Sarcoidosis ACOI 2021

David H. Lindner, D.O. MBA, FACOI, FCCP

Subdivision Head Pulmonary Critical Care & Sleep Medicine

Instructor Mayo Clinic School of Medicine and Science

Associate Professor of Medicine University of Central Florida

Adjunct Associate Professor of Medicine NOVA Southeastern

Medical Director of COVID19 NCH & NCH Healthcare Intensive Care Units and Respiratory Care

Pulmonary Program Director NCH Healthcare System Internal Medicine Residency

Conflicts

I wish to acknowledge and thank Mallinckrodt Pharmaceuticals for assistance with these educational materials and slide set in the midst of the pandemic, no compensation was associated with the production of these slides or this presentation.

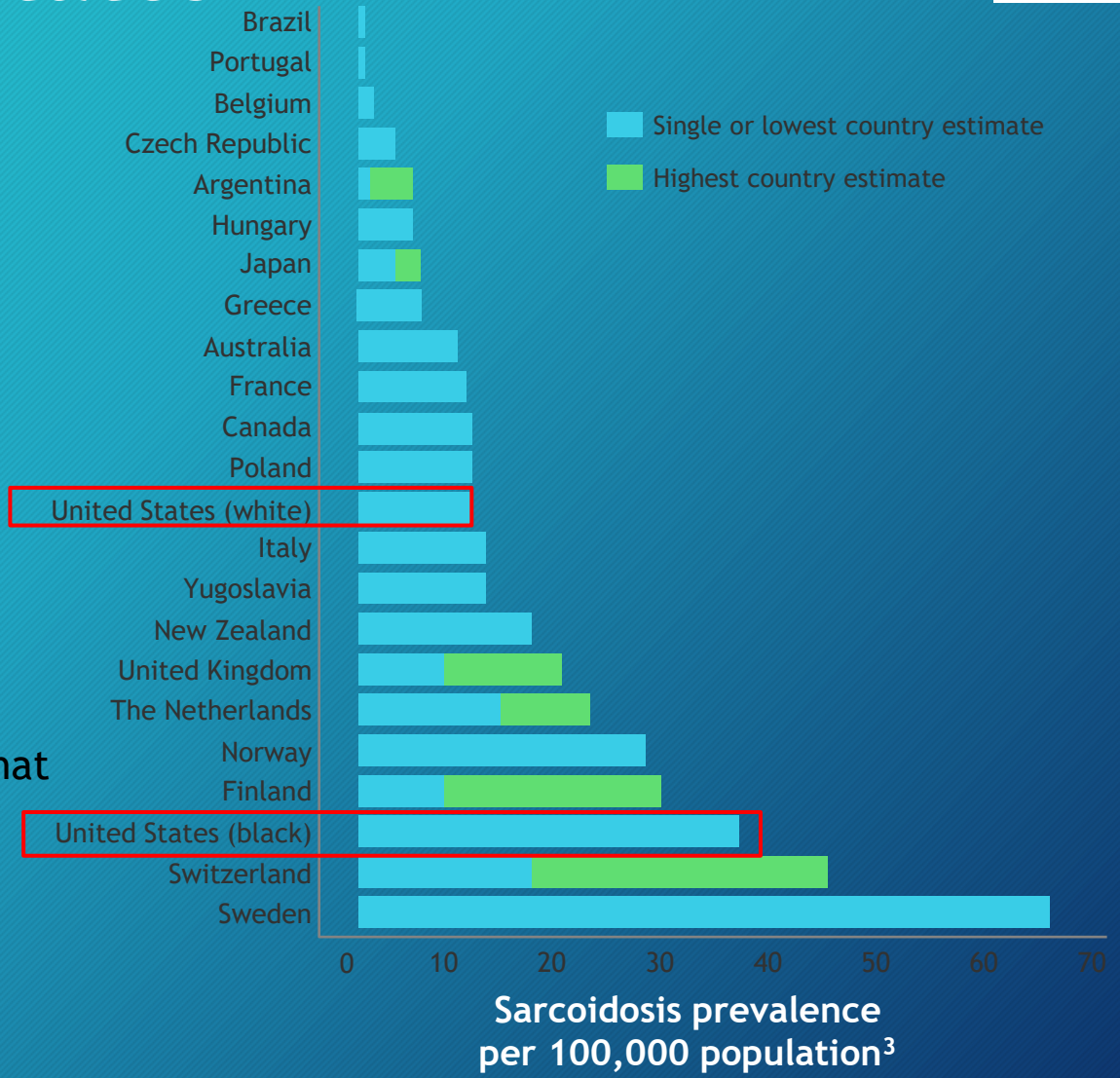
Goals and Objectives

- To understand the epidemiology of Sarcoidosis
- To understand the proposed pathophysiology of Sarcoidosis
- To understand the initial diagnostics for Sarcoidosis
- To understand the treatment approach to Sarcoidosis
- To understand some facets of special circumstances in Sarcoidosis

Sarcoidosis Affects Approximately 185,000 Individuals in the United States[1]

United States: ~185,000[1]

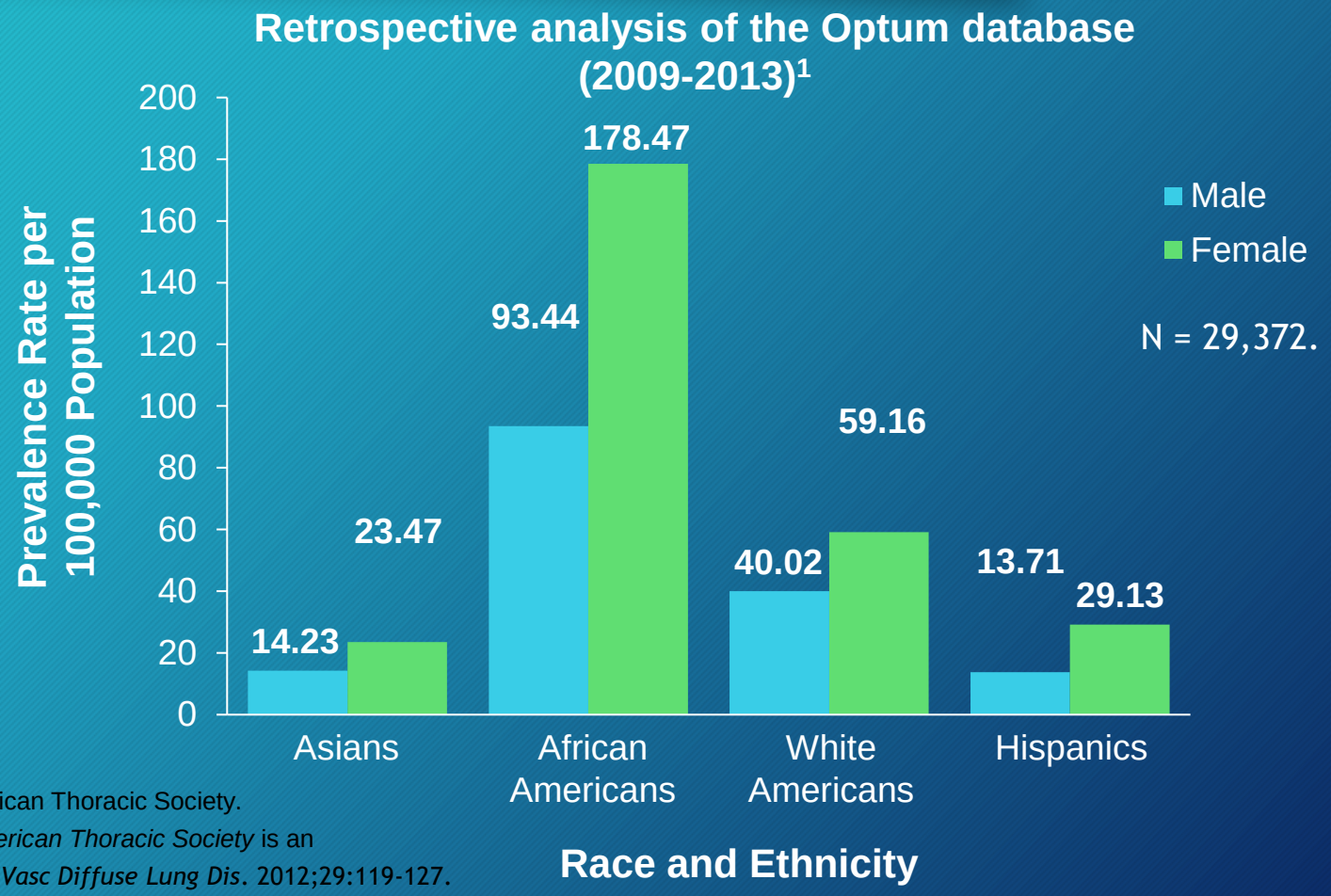
- A study examining prevalence in central Ohio found that regional prevalence may be as much as 4-fold greater than previously estimated, suggesting the true prevalence of sarcoidosis is underestimated.[2]



1. Baughman RP et al. Ann Am Thorac Soc. 2016;13:1244-1252. 2. Erdal BS et al. *Respir Med*. 2012;106:893-899. 3. Denning DW et al. *Eur Respir J*. 2013;41:621-626.

Sarcoidosis Has an Increased Incidence in Older Population and Is Most Common in African Americans[1]

- Although earlier studies characterized sarcoidosis as a disease of young people, recent studies have shown an increased incidence in the older population.[1]
  - Among patients with sarcoidosis, 59% were 55 years of age or older.[1]
- Sarcoidosis 3× more prevalent in African American women than in white American women.[1]
  - In a separate study, the disease was more severe in African Americans than in white Americans.[2]



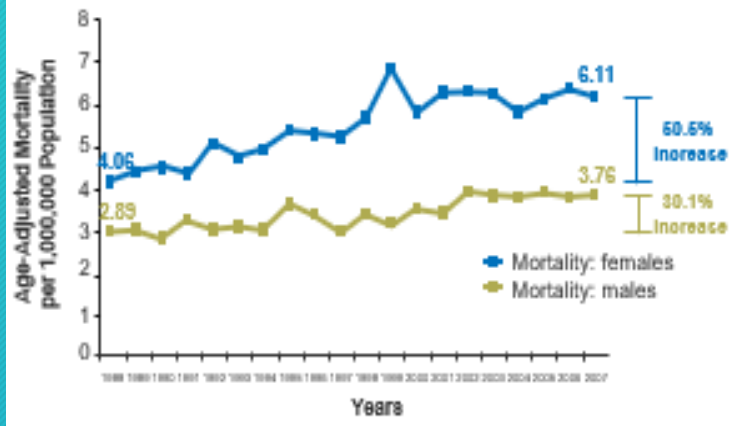
1. Baughman RP et al. *Ann Am Thorac Soc*. 2016;13:1244-1252. *Annals of the American Thoracic Society* is an
2. official journal of the American Thoracic Society. **2**. Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127.

