiographic characteristics	Prognosis
0	No visible findings	Not applicable
I	Bilateral hilar lymphadenopathy	Spontaneous resolution in most cases
II	Bilateral hilar lymphadenopathy and parenchymal infiltration	Spontaneous resolution possible
III	Parenchymal infiltration without hilar adenopathy in regular chest radiography	Spontaneous resolution in rare cases
IV	Advanced fibrosis with evidence of honeycombing bronchiectasis, hilar retraction, bulla and cysts	Permanent organ damage



Chest CT Characteristics



Chest CT Characteristics

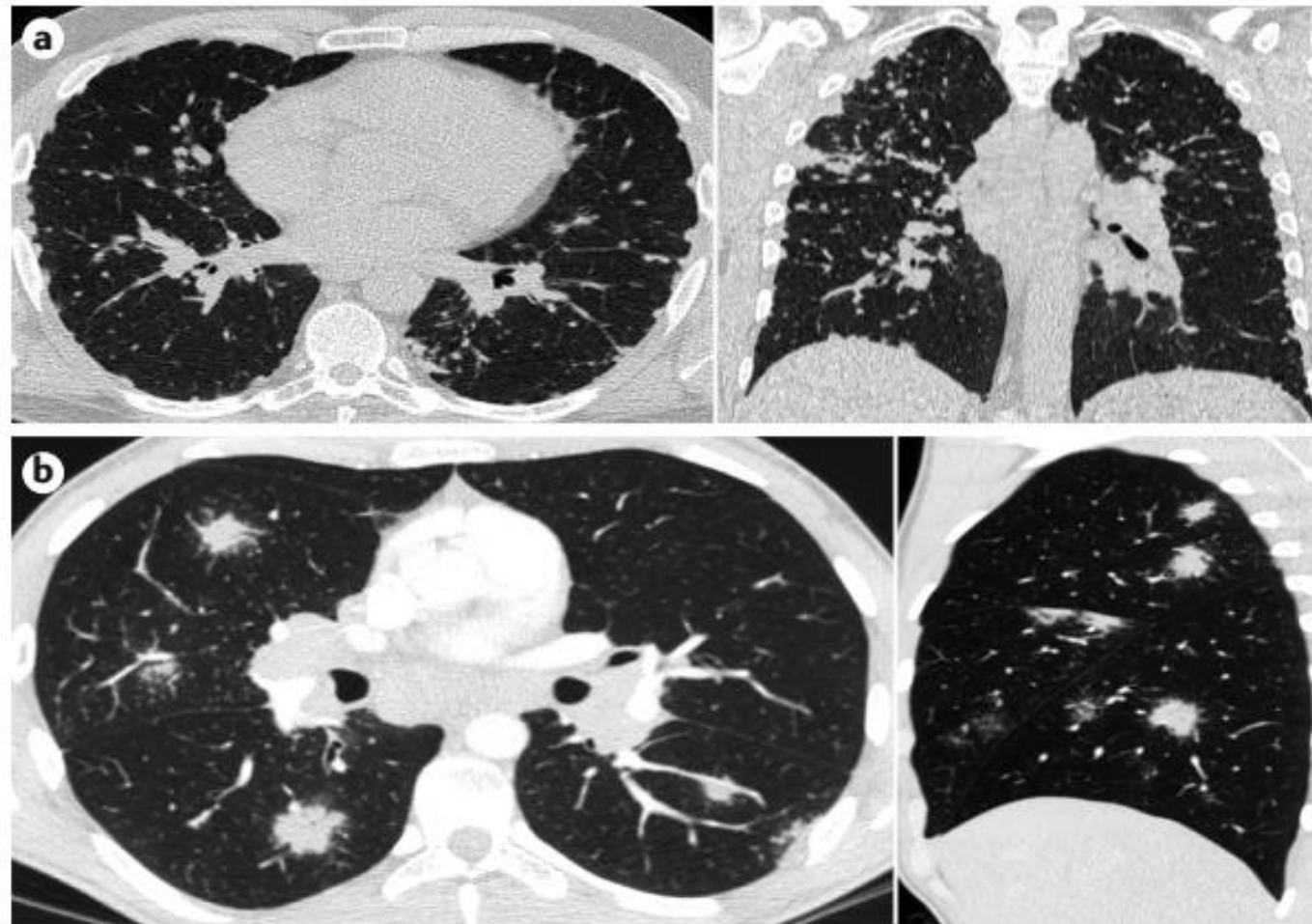


Fig. 9 | **High-resolution CT imaging of pulmonary sarcoidosis.** **a** | 'String of beads' appearance of peribronchovascular nodules in a patient with sarcoidosis. **b** | 'Galaxy' appearance of granulomas in a patient with sarcoidosis. Images courtesy of H. W. van Es, St Antonius Hospital, Netherlands.

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



Who do we treat?

Predominantly based on symptoms or evidence of disease progression by organ system: cardiac, neuro, ocular, hyperCa and progressive pulmonary disease

Management of sarcoidosis is a major clinical challenge because of the highly variable disease manifestations. The decision of whether (and, if so, when) to treat an individual patient who has sarcoidosis depends on two major factors: the risk of organ failure or death and the extent to which the patient's quality of life is impaired.^{3,12,46,48,49} The decision is complex and cannot be standardized.^{3,48} In most patients with sarcoidosis, the disease resolves spontaneously and does not require systemic therapy. However, for patients with severe disease, timely treatment can mitigate disease manifestations and prevent long-term complications.