4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

ΠΡΟΓΡΑΜΜΑ 10ου ΚΥΚΛΟΥ

Σάββατο 8 Απριλίου 2023

ΣΥΣΤΗΜΑΤΙΚΕΣ ΡΕΥΜΑΤΙΚΕΣ ΠΑΘΗΣΕΙΣ V ΚΑΙ ΑΛΛΕΣ ΠΑΘΗΣΕΙΣ

ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ΝΟΣΗΜΑΤΩΝ ΘΩΡΑΚΟΣ ΑΘΗΝΩΝ
Η ΣΩΤΗΡΙΑ

Σαρκοείδωση

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ΓΝΘΑ "Η ΣΩΤΗΡΙΑ"

American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Statement on Sarcoidosis

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), THE EUROPEAN RESPIRATORY SOCIETY (ERS) AND THE WORLD ASSOCIATION OF SARCOIDOSIS AND OTHER GRANULOMATOUS DISORDERS (WASOG) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS AND BY THE ERS EXECUTIVE COMMITTEE, FEBRUARY 1999

Sarcoidosis is a multisystem granulomatous disorder of unknown cause(s)

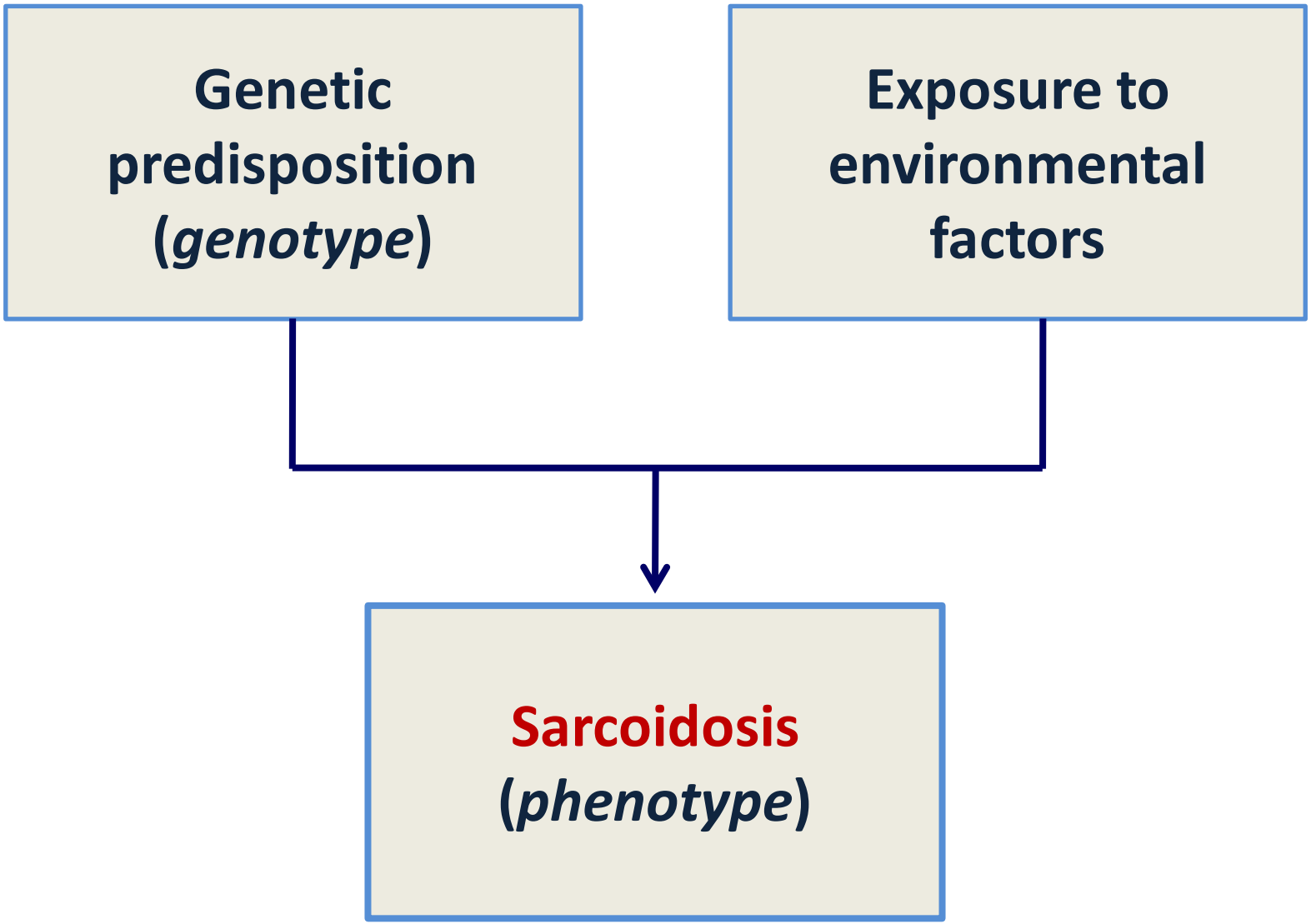
- young and middle-aged adults
- increased risk for the disease among family members
- genetically complex disease - many genes contributing
- the strongest genetic associations within human leukocyte antigen (HLA) - region on chromosome 6