Sarcoidosis Associated Disease Burden[1-5]

Increased Mortality

- Average age- and sex-adjusted sarcoidosis-related mortality was 4.32 per 1,000,000 population in the United States over a 20-year period.[1]
- The age-adjusted mortality rate for non-Hispanic black Americans is 12 times higher than for whites.[5]

Retrospective analysis of data collected from the National Center for Health Statistics (1988-2007; N = 46,450,489)



Decreased Quality of Life (QOL)

- Patients with sarcoidosis had significant decrements in their QOL.[2-4]

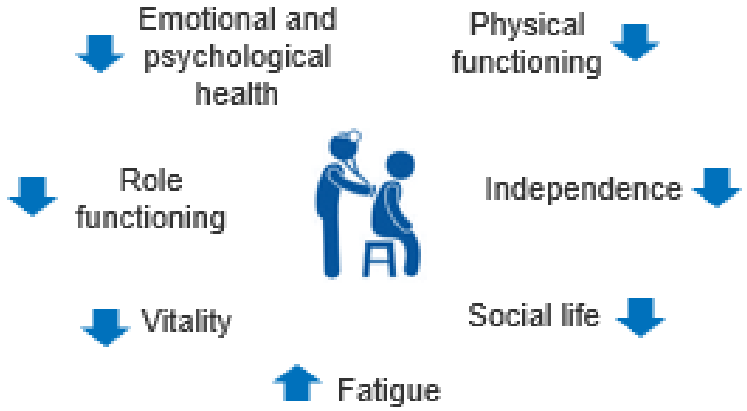


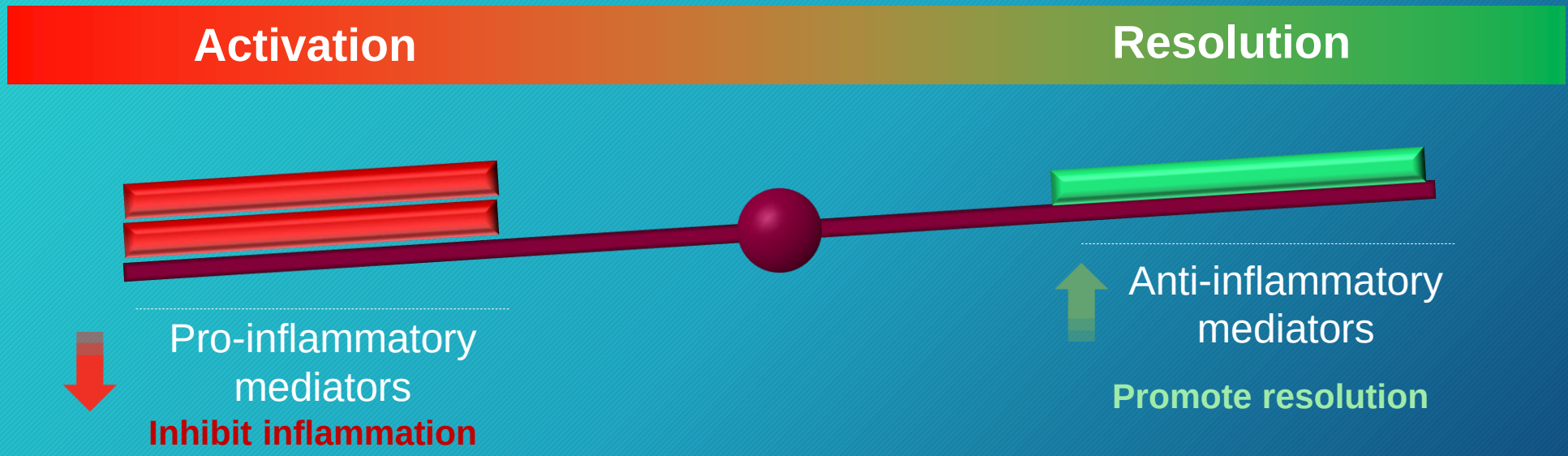
Figure reproduced and adapted with permission from Swigris JJ et al. **1.** Swigris JJ et al. *Am J Respir Crit Care Med*. 2011;183:1524-1530. **2.** Cox CE et al. *Chest*. 2004;125(3):997-1004. **3.** De Vries J et al. *Semin Respir Crit Care Med.* 2010;31(4):485-493. **4.** de Boer S et al. *Respirology*. 2014;19(7):1019-1024. **5.** Mirsaeidi M et al. *Chest*. 2015;147:438-449.

Immune Dysregulation Is Believed in Sarcoidosis to Lead to Chronic Disease[1,2]

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Broos CE et al. *Front Immunol*. 2013;4:437.

NCH Physician Group

Mitigating Immune Diseases Primarily Focuses on Restoring Immune Balance[1,2]



- Activation and resolution are key in balancing the immune response.[1,2]
- Melanocortin system may play an important role in anti-inflammatory and proresolution processes.[3,4]

1. Tabas I and Glass CK. *Science.* 2013;339:166-172. **2.** Silverman M et al. *Viral Immunol*. 2005;18:41-78. **3.** Ahmed TJ et al. *Int J Inflam*. 2013;2013:985815. **4.** Catania A et al. *Pharmacol Rev.* 2004;56:1-29.

NCH Physician Group

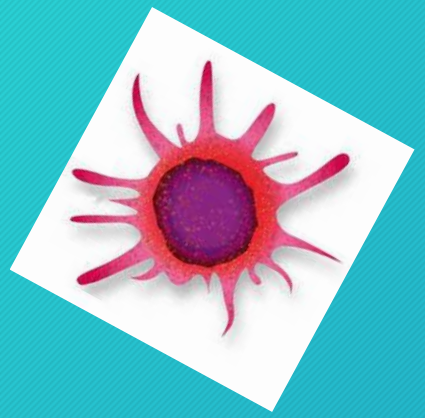
Sarcoidosis Immune Dysregulation Involving Multiple Immune Cells[1-3]

- Migrate to affected tissue as one of first responders[1]
- Release TNF-α inducing vasodilation and monocyte/lymphocyte infiltration[1]
- Release pro-inflammatory cytokines (eg, IL-1, -6, -12, -23) promoting[1]:
  - Leukocyte infiltration
  - T-cell activation
  - T_{reg} inhibition
  - T-cell apoptosis inhibition

Cell-mediated damage
Inflammation & fibrosis

1. Timmermans WM et al. *Clin Transl Immunology.* 2016;5(12):e118. **2.** Mortaz E et al. *Iran J. Allergy Asthma Immuno*l. 2014;13(5):300-306. **3.** Loke WS et al. *Int J Chronic Dis*. 2013;2013:928601.

Sarcoidosis Immune Dysregulation Involving Multiple Immune Cells[1-3]



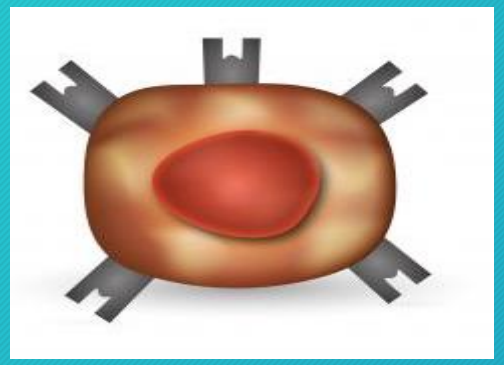
Dendritic cells (DCs)

- Inflammation causes DC activation, maturation and migration to lymph nodes[2]
- Drive T-cell expansion and Th1 polarization[2]
- Produce a battery of mediators that facilitate the sarcoid immune reaction[3]
- TNF-α production leads to CD4+ T-cell proliferation[3]

1. Timmermans WM et al. *Clin Transl Immunology.* 2016;5(12):e118. **2.** Mortaz E et al. *Iran J. Allergy Asthma Immuno*l. 2014;13(5):300-306. **3.** Loke WS et al. *Int J Chronic Dis*. 2013;2013:928601.

Sarcoidosis Immune Dysregulation Involving Multiple Immune Cells[1-3]

T-cells

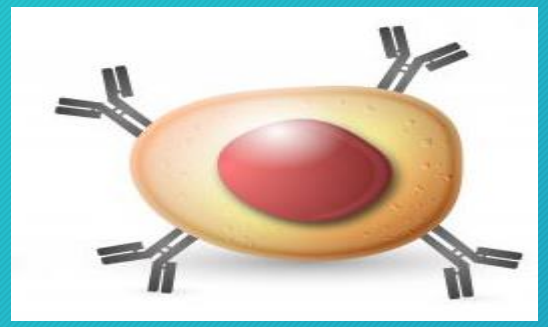


- CD4+ T cell infiltrates at site of inflammation[1]
- T-cell lymphopenia in peripheral blood[1]
- Abnormal T-cell response in nongranulomatous tissue[1]
- Initial Th1 response during inflammation shifts to Th2 leading to fibrosis[1]
- CD8+ T cells accumulate in the sarcoid lung[2]
- Th17 T cells are increased in inflammatory tissue and peripheral blood[1]
- T_{reg} are increased outside granulomas but exhibit decreased function[1]

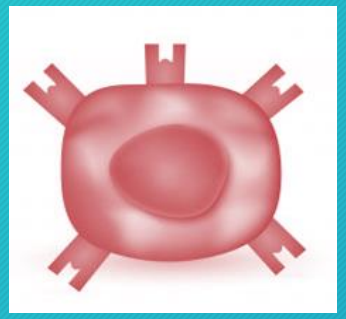
1. Timmermans WM et al. Clin Transl Immunology. 2016;5(12):e118. 2. Mortaz E et al. Iran J. Allergy Asthma Immunol. 2014;13(5):300-306. 3. Loke WS et al. Int J Chronic Dis. 2013;2013:928601.

Sarcoidosis Immune Dysregulation Involving Multiple Immune Cells[1-3]

B-cells

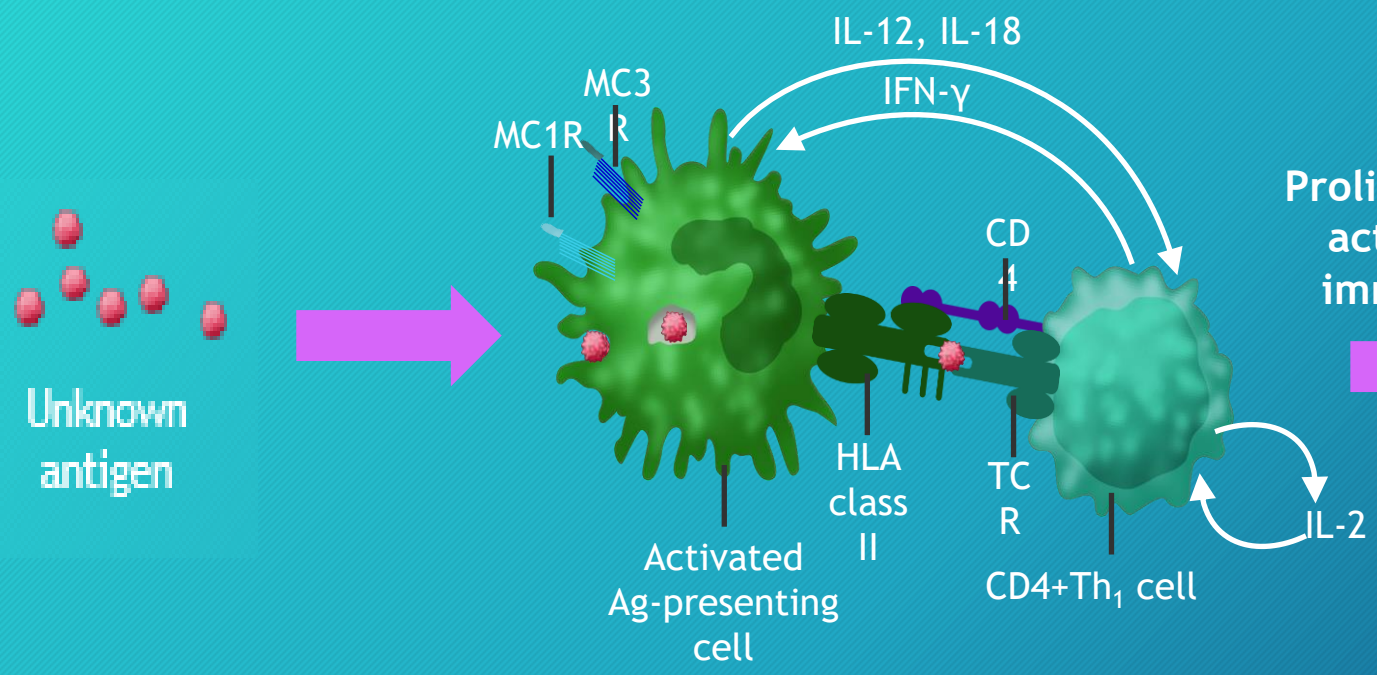


NK Cells



1. Timmermans WM et al. Clin Transl Immunology. 2016;5(12):e118. 2. Mortaz E et al. Iran J. Allergy Asthma Immunol. 2014;13(5):300-306. 3. Loke WS et al. Int J Chronic Dis. 2013;2013:928601.

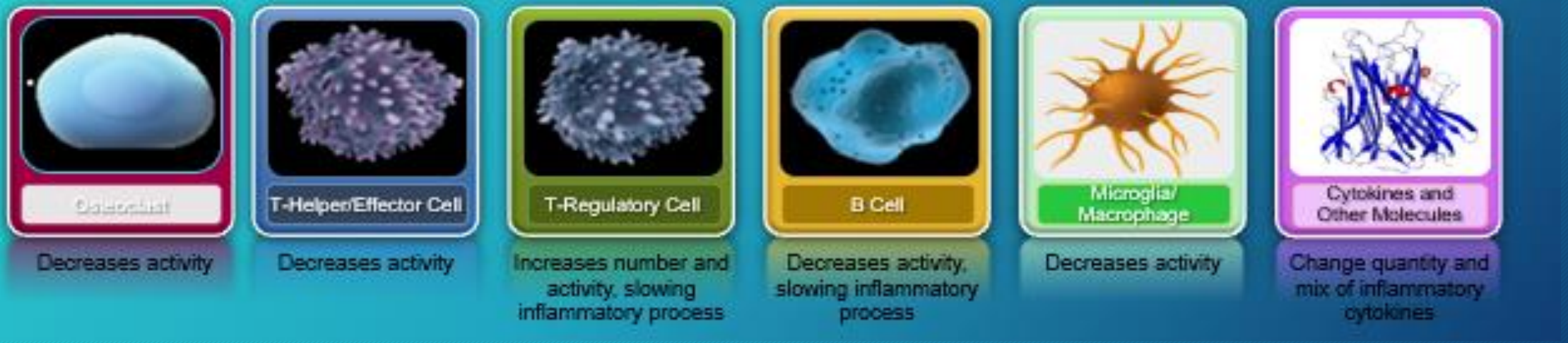
Granuloma Formation May Result in Persistent Chronic Disease and Fibrosis[1,2]



Ag = antigen; HLA = human leukocyte antigen; IFN = interferon; MC1R = melanocortin receptor 1; MC3R = melanocortin receptor 3; TCR = T-cell receptor; TNF = tumor necrosis factor. 1. Adapted with permission from Baughman RP et al. Am J Respir Crit Care Med. 2011;183:573-5811. 2. Iannuzzi MC et al. N Engl J Med. 2007;357:2153-2165.