⁴⁸ Current treatment standards are based on low-quality evidence,⁶⁴ but experts agree that therapeutic goals should focus on suppression of inflammation-induced organ dysfunction, assessed on the basis of objective metrics (e.g., lung function), and on the avoidance of toxic effects of drugs.^{1,12,48,49} However, these two measures of disease manifestations can be misleading, since many patients continue to feel unwell despite objective resolution.

Drent M, et al. N Engl J Med. 2021 Sep 9;385(11):1018-1032.

INDICATIONS FOR TREATMENT

Over half of patients with sarcoidosis will incur spontaneous resolution or never have clinical manifestations of the disease, whereas the remaining half will experience a more chronic course, often requiring treatment. Mortality appears to be increasing over time, and burden of disease can be substantial due to complications of the disease or its treatments (25). It is unclear if treatment with corticosteroids alters the natural history of disease; therefore, treatment is recommended only for those with high symptom burden and/or evidence of organ damage (26). For those requiring treatment due to symptoms or suspicion of injury to organs, a stepwise approach to therapy is recommended, although more aggressive therapeutic management can be considered in particularly severe cases of neurologic, ophthalmic, or cardiac involvement (23). In general, there are very few large clinical trials for treatment in sarcoidosis (27). Therefore, in clinical practice, use of corticosteroids and other immunomodulatory agents is often modeled by use on other autoimmune and inflammatory diseases in which suppression of the immune system is desired.

Gerke AK. Front Immunol. 2020 Nov 19;11:545413.