Disease progression → death due to progressive ILD, PH or to cardiac or CNS involvement

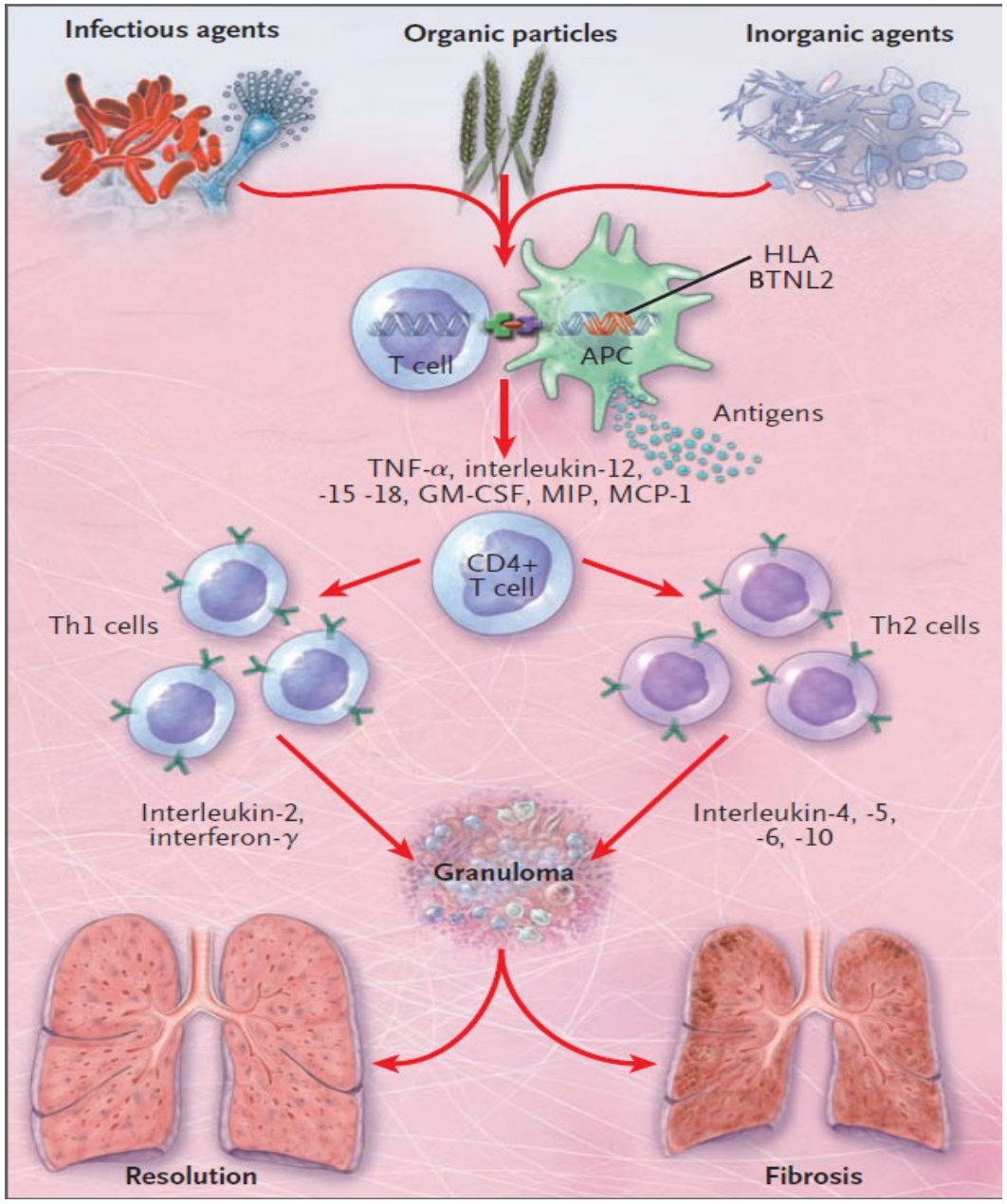
Lung	90%	Lymph nodes	75-90%
Liver	60-90%	Spleen	50-60%
Skin lesions	25%	Heart	5%
Ocular lesions	25%	Nervous system	5%
Joints	25-50%	Bone marrow	15-40%
Bones	5%	Parotid gland	10%