Melanocortin System May Be Involved in Immunological and Physiological Processes[1-3]

- The melanocortin system may play an integral role in a diverse array of effects[1-3]
  - Regulation of immune cell adhesion and trafficking
  - Inhibition of NF-κB signaling and activation & Steroidogenesis



The natural melanocortins α-, β-, and γ-MSH and ACTH bind to melanocortin receptors on cell surfaces.[1]

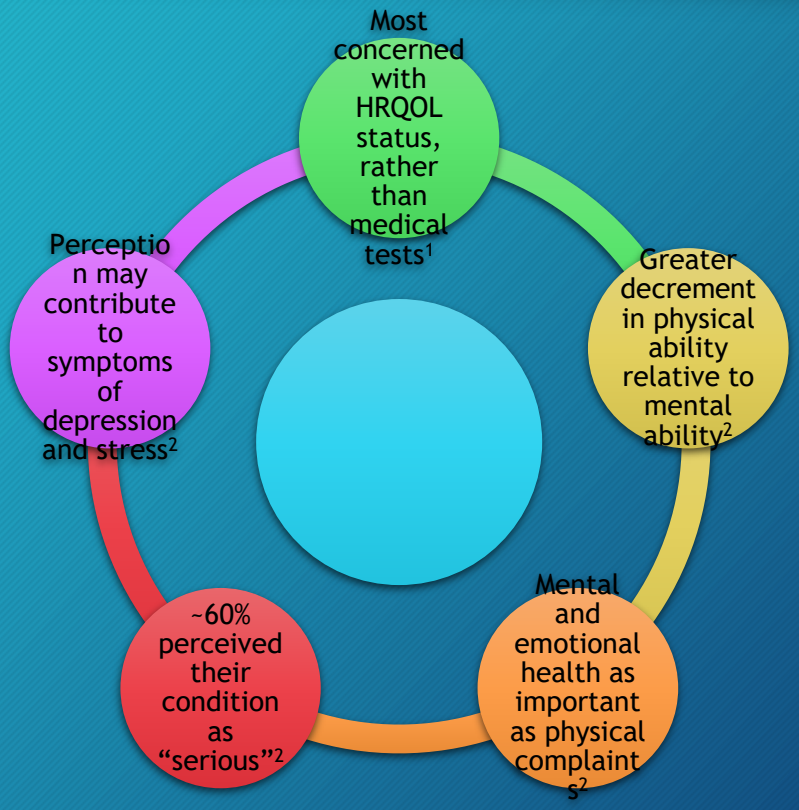
ACTH = adrenocorticotropic hormone; MSH = melanocyte-stimulating hormone; NF-κB = nuclear factor kappa light-chain enhancer of activated B cells.

1. Brzoska T et al. *Endocr Rev*. 2008;29:581-602. **2.** Catania A et al. *Pharmacol Rev.* 2004;56:1-29. **3.** Gong R. *Nat Rev Nephrol*. 2011;8:122-128.

Clinical Presentation

Clinical Diagnosis of Sarcoidosi

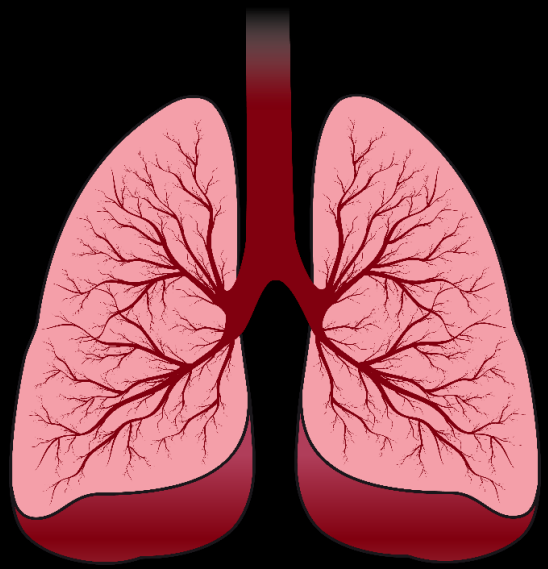
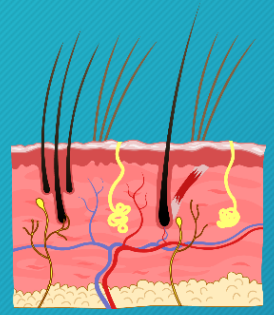
- Only 15.3% of patients were diagnosed on the first physician visit and ~46% of patients required ≥4 physician visits until diagnosis.
- >20% of cases required 6 or more visits until the diagnosis was established.
- Multiple factors caused diagnosis and treatment delay.
  - Initial disease was often asymptomatic.
  - Symptoms are nonspecific
  - Involvement of any organ system.
  - Economic factors and/or other barriers



HRQOL = health-related QOL.

Judson MA et al. Am J Respir Crit Care Med. 2015;191(7):786-795. 2. Cox CE et al. Chest. 2004;125(3):997-1004

Sarcoidosis Involves Both Pulmonary and Extrapulmonary Manifestations

Lungs	Skin	Eyes	Liver	Others
				Lymph nodes Ear, nose, throat Neurologic Bone, marrow Spleen Bone, joints Cardiac Salivary, glands Muscle Renal
89%	**26%**	**23%**	**20%**	**< 15%**

N = 1582.

Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127.

Sarcoidosis Patients Diverse Symptoms

Pulmonary[1,2]	Systemic[1,2]	Extrapulmonary[1,2]
Dyspnea	Fatigue	Erythema nodosum
Cough and wheezing	Night sweats	Anterior uveitis
Bronchial hyperreactivity	Weight loss	Cranial nerve palsy
Bilateral hilar adenopathy		Hypercalciuria
Fibrosis		Cardiomyopathy
Pulmonary hypertension		

At least one-third of patients are asymptomatic[3]

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2156. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586.
3. Baughman RP, Lower EE. *Eur Respir Mon*. 2005;32:301-315.

Sarcoidosis : Probable

- African American or Northern European[1,2]
- Aged 20-39 years (males and females); aged > 40-50 years in females[3,4a]
- Increased age[1,2]
- Nonsmoker[1]
- Asymptomatic presentation (especially with consistent radiographic findings)[1,2]
- Hypergammaglobulinemia[2]
- Peripheral blood lymphopenia[2]
- Elevation of liver enzymes or serum calcium[2]
- Family history of sarcoidosis[1,2]
- Elevated biomarkers (sIL2R, ACE, 1,25-(OH)2-vitamin D, CD4, lysozymes)1,2
- Multiorgan disease[1,2]
- Radiographic findings: bilateral hilar adenopathy (especially if without symptoms); HRCT: disease along the bronchovascular bundle; PET/CT Scan[2]

1. Judson MA. *Clin Chest Med*. 2008;29:415-427. 2. Culver DA. Curr Opin Pulm Med. 2015;21:499-509. 3. Dumas O et al. Ann Am Thorac Soc. 2016;13:67-71. 4. Iannuzzi MC et al. N Engl J Med. 2007;357:2153-2165. Studies in northern Europe and Japan have described a bimodal pattern of age-specific incidence among women.3,4

Sarcoidosi: Less Probable

- Aged <18 years[1,2]
- Aged >50 years in males[1]
- Exposure to beryllium and other metal dusts[1,2]
- Exposure to tuberculosis[1,2]
- Recurrent infections[2]
- Hypogammaglobulinemia[2]
- Systemic disease capable of inducing granulomatous reactions[2]
    - Malignancy
    - Inflammatory bowel disease
    - Immunodeficiency
- Rales[2]
- Clubbing[2]

1. Judson MA. Clin Chest Med. 2008;29:415-427. 2. Culver DA. Curr Opin Pulm Med. 2015;21:499-509. 3. Dumas O et al. Ann Am Thorac Soc. 2016;13:67-71. 4. Iannuzzi MC et al. N Engl J Med. 2007;357:2153-2165. Studies in northern Europe and Japan have described a bimodal pattern of age-specific incidence among women.3,4

Diagnosis

History & Physical: Sarcoidosis

- Any symptom may represent a manifestation of sarcoidosis, because sarcoidosis may affect any organ in the body.
- Temporal presentation of symptoms may be useful.
- Parasarcoidosis syndrome: causing symptoms and/or dysfunction not directly related to deposition of sarcoid granulomas.
  - Systemic increase of mediators (?) from sarcoid granulomas:
    - Small fiber neuropathy
    - Erythema nodosum
    - Fatigue
    - Pain syndromes
  - May not respond to antigranulomatous therapy

Sarcoidosis: International Consensus Statement

- Three criteria for diagnosing sarcoidosis:

(1) compatible clinical and radiologic presentation

(2) pathologic evidence of noncaseating granulomas

(3) exclusion of other diseases with similar findings

Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline
https://doi.org/10.1164/rccm.202002-0251ST

NCH Physician Group

Siltzbach Classification System [1-3]

Stage[1,2]	Radiologic Abnormalities	Stage at Diagnosis, %
0	None	5-10
I	Bilateral hilar lymphadenopathy without infiltration	50
II	Bilateral hilar lymphadenopathy with infiltration	25-30
III	Infiltration alone	10-12
IV	Fibrotic bands, bullae, hilar retraction, bronchiectasis, diaphragmatic tenting	5 (up to 25 over disease course)

Image reproduced with permission from Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586. **3.** Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

Lung and Lymph Node Involvement Detected by Chest Radiography[1-3]

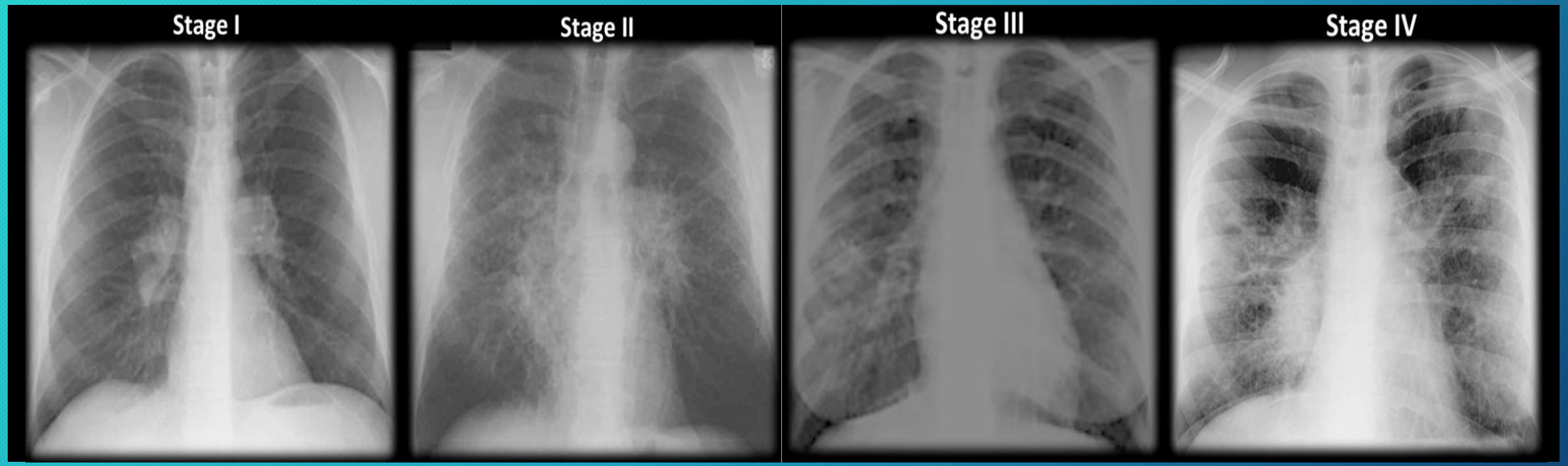


Image reproduced with permission from Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586. **3.** Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

Sarcoidosis Radiology

- Bilateral lymphadenopathy
- Micronodular changes
- Perilymphatic distribution, including spreading along the fissures.
- Highly specific for Sarcoidosis