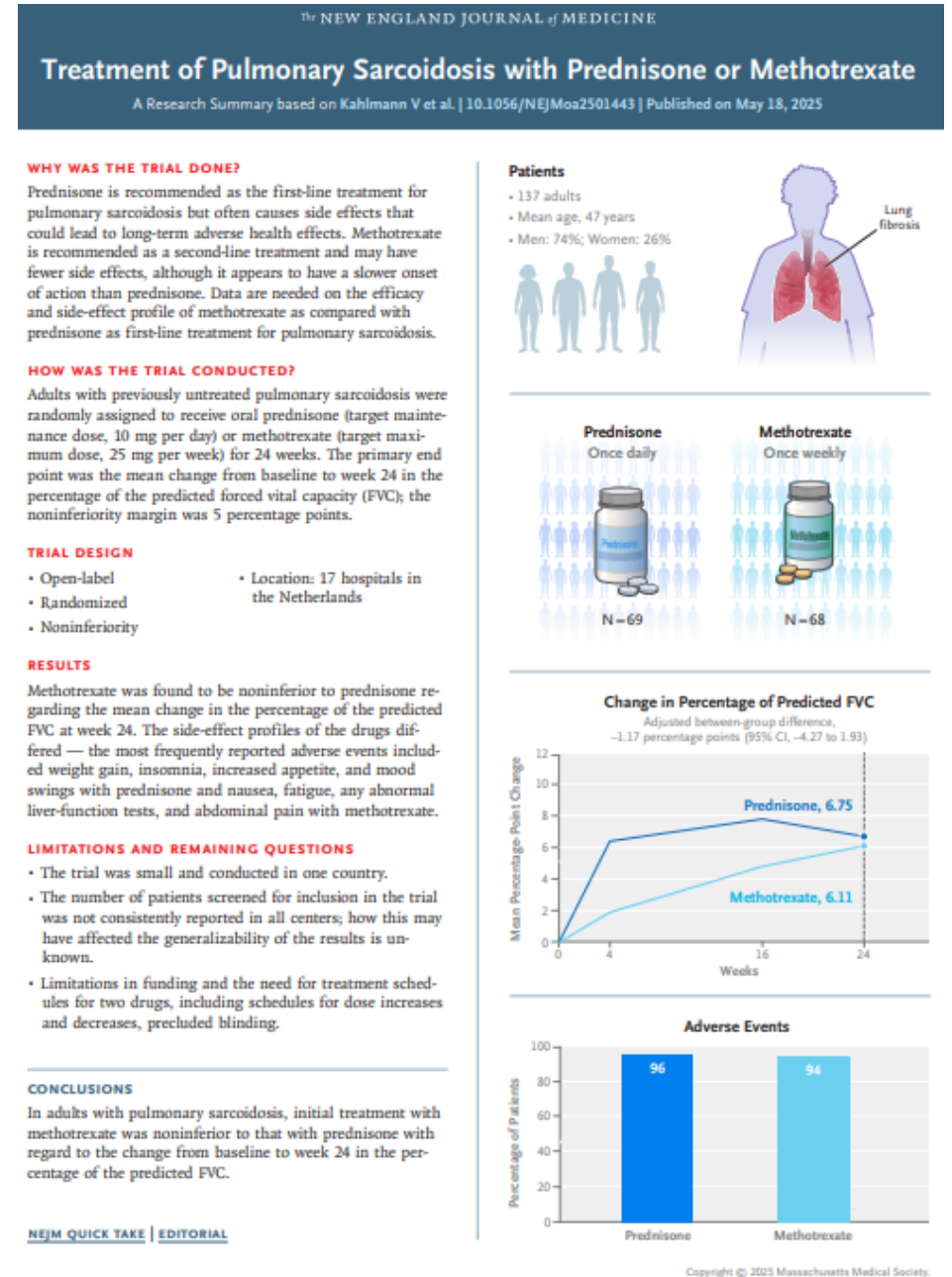
Treatment Options

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)
- ?JAKi



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

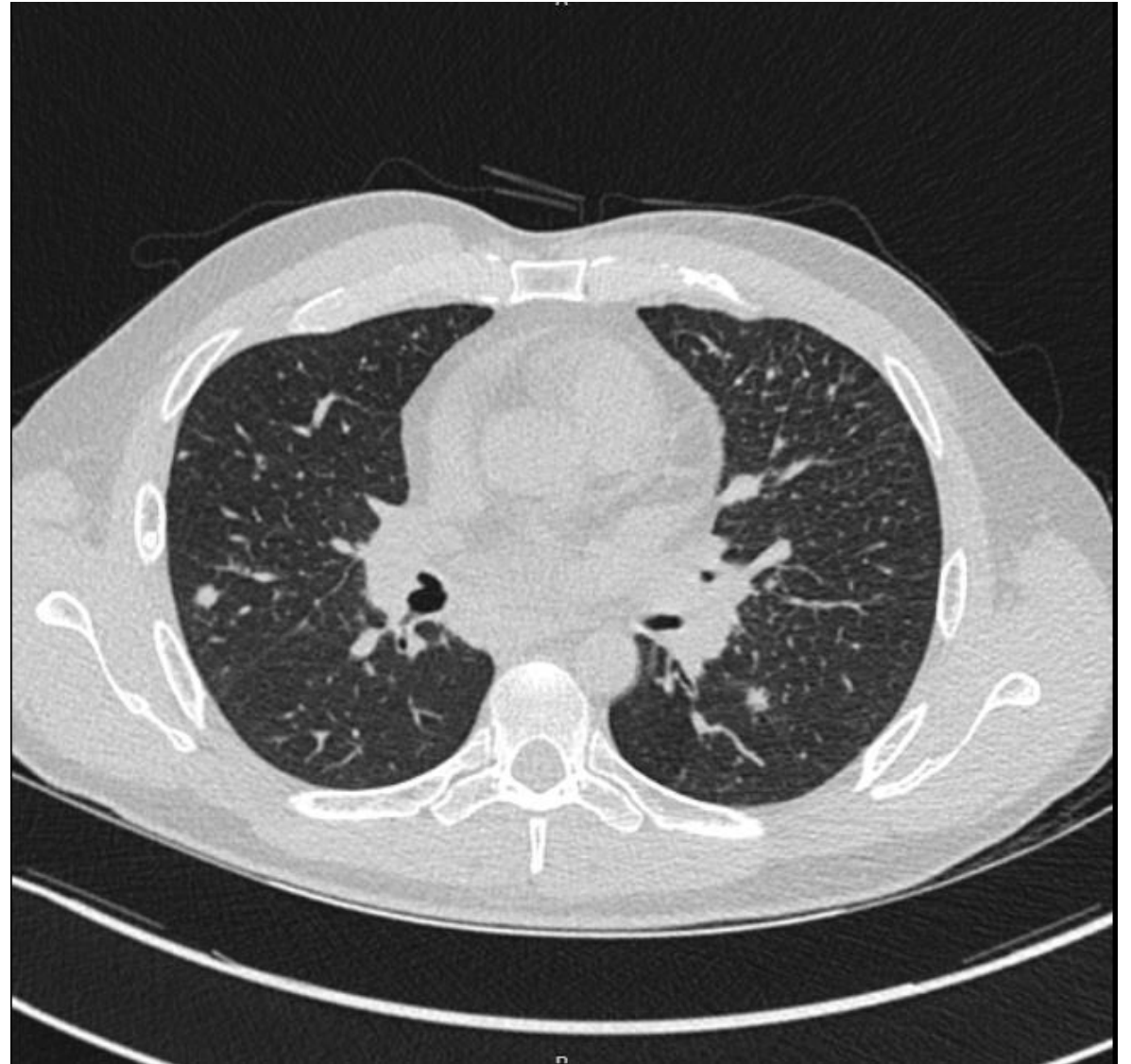
- Present in less than 5-10% of patients with sarcoidosis
- Combination of erythema nodosum (EN), hilar lymphadenopathy, migratory polyarthralgias, and fever – more common in women
 - Men often present with bilateral ankle arthritis and *without* erythema nodosum

The presence of this constellation of symptoms is 95% specific for the diagnosis of sarcoidosis
Associated with a good prognosis and spontaneous remission



Question 1

55 yo male developed wheezing and sore throat, then chronic cough and some dyspnea on exertion. CXR revealed lobar collapse, CT chest ordered and shown on right. Denies sweats, fevers, weight loss; endorses GERD sx. Underwent transbronchial biopsy, EBUS and lymph node FNA. FNA with granulomatous inflammation. Pulmonary function tests with normal spiro, lung volumes and DLCO. Which is the most appropriate next management step?



Question 1

Which is the most appropriate next management step?

1. Observation
2. Mycophenolate
3. Check angiotensin-converting enzyme
4. Corticosteroids



Question 1

Which is the most appropriate next management step?

1. Observation
2. Mycophenolate
3. Check angiotensin-converting enzyme
4. Corticosteroids



Answer

Patient has symptoms and inflammatory nodules suggestive of disease activity, steroids would be considered first line (ie, a symptomatic patient with abnormal imaging)



Question 2

A 22-year-old man presents with acute onset of fever, chills, dyspnea, and nonproductive cough. He is a college student and spends his summers working on a farm, he does not wear a mask. His symptoms worsen during the week to the point that he will miss several days of work, away from work his symptoms improve, then the cycle begins again. 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 diffuse crackles. 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. Inhaled glucocorticoids
- C. Pirfenidone
- D. Sirolimus



Question 2

Which of the following is the most appropriate treatment?