AJRCCM 1999

Aetiology


Genetic predisposition (*genotype*)
Exposure to environmental factors
Sarcoidosis (*phenotype*)

Immunopathogenesis



The interaction between antigen-presenting cells (APCs) expressing HLA class II molecules and CD4+ T lymphocytes is considered pivotal for the inflammatory process that eventually leads to granuloma formation

Iannuzzi M, *et al. NEJM 2007*

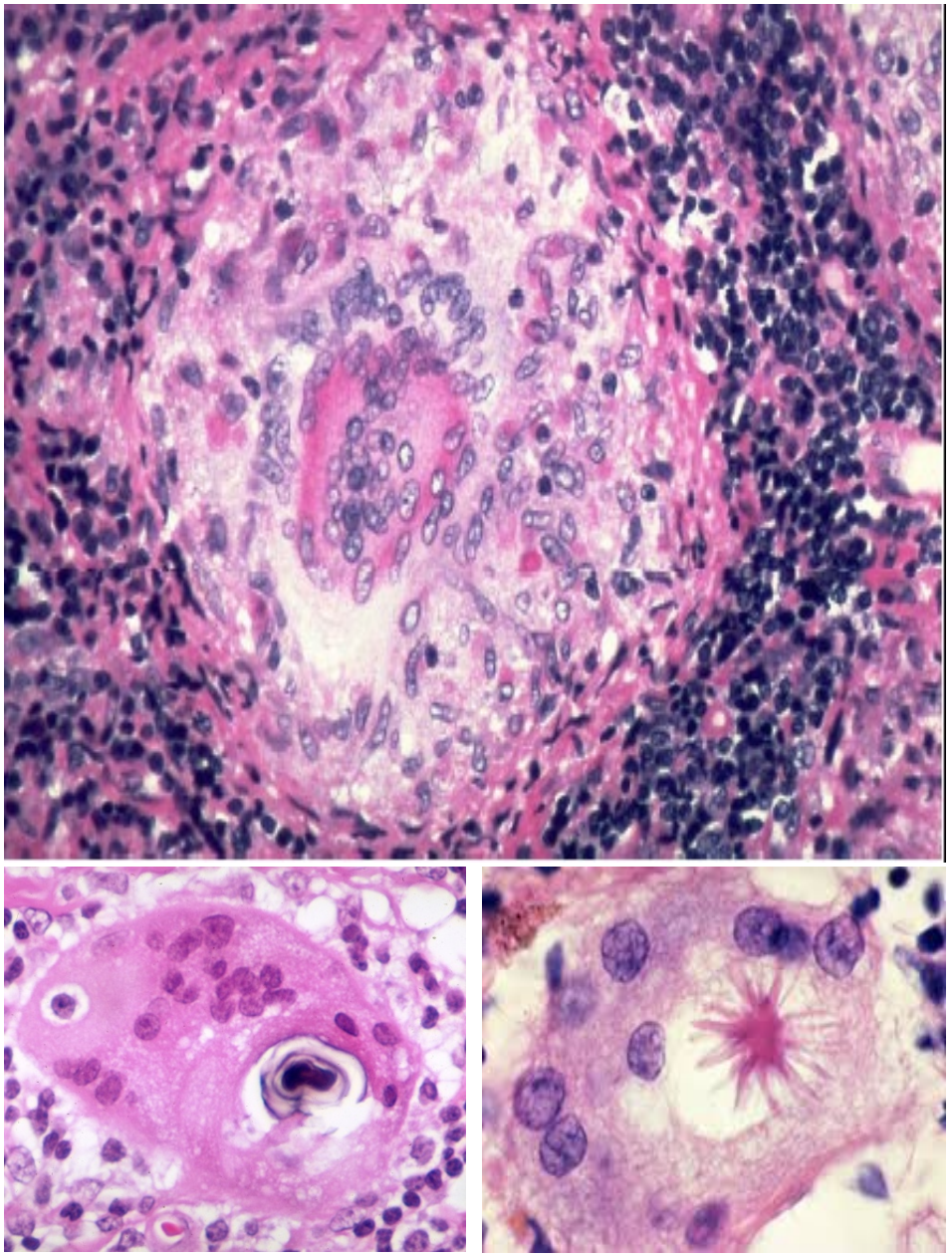
Sarcoidosis Granuloma

The sarcoid granuloma usually consists of a compact (organized) collection of mononuclear phagocytes **(macrophages and epithelioid cells)**

There is no necrosis within the sarcoid granuloma; on occasion, there is a small to moderate amount of necrosis

Giant cells fuse within the sarcoid granuloma to form **multinucleated giant cells**. These granulomas are **typically surrounded by lymphocytes in the periphery**

A variety of inclusions may be present within the sarcoid granuloma (e.g. asteroid bodies, Schaumann's bodies, birefringent crystals, and Hamazaki–Wesenberg bodies; these inclusions are **not specific or diagnostic of sarcoidosis.**