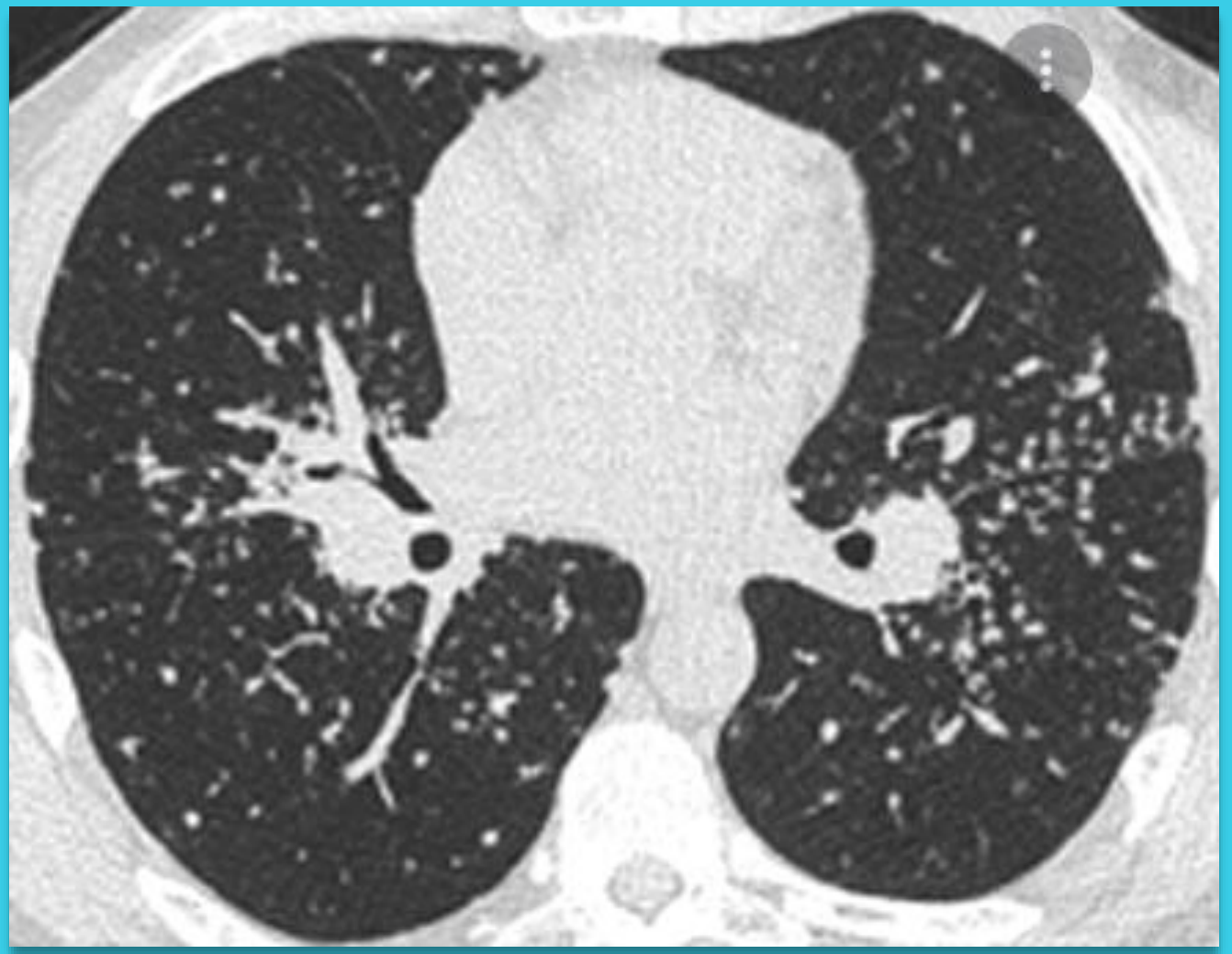
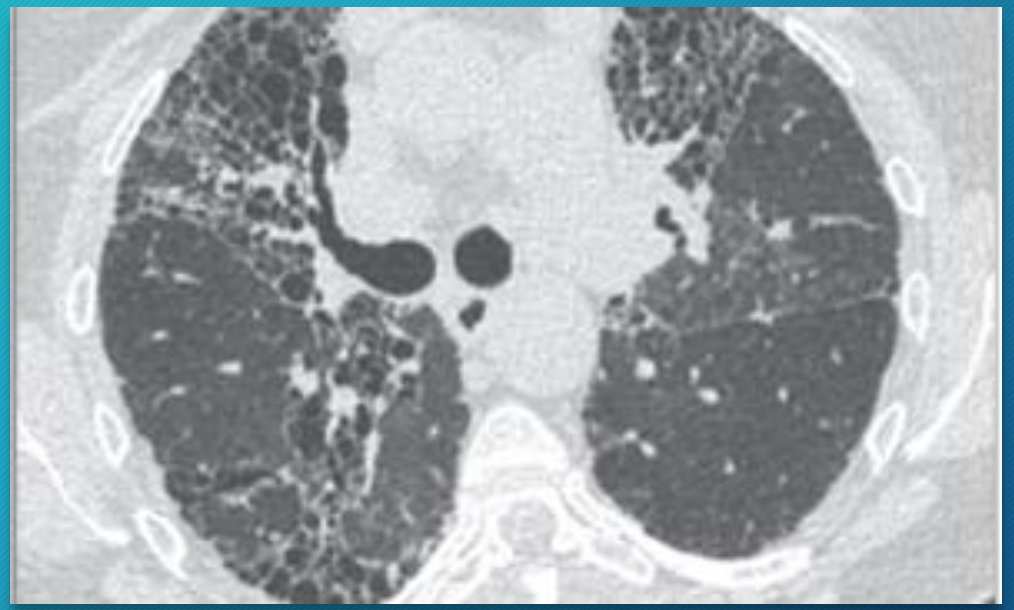
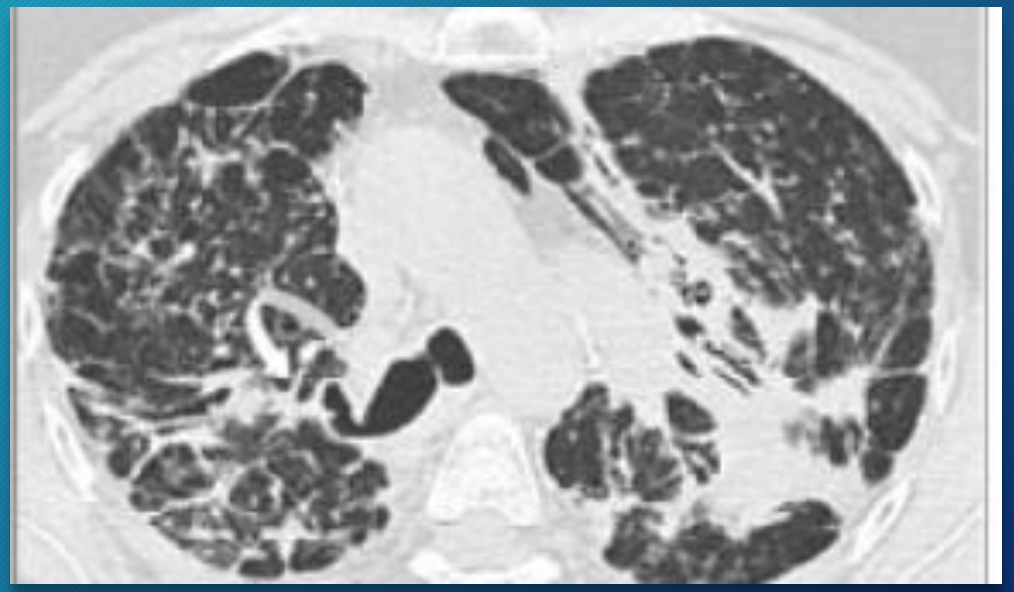


Image reproduced with permission from Nunes et al. Eur Respir J. 2012;40:750.

Sarcoidosis Radiology

- Patterns specific for Sarcoidosis.
- High-resolution chest CT scan demonstrating fibrotic conglomerate mass in the upper left lobe with traction bronchiectasis
- Honeycombing, predominantly in the upper and pre-hilar regions and along the bronchovascular bundles





Images reproduced with permission from Valeyre et al. Semin Respir Crit Care Med. 2014;35:336, and Nunes et al. Eur Respir J. 2012;40:750.

Screening of Asymptomatic Patients

- Screening in asymptomatic patients is not indicated for all organs.
- Probability of asymptomatic involvement may be low or detection of involvement may not be beneficial.

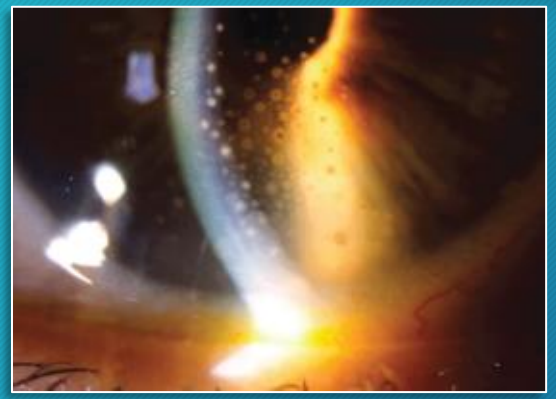
Organ	Screening Test(s)	Typical Results Suggesting Sarcoidosis
Liver	Serum liver function tests	Isolated elevation of alkaline phosphate Alkaline phosphates elevated greater than transaminase elevation
	Chest CT scan	Hepatomegaly Liver nodules
Spleen	Complete blood count	Diminished cell lines
	Peripheral smear	Howell-Jolly bodies
	Chest CT scan	Splenomegaly Splenic nodules
Kidney	Serum creatinine,[a] uric acid	Elevated creatinine,[b] elevated proteinuria, hypercalciuria
Bone marrow	Complete blood count	Diminished cell lines

Table adapted with permission from Judson MA.
Judson MA. *Respir Med*. 2016;113:42-49.

NCH Physician Group

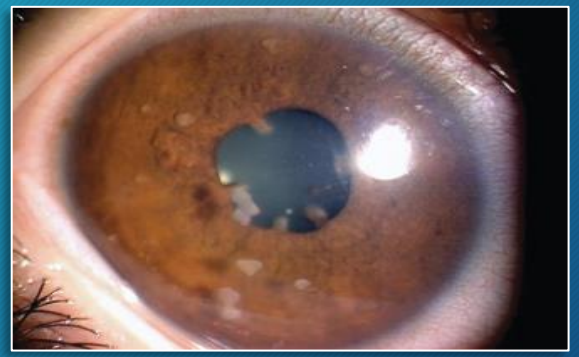
Screening for Ocular Sarcoidosis

- **Trabecular nodules**
- **Tent-like periph anterior synechia**
- **Retinal perivasculitis**
- **Granulomatous iritis**
- **Mutton fat keratic precipitates**
- **Iris nodules**
- **Snowball or string of pearls**
- **Retinochoroidal patchy exudates**
- The presence of any three of these is highly suggestive of sarcoidosis; the presence of any two is suggestive of sarcoidosis.



Keratic precipitates[2b]

Koeppe nodules[2b]



Busacca nodules[2b]

common manifestations of ocular sarcoidosis

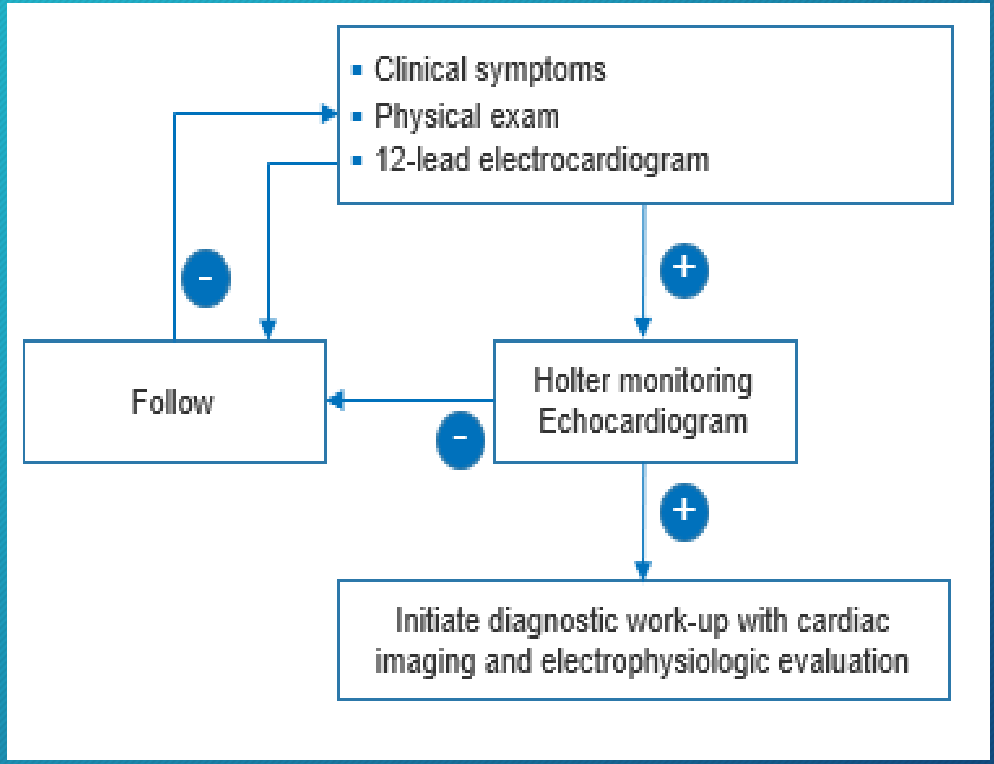
Images reproduced with permission from the publisher (Taylor & Francis Ltd): Herbort CP et al. Ocul Immunol Inflamm. 2009;17:160-169.