- A. Counsel the patient not to return to work
- B. Inhaled glucocorticoids
- C. Pirfenidone
- D. Sirolimus



Answer

This patient has acute hypersensitivity pneumonitis most likely related to exposures at his new job working on the farm, he currently has mild symptoms, that are improving with antigen avoidance, so he should be counseled not to return to work



Granuloma Etiologies and Diagnostic Algorithm

Box 1

Common etiologies of pulmonary granulomas

• Infectious

- Mycobacteria
 - *Mycobacterium tuberculosis*
 - Nontuberculous mycobacteria
- Fungi
 - *Histoplasma*
 - *Blastomyces*
 - *Cryptococcus*
 - *Coccidioides*
 - *Pneumocystis*
- Parasites
 - *Paragonimus*
 - *Dirofilaria*
 - *Schistosoma*
 - *Strongyloides*

• Noninfectious

- Hypersensitivity pneumonitis
- Sarcoidosis
- Berylliosis
- Hot tub lung
- Lymphoid interstitial pneumonia
- Granulomatous-lymphocytic interstitial lung disease
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis
- Aspiration
- Talc granulomatosis
- Rheumatoid nodule
- Adverse drug reaction

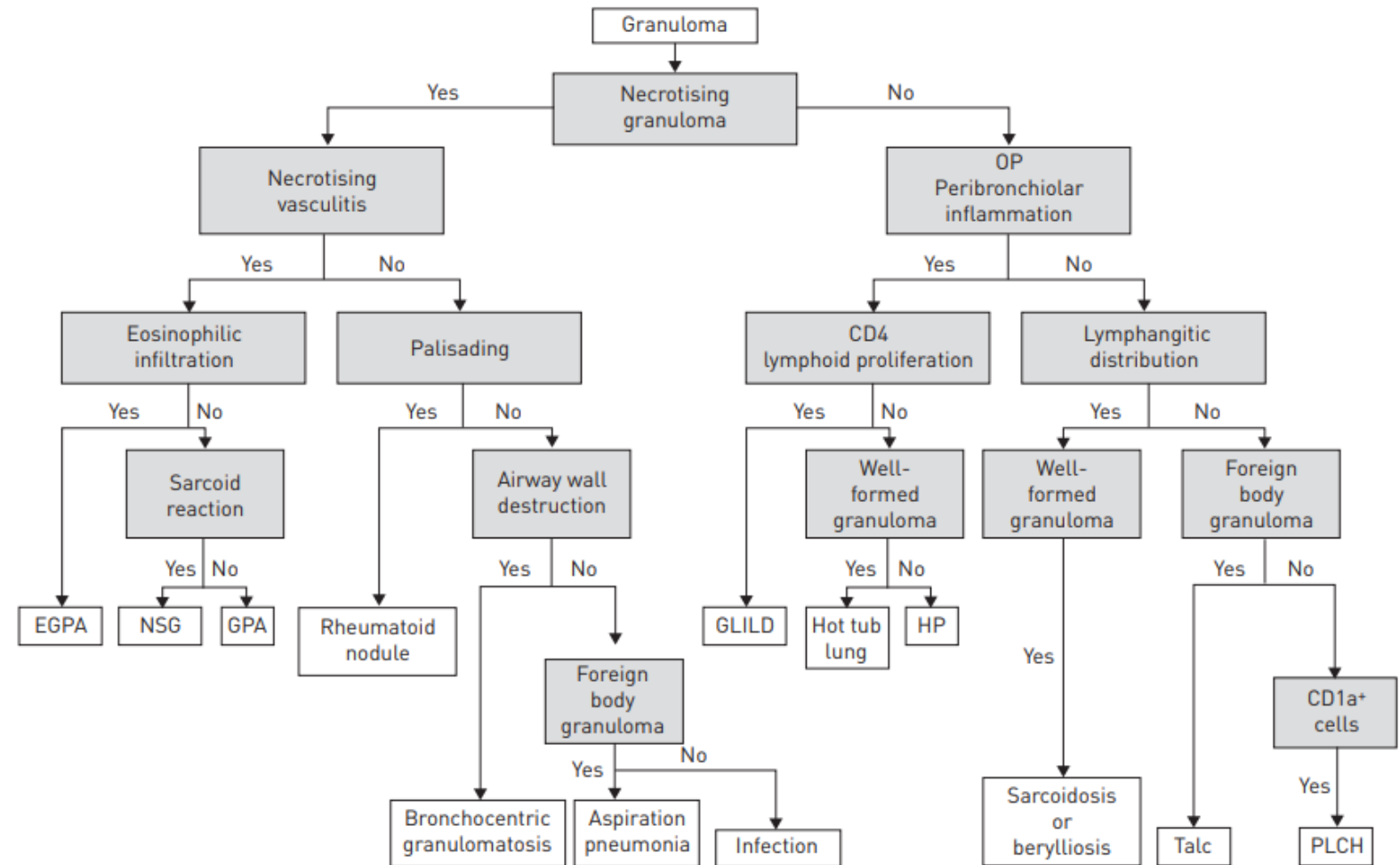


FIGURE 2 Diagnostic algorithm of granulomatous lung diseases. OP: organising pneumonia; EGPA: eosinophilic granulomatosis with polyangiitis; NSG: necrotising sarcoid granulomatosis; GPA: granulomatosis with polyangiitis; GLILD: granulomatous-lymphocytic interstitial lung disease; HP: hypersensitivity pneumonitis; PLCH: pulmonary Langerhans cell histiocytosis.



MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

There are several etiologies for granulomatous lung disease. Radiographic patterns, clinical history, possible labs and bronchial/lymph node sampling can help elucidate a diagnosis.

Major non-infectious etiologies include hypersensitivity pneumonitis and pulmonary sarcoidosis.