NCH Physician Group

Cardiac Sarcoidosis: Screening

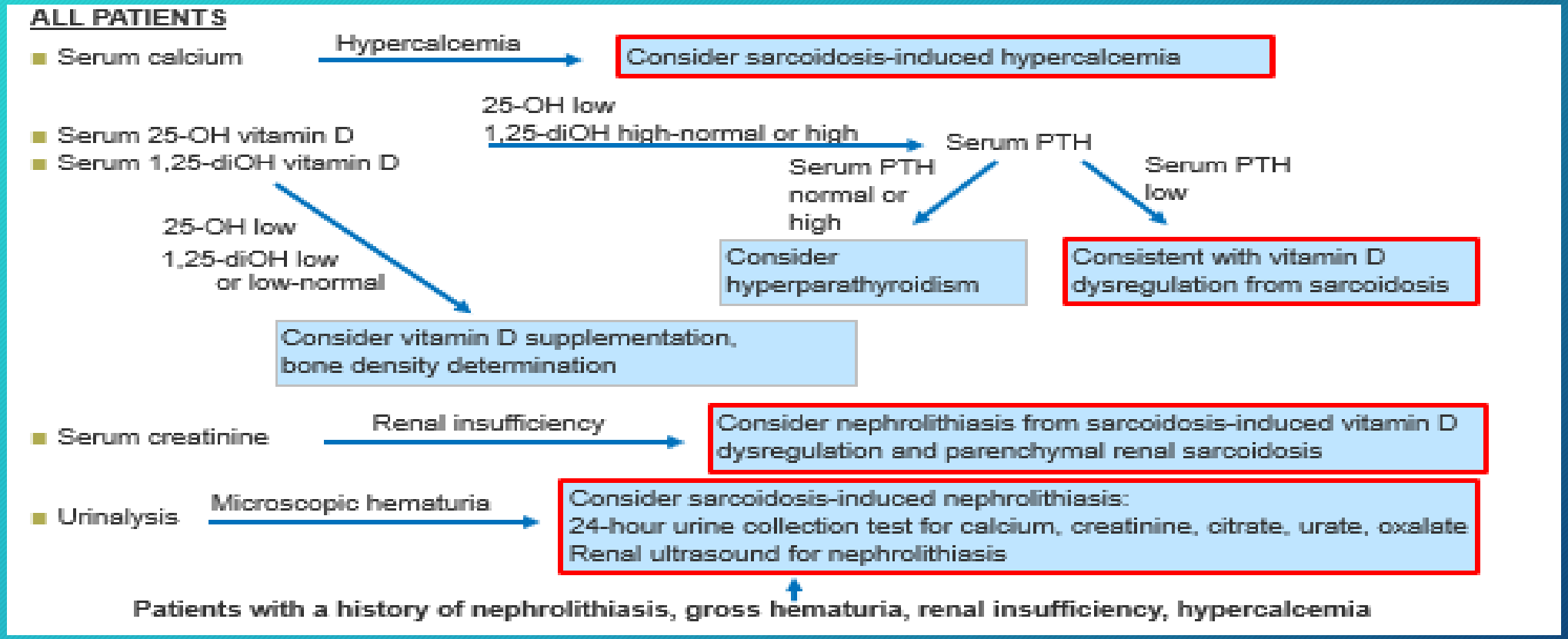
- Screen for cardiac involvement
- Cardiac sarcoidosis has a poorer prognosis
- Acute cardiac granulomatous inflammation can become life-threatening.[1]
- Determining the presence of cardiac symptoms is an important screening test.[1,2]

HRS review and a Modified Delphi Study[2]



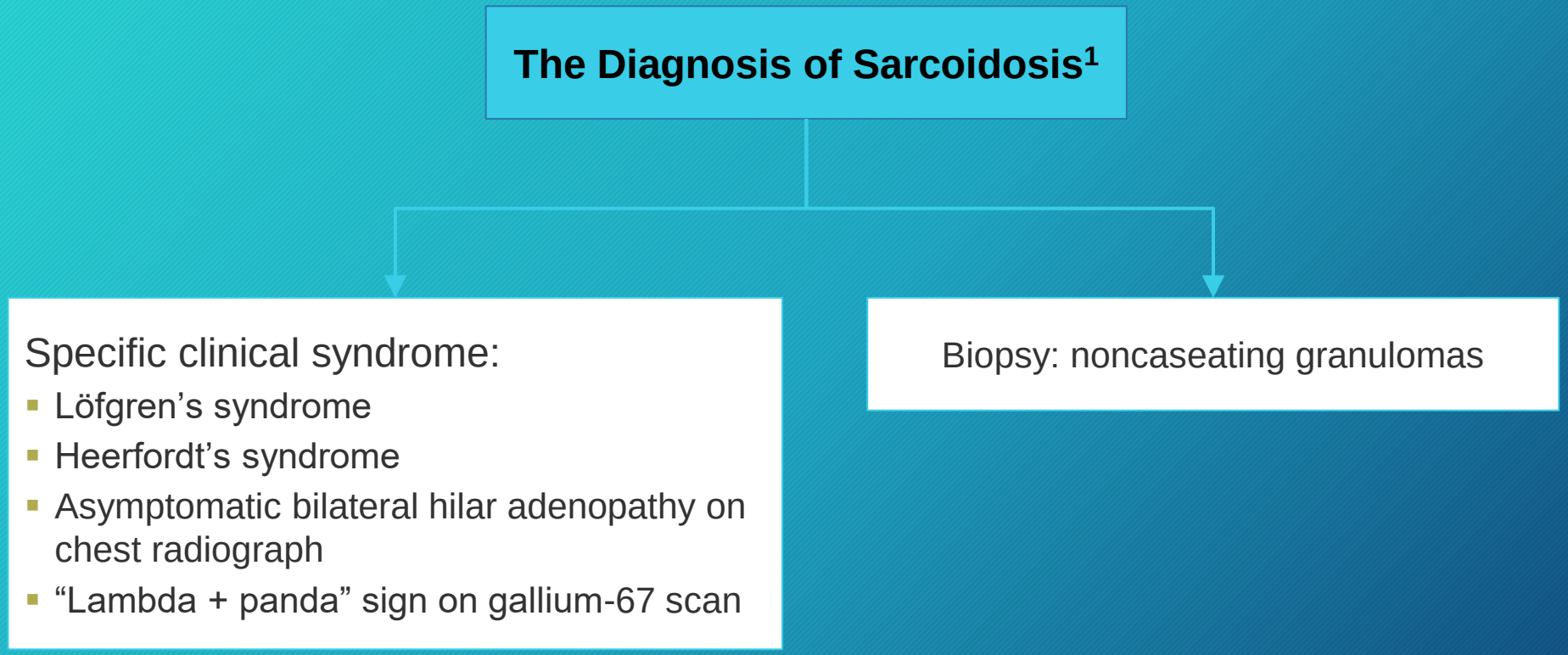
Birnie DH et al. Heart Rhythm. 2014;11:1305-1323. 2. Hamzeh N et al. Chest. 2012;141:154-162.

Sarcoidosis: Vitamin D Dysregulation



Judson MA. Respir Med. 2016;113:42-49.

Probable Diagnosis Made in Patients Who Present With Clinical Findings Specific for Sarcoidosis[1,2]

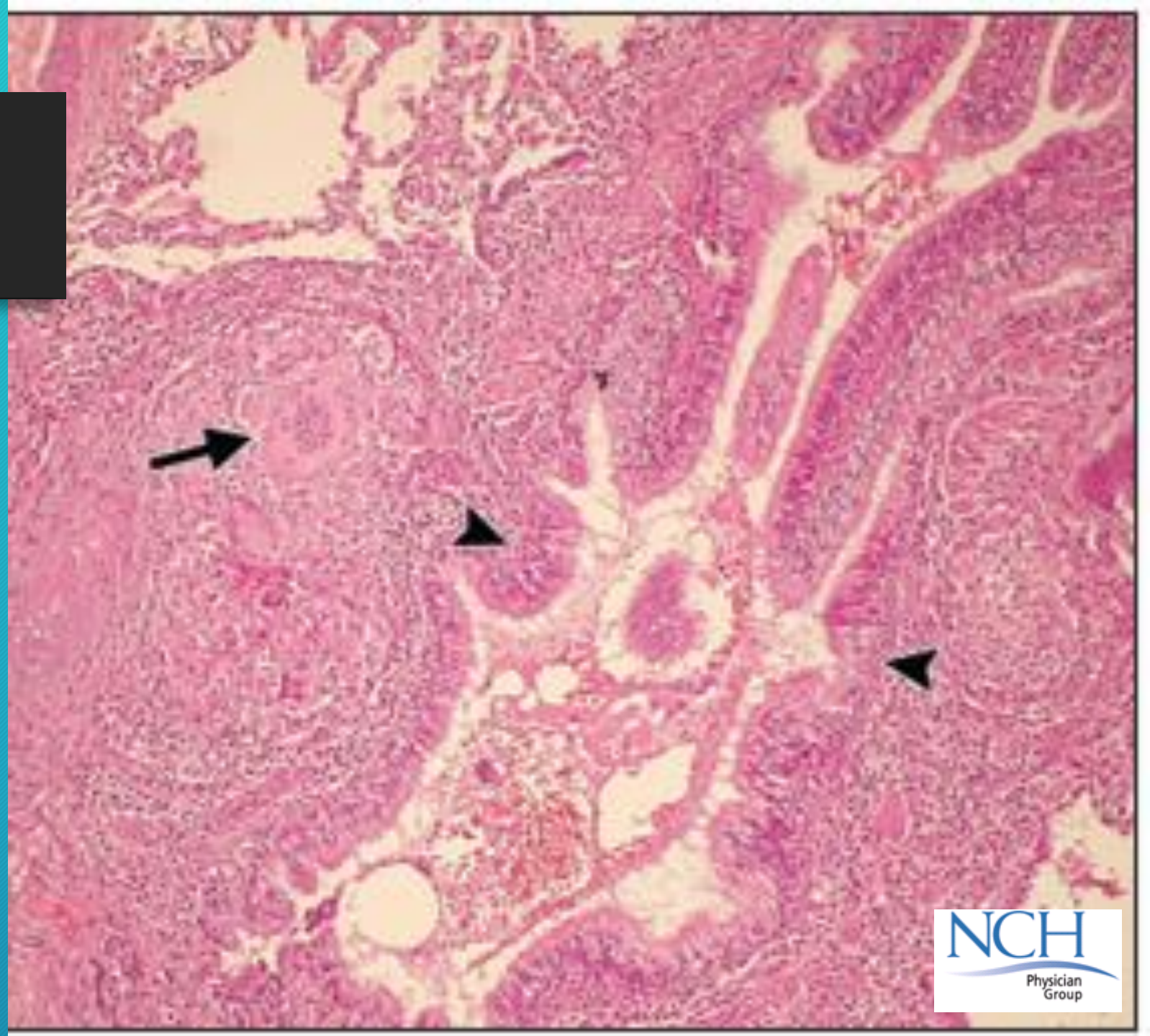


1. Judson MA. *F1000Prime Rep*. 2014;6:89; **2.** Birnie DH et al. *Heart Rhythm.* 2014;11:1305-1323.

NCH Physician Group

Sarcoidosis Biopsy

- Biopsy should be used to exclude alternate causes of granulomatous inflammation[1]
- Noncaseating epithelioid granulomas with tightly packed epithelioid cells, Langhans giant cells and lymphocytes (T cells), often adjacent to bronchioles and around and within vessel walls, pleura and connective tissue septa

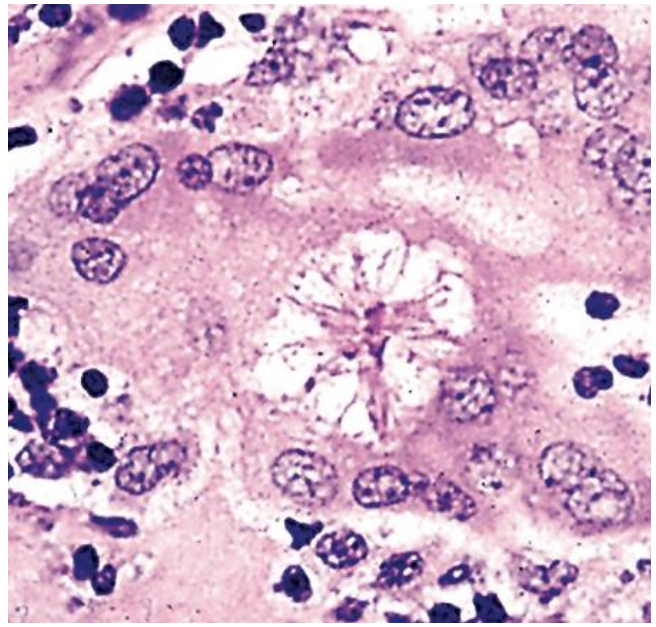


Images reproduced with permission from Criado E et al.

1. Judson MA. *F1000Prime Rep*. 2014;6:89. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586.

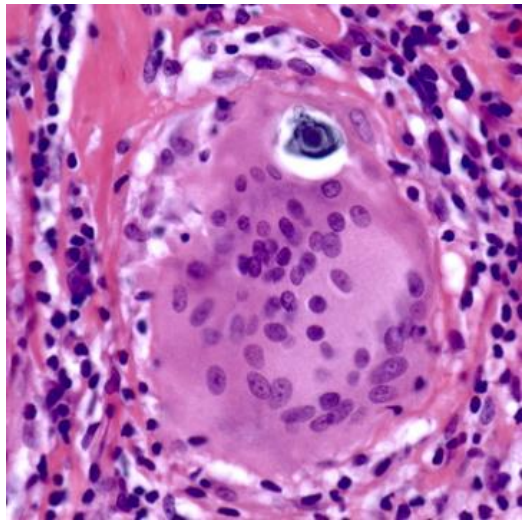
Sarcoidosis Biopsy

- **Schaumann bodies:** laminated concretions of calcium and protein with **multinucleated Langhans giant cells**
- **Asteroid bodies:** stellate inclusions within giant cells, in 60% of granulomas
- Neither is specific for sarcoid (also seen in berylliosis)
- Other Forms also exhist : necrotizing sarcoid granulomatosis

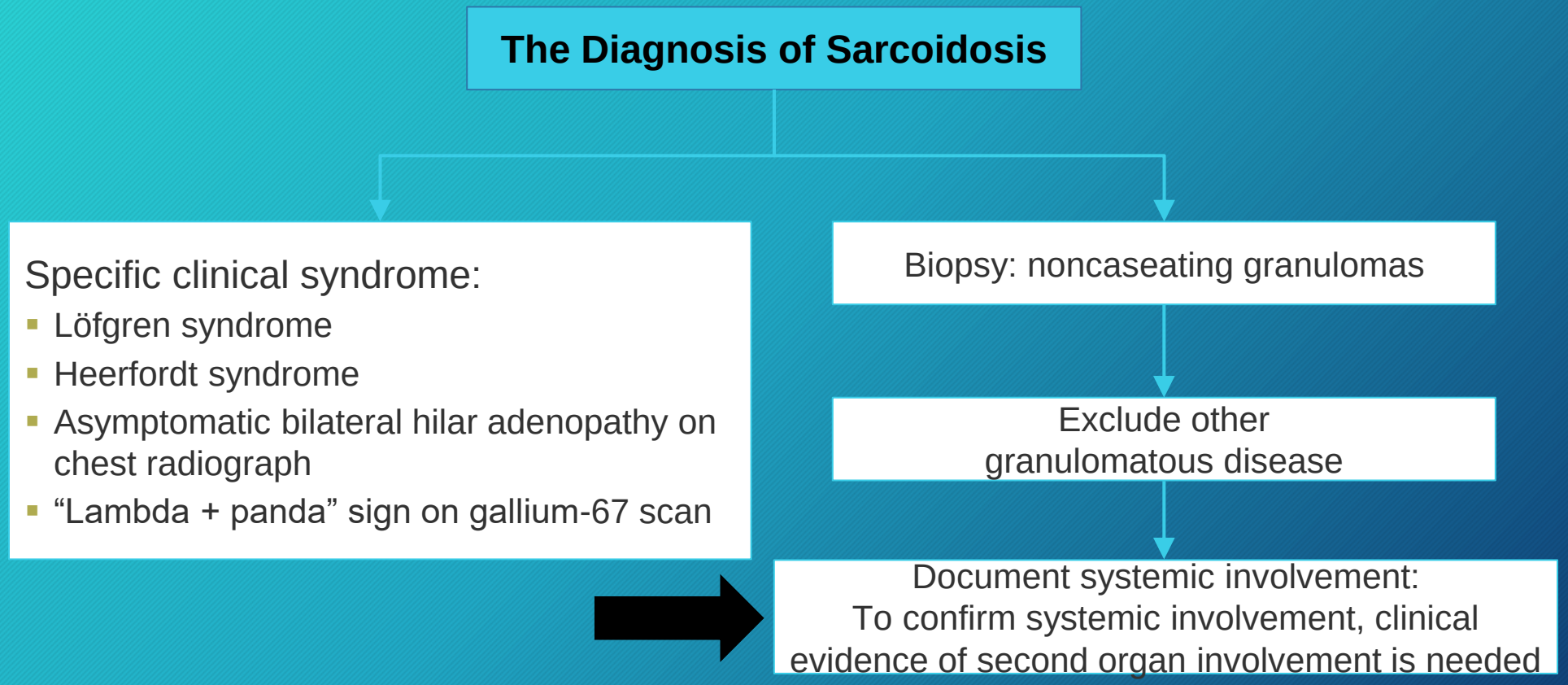


Asteroid bodies

Schaumann bodies



Granulomatous Inflammation, Is Insufficient to Establish a Diagnosis of Systemic Sarcoidosis



Judson MA. *F1000Prime Rep*. 2014;6:89.

Serologic Biomarkers: Development of Granulomas or Fibrosis

Clinical Utility of Various Serum Biomarkers of Sarcoidosis

Biomarker	Activity of Biomarker	Diagnostic Utility	Prognostic Utility	Disease Activity Monitoring Utility
SACE	Granuloma burden	+[a]	-	++
sIL-2R	CD4+ T-helper cell activation	-	+	++
Chitotriosidase	Activated macrophages and neutrophils	-	-	++
Chemokines (CXCL9, 10, 11)	Presence of CD4+ T helper Th1 cells	-	+	+
Lysozyme	Activated macrophages and epithelioid cells	-	-	+
KL-6	Lymphocytic alveolitis	-	+	+
Vitamin D dysregulation[b]	Activated macrophages	-	-	+
SAA	Activated macrophages	+[c]	-	+

+ = positive; - = negative; CXCL = (C-X-C motif) ligand; KL-6 = Krebs von del Lungen-6; OH = hydroxide; PTH = parathyroid hormone; SACE = serum angiotensin converting enzyme; sIL-2R = soluble interleukin-2 receptor; SAA = serum amyloid A; ULN = upper limit of normal.

NCH Physician Group

Biomarkers & Imaging

Biomarkers

- Clinical data and biomarkers role in management.
- No gold-standard
- Unidimensional biomarkers probably do not represent true extent of the disease.
- There is often a poor correlation between the objective measures of sarcoidosis disease activity, disease severity and the patient's QOL.

Imaging

- Provides detail on specific organ involvement
- Radiography and CT can detect granuloma conglomerations.
- ^{18}F-FDG-PET can indicate tissues with active sarcoidosis and is particularly useful for pulmonary and cardiac sarcoidosis.
- MRI is useful for cardiac sarcoidosis and neurosarcoidosis

Chopra A et al. Expert Rev Clin Immunol. 2016;12(11):1191-1208.

Major Clinical Factors for Pulmonary Sarcoidosis[1,2]

Factor	Finding	Diagnostic Utility	Prognostic Outcome[a]	Disease Activity Monitoring[a]
CXR	Scadding stage 1		Good	
	Scadding stage 1, no symptoms	✓[b]		
	Scadding stage 4		Poor	
HRCT	Perilymphatic nodules	✓[b]		✓[b]
	Galaxy sign	✓[b]		✓[b]
^{18}F-FDG-PET	FDG uptake		Poor	✓[c]
FVC	< 1.5 L		Poor	
DLCO	< 80% predicted	✓[d]		
BAL	Lymphocytosis			✓[c]
	CD4:CD8 > 3.0	✓[b]		✓[c]
	TNF-α elevated		Poor	

[a]Assumes the diagnosis of sarcoidosis has been established. [b] Specific (true negative rate).
[c] Sensitive (true positive rate).[d] Sensitive for pulmonary hypertension.

1. Chopra A et al. *Expert Rev Clin Immunol*. 2016;12(11):1191-1208
2. Mostard RLM et al. *Curr Opin Pulm Med.* 2013;19(5):538-544.

Advanced Pulmonary Sarcoidosis May Encompass Several Features

Physiologic impairments

- Pulmonary hypertension
- Bronchiectasis
- Airways stenosis
- Mycetoma

Radiographic abnormalities

Predominant fibrotic pattern on chest radiography

(Scadding stage 4)

Histopathologic features

"Fibrotic granulomatous" histopathologic pattern

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Fibrosis Is Observed in Some Patients With Advanced Sarcoidosis

Chronic granulomatous inflammation

Fibrosis of sarcoidosis

- ~5% to 10% fibrotic lung
- Same distribution (mid to upper lobes)
- Some granulomas hyalinize with time leading to scarred granulomas

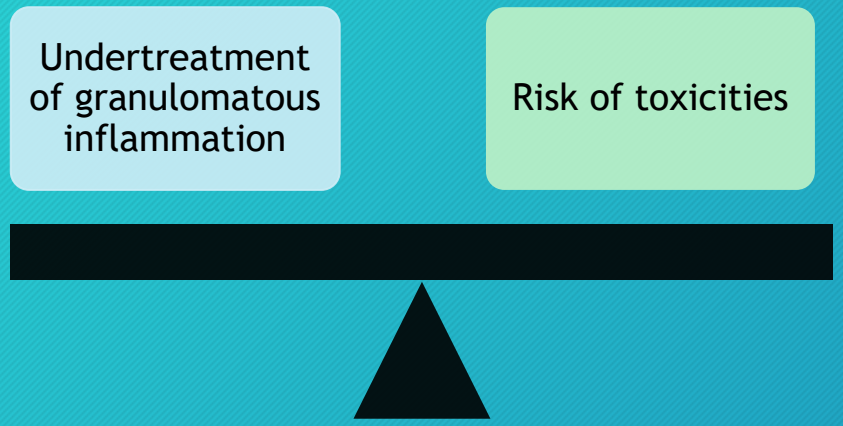
- **Fibrocystic cavities**
- **Architectural distortion of the airways**

Most will stabilize without the need for indefinite medical therapy

A minority will develop respiratory failure due to complications or infections

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Treatment Balance Risk of Undertreatment With Risk of Toxicity