Exposure history and avoidance is important in HP; steroids in pulmonary sarcoidosis may be indicated based on clinical, radiographic, physiological parameters.



REFERENCES

- Mukhopadhyay S. Arch of Path Lab Med. 2010; 134(5); 667-90.
- Poulsen A. Acta Tuberc Scand. 1957;33(1-2):37.
- Teirstein AS, et al. Mt Sinai J Med. 1990;57(4):209.
- Reich JM, Johnson RE. Chest. 1992;101(6):165.
- Cormier Y, Lacasse Y. Clin Pulm Med. 1996; 3:72.
- Richerson HB, Bernstein IL, Fink JN, et al. J Allergy Clin Immunol 1989; 84:839.
- 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.
- Culver, DA. et al. BMJ. 2019;367:l5553.
- Rybicki BA. et al. Am J Epidemiol. 1997; 145(3): 234-41.
- 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.
- Statement on Sarcoidosis. Am J Respir Crit Care Med. 1999; 160(2); 736-55.
- Kirkil G., et al. Chest 2018 Jan;153(1):105-113.
- Grunewald J, Eklund A. Am J Respir Crit Care Med. 2007;175(1):40.
- Paramothayan NS. Cochrane Database Syst Rev. 2005; 2: CD002994.
- Paramothayan NS. Cochrane Database Syst Rev. 2006; 3: CD03535.
- Baughman RP et al, Am J Respir Crit Care Med. 2011; 183(5): 573-81.
- Ohshimo S et al. Eur Respir Rev. 2017 Aug 9;26(145):170012.
- Chan JCK et al. Surg Pathol Clin. 2024 Jun;17(2):173-192.
- Pai, M.*et al.* Tuberculosis. *Nat Rev Dis Primers* **2**, 16076 (2016).
- Warner, D.F., et al. *Nat Rev Microbiol* **23**, 788–804 (2025)
- Kumar K, Loebinger MR. Chest. 2022 Mar;161(3):637-646.
- Shu CC, et al. J Formos Med Assoc. 2020 Jun;119
- Grunewald J, et al. Sarcoidosis. *Nat Rev Dis Primers*. 2019 Jul 4;5(1):45.
- Drent M, et al. N Engl J Med. 2021 Sep 9;385(11):1018-1032.
- Ryerson CJ, et al. Eur Respir J. 2025 Dec 4;66(6):2500158.
- Ryerson CJ et al. Am J Respir Crit Care Med. 2025 Oct;211(10):1756-1774.





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