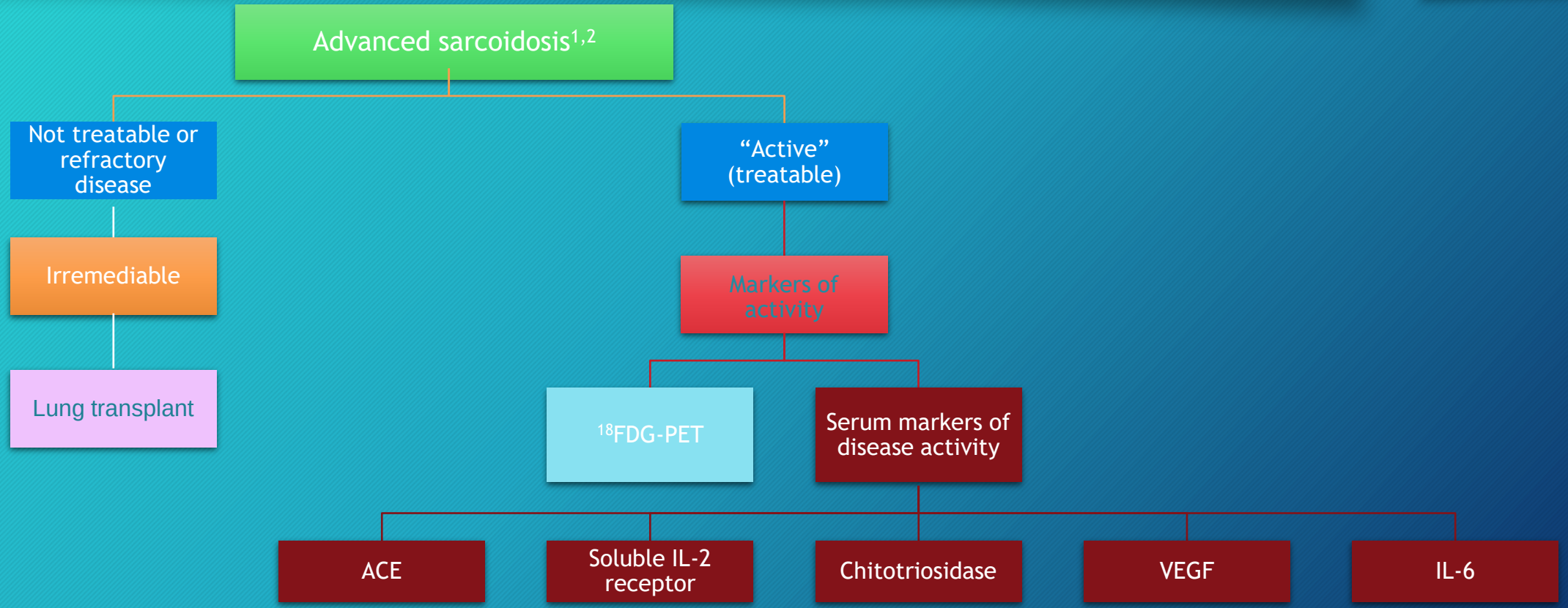
Goal of therapy

- Reduce the burden of granulomatous inflammation with an intention to modify symptoms and decrease functional impairment

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Treatment

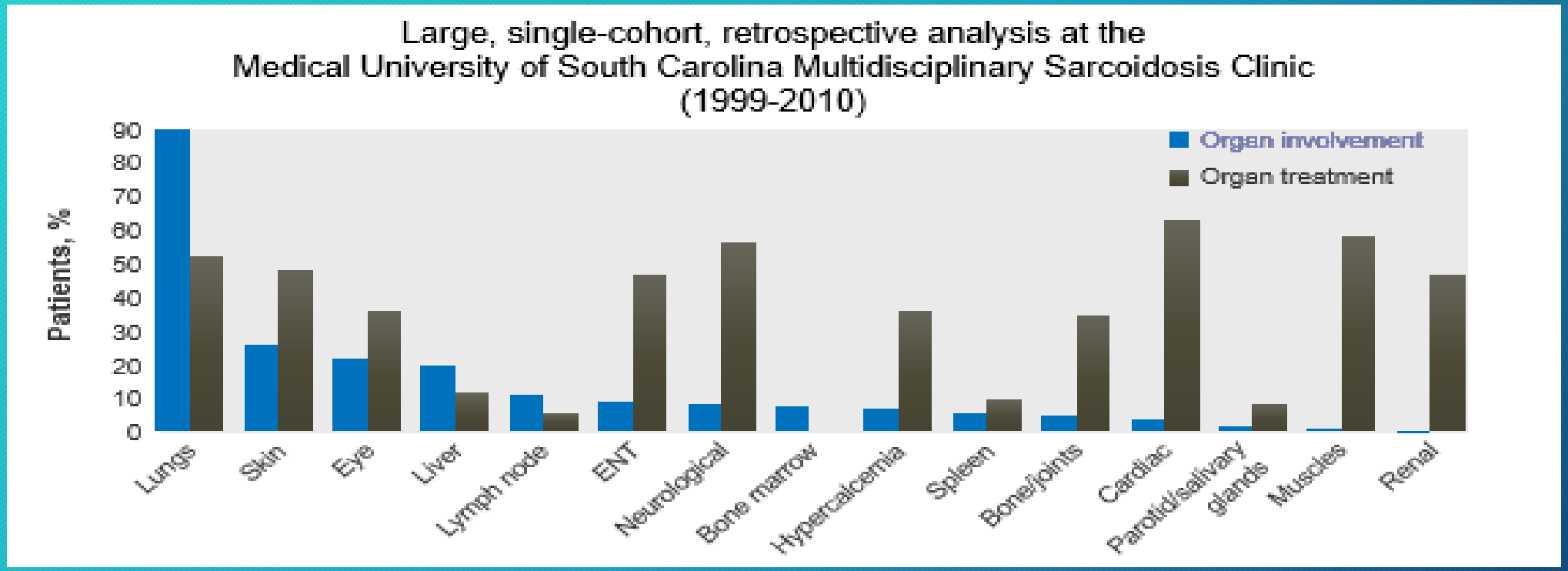
Advanced Sarcoidosis Might Not Equate With Irremediable Disease, Could Potentially Be Treated



ACE = angiotensin converting enzyme; FDG-PET = ^{18} fluorodeoxyglucose positron emission tomography; IL = interleukin; VEGF = vascular endothelial growth factor.

1. Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110. **2.** Aryal S, Nathan SD. *Ther Adv Respir Dis*. 2019.13:1-15.

Multi-specialty Disease



Judson MA et al. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29:119-227

Clinical Manifestations Associated With a Worse Prognosis

Pulmonary[1]

Stage III-IV chest radiograph

Pulmonary hypertension

Significant lung function impairment

Moderate to severe dyspnea on presentation

BAL neutrophilia at presentation

Extrapulmonary[1,2]

Cardiac

Neurologic (except isolated CN palsy)

Lupus pernio

Splenomegaly

Hypercalcemia

Osseous disease

Other[1,2]

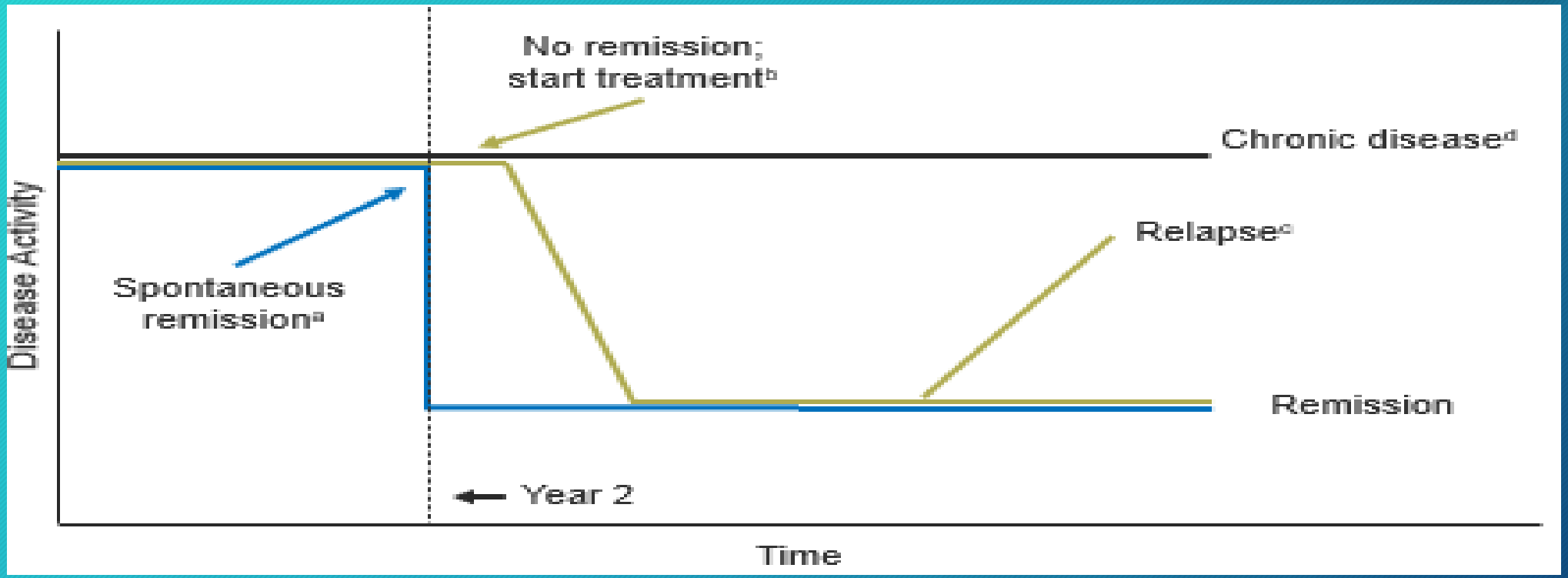
Age > 40 years at onset

African American

Requirement for steroids within 6 months of presentation

1. Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518.
2. **2.** American Thoracic Society. *Am J Respir Crit Care Med*. 1999;160:736-755

Natural History Sarcoidosis

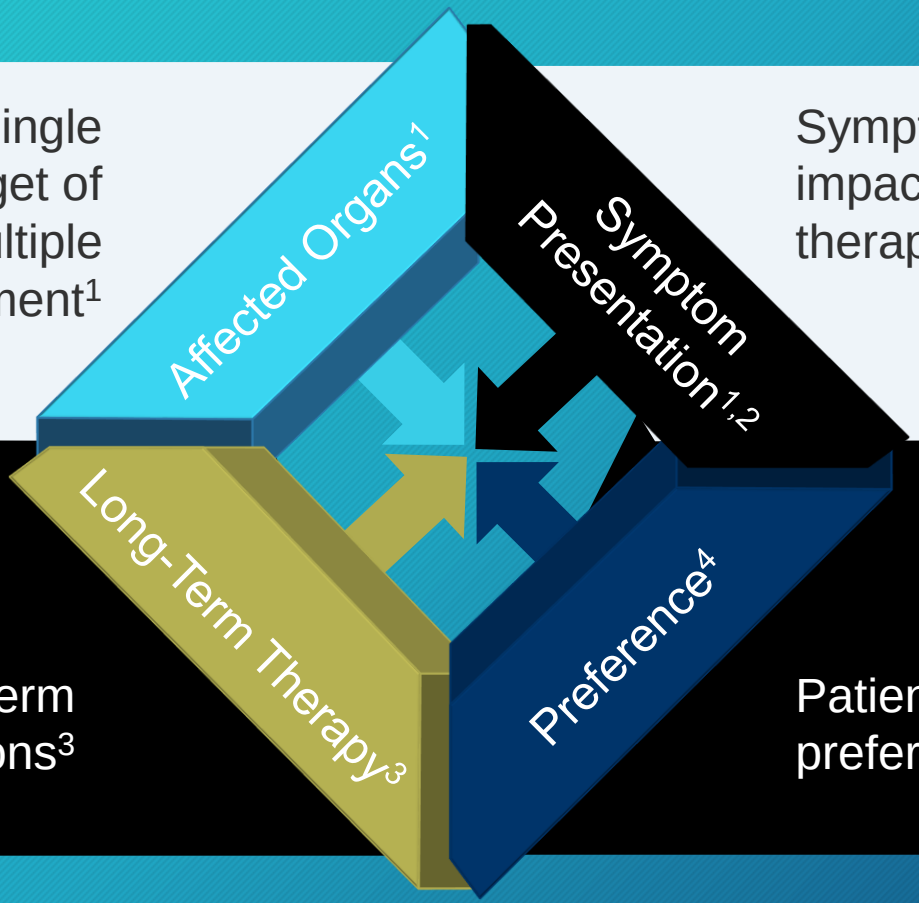


1. Lazar CA, Culver DA. Semin Respir Crit Care Med. 2010;31:501-518. 2. Culver DA et al. Cleve Clin J Med. 2004;71:88-106

Choice of Therapy

The most significant single organ is often the target of therapy, even if multiple organs require treatment[1]

Symptom presentation impacts decision to treat and therapies used[1,2]



Consider long-term toxicities of medications[3]

Patient and physician preference[4]

1. Baughman R et al. *Semin Respir Crit Care Med*. 2014;35:391-406. **2.** Pulmonary, Critical Care, Sleep Update. Sarcoidosis New Concepts in Cause and Treatment. http://www.chestnet.org/Education/eLearning/e-Learning/Sarcoidosis-New-Concepts-in-Cause-and-Treatment Accessed July 10, 2020. **3.** Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **4.** Baughman RP, Lower EE. *Eur Respir Mon*. 2005;32:301-315.

Immunosuppressants Used to Treat Sarcoidosis

Classification of Immunosuppressants

- Immunosuppressants are agents that suppress the immune system and are used for the control of pathological immune response in autoimmune disease.[1]

Mechanism of Action[1]	Biological Effect[1]	Example[1]	Used in Sarcoidosis[2]
Inhibitors of lymphocyte gene expression	Reduce inflammatory response	Glucocorticoids	✓
Inhibitors of lymphocyte signaling	Prevent immune cell activation and proliferation	• Calcineurin inhibitors • mTOR inhibitors	
Cytotoxic agents	Reduce lymphocyte proliferation	• Antimetabolites • Alkylating agents	✓
Cytokine inhibitors	Inhibit proinflammatory or lymphocyte-stimulating cytokines	• TNF-α inhibitors	✓
Anti-immune cell molecule antibodies	Inhibit specific immune cell molecules	Monoclonal or polyclonal antibodies	

1. Reprinted from Patil US et al. *Int J Pharm Pharm Sci*. 2012;4(Suppl 1):30-36. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **2.** Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020.

When Immunosuppressive Therapy Be Initiated?

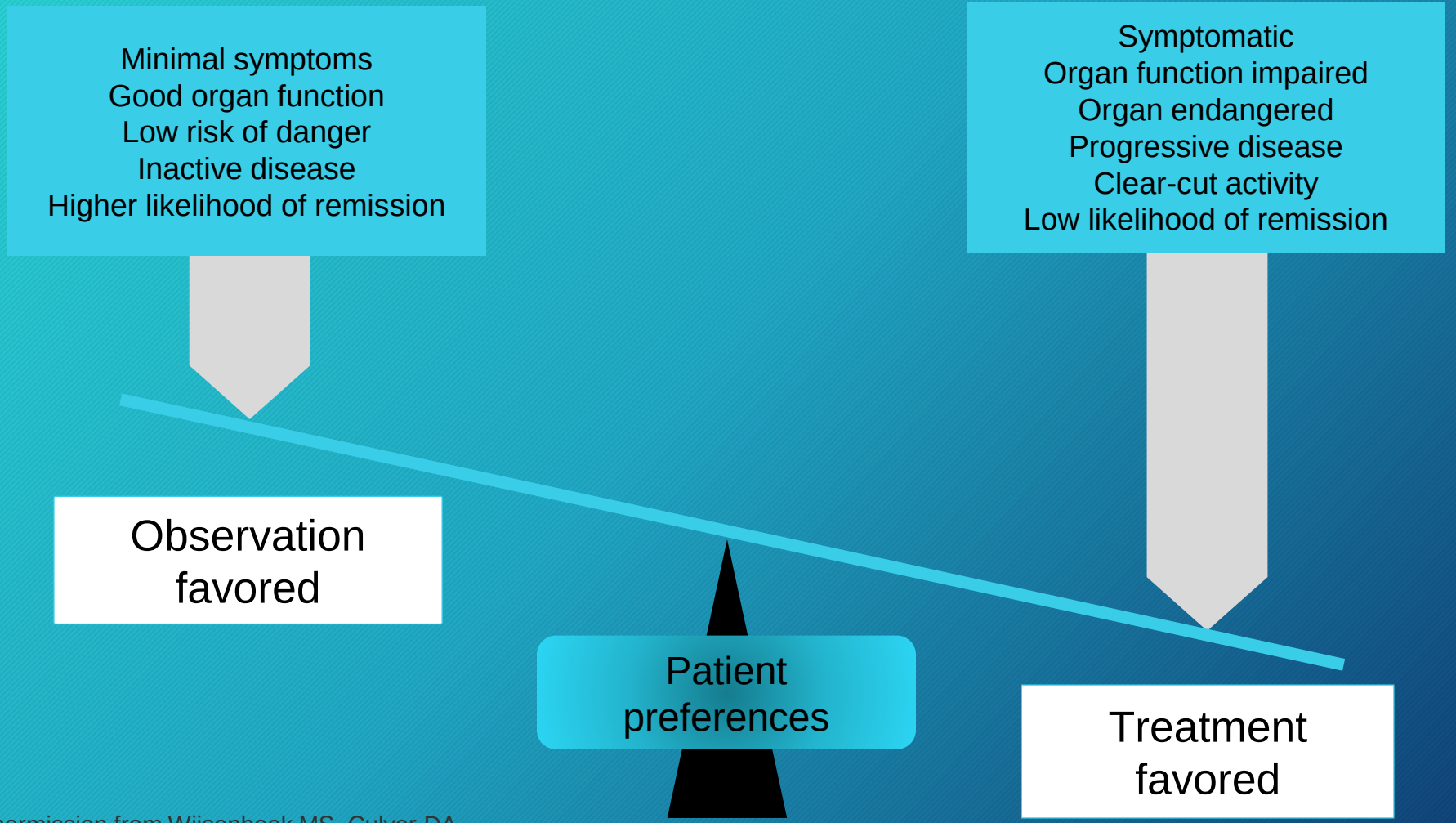


Figure reproduced with permission from Wijsenbeek MS, Culver DA.
Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767 *Clin Chest Med.* 2015;36:751-767.

Symptomatic Sarcoidosis: Strength of Recommendation and Level of Evidence

Therapy[1-3]	Grade of Recommendation[a,b]
Biologics	1A, 1B
Corticosteroids	1A
Corticotropin	1C
Cytotoxics	1A, 1B, 1C

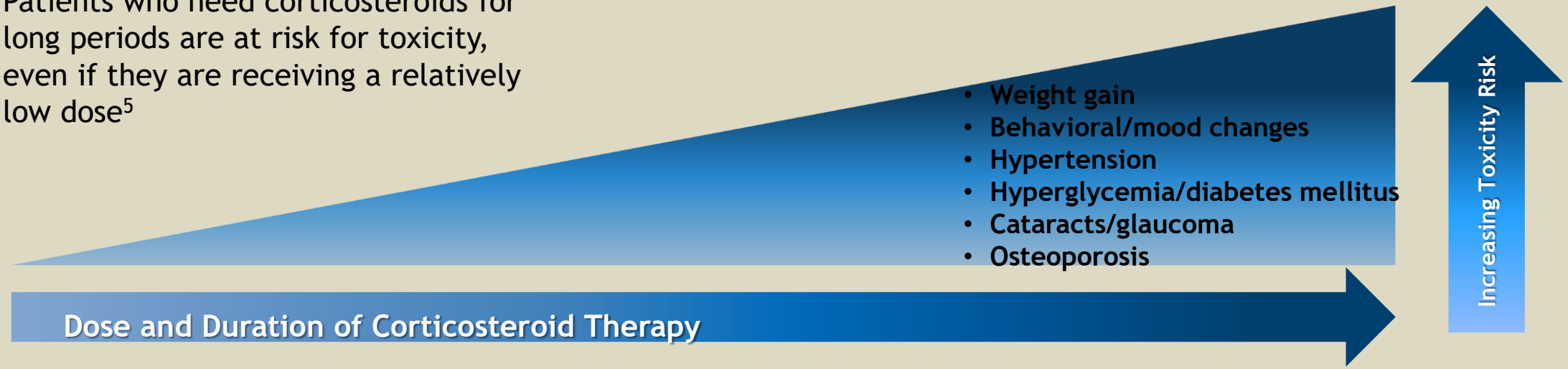
[b] Level of evidence: A, high-quality evidence; B, moderate-quality evidence; C, low-quality evidence.

1. Zhou Y et al. *Expert Rev Respir Med.* 2016;10:577-591. **2.** Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020. **3.** Guyatt G et al. *Chest*. 2006;129:174.

Goal of Sarcoidosis Treatment: Reduce Corticosteroids Toxicity

- Corticosteroids are FDA approved for the treatment of patients with symptomatic sarcoidosis.[1-3]
- Corticosteroids are recommended as first-line treatment in the clinical guidelines.[1]
- As with most sarcoidosis therapies, optimal dose and duration of treatment remain unclear.[4]

Patients who need corticosteroids for long periods are at risk for toxicity, even if they are receiving a relatively low dose[5]



1. Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020. **2.** Rayos prescribing information, Horizon Pharma USA, Inc. **3.** Orapred ODT prescribing information, Alliant Pharmaceuticals, Inc. **4.** Judson MA. *Chest*. 1999;115:1158-1165. **5.** Beegle et al. *Drug Des Devel Ther*. 2013;7:325.

Steroids vs Steroid-Sparing Drugs?

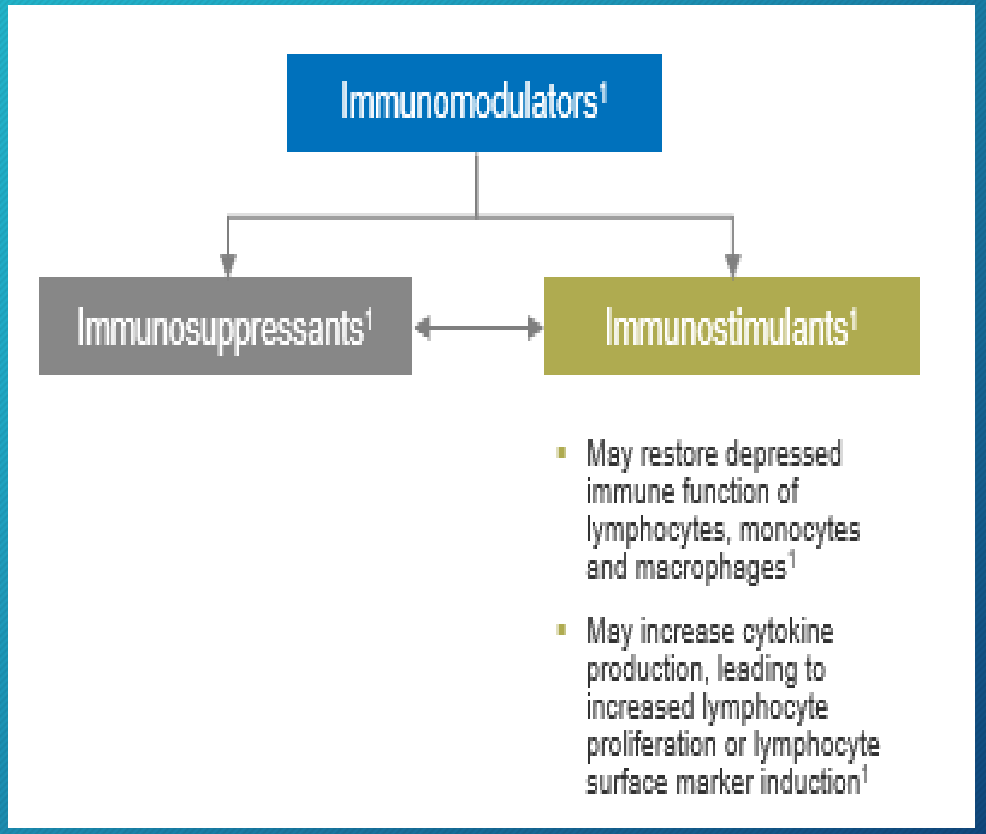
Steroid-sparing agents should be considered for patients who require long-term therapy, have persistent disease or are intolerant to corticosteroids[1,2]

Image reproduced with permission from Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767.

1. Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **2.** Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767.

Immunomodulators : Novel Approach to the Treatment of Sarcoidosis[1]

- Immunomodulators : goal is to optimize the immune system.[1]
- Focusing on a single aspect of the immunopathogenesis of sarcoidosis instead of the broad picture could lead to the oversimplification of the immunological process and divert efforts away from other mechanisms.[2]

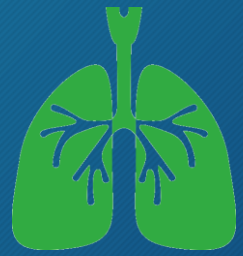


1. Reprinted from Patil US et al. Int J Pharm Pharm Sci. 2012;4(Suppl 1):30-36. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). 2. Loke WS et al. Int J Chronic Dis. 2013;2013:928601.

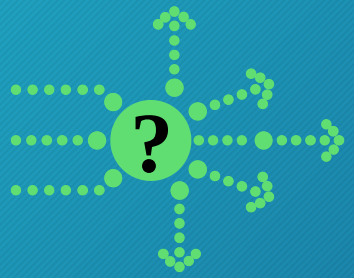
Sarcoidosis: Unmet Clinical Needs

Definitive diagnostic criteria[1]

Clear indicators for treatment and optimal approach[1]



Identification of patients with advanced disease[2]



Elucidation of natural course of the disease[1]

Clinical data on steroid-sparing therapies[1]

Differentiation of advanced disease from irreversible disease[2]

Rep. 2014;6:89. **2.** Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110. **1.** Judson MA. *F1000Prime*

THANK YOU !

David H. Lindner, D.O. MBA, FACOI, FCCP
Subdivision Head Pulmonary Critical Care & Sleep Medicine
Instructor Mayo Clinic School of Medicine and Science
Associate Professor of Medicine University of Central Florida
Adjunct Associate Professor of Medicine NOVA Southeastern
Medical Director of COVID19 NCH & NCH Healthcare Intensive Care Units and Respiratory Care
Pulmonary Program Director NCH Healthcare System Internal Medicine Residency