AJRCCM 1999

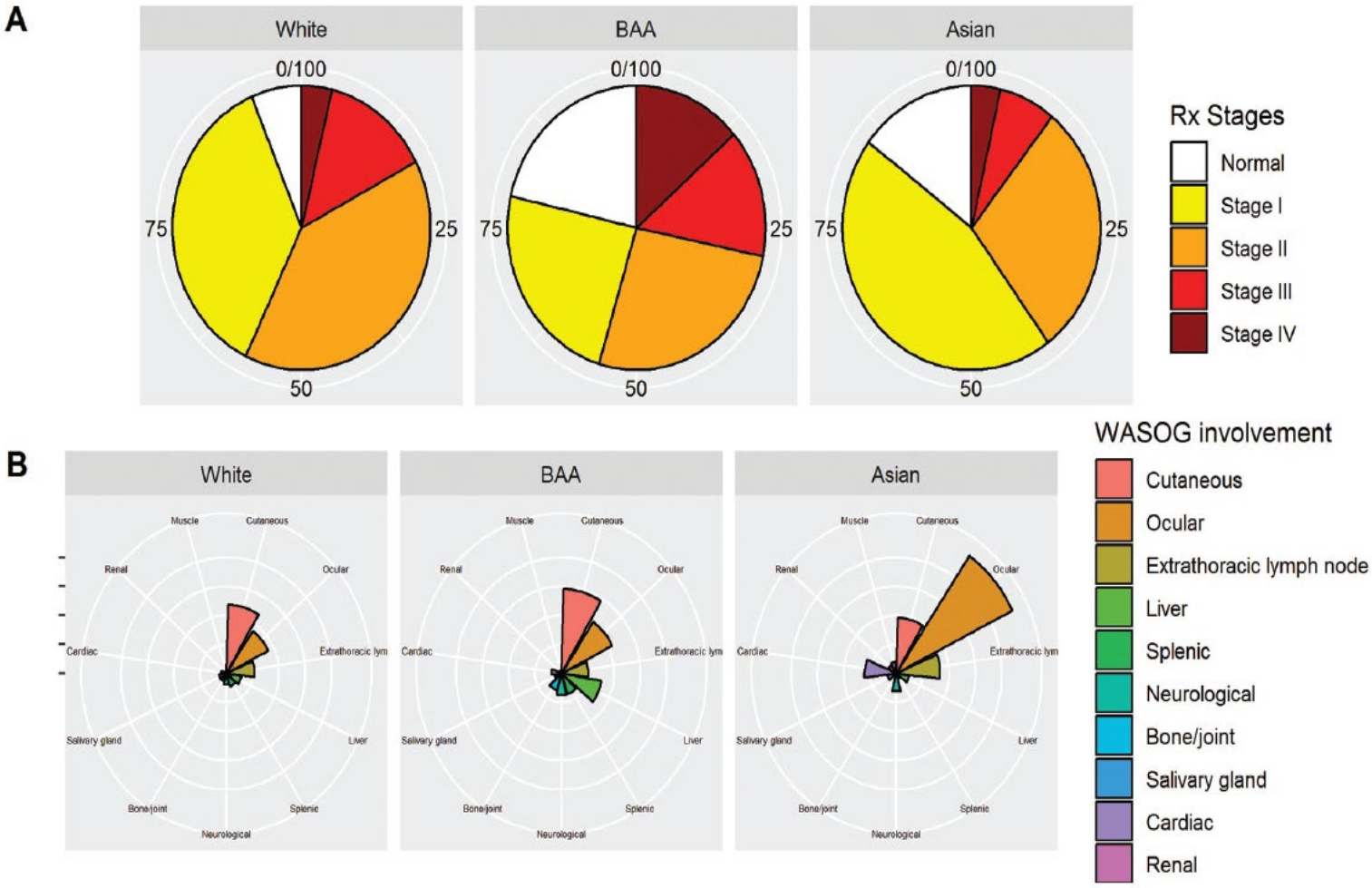
Epidemiology

Ethnic Group	Incidence per 100,000	Peak Decade of Incidence	Percent Increased Risk in Females
European Americans	3–10	4th–5th	10–20
African Americans	35–80	3rd–4th	30
Northern Europeans	15–20	3rd	30
Southern Europeans	1–5	4th–5th	33
Japanese	1–2	3rd	10–20
Greece	1,07		

Rybicki A, *et al. Semin Respir Crit Care Med 2007*
Karakatsani A, *et al. Respir Med 2007*

Epidemiology

Radiological patterns and extrathoracic WASOG organ-by-organ involvements in the three ethnic groups most frequently reported in sarcoidosis



Brito-Zeron P. *Clin Exp Rheumatol 2019*

Clinical Aspects

- **Presentation depends on the extent and severity of the organ/s involved**
- **Approximately 5% of cases are asymptomatic and incidentally detected by CXR**
- **Systemic symptoms occur in 45% of cases:**
  - Fever
  - Fatigue
  - Weight loss
  - Anorexia
  - Night sweats
- **Dyspnea on exertion, cough, chest pain occur in 50% of cases.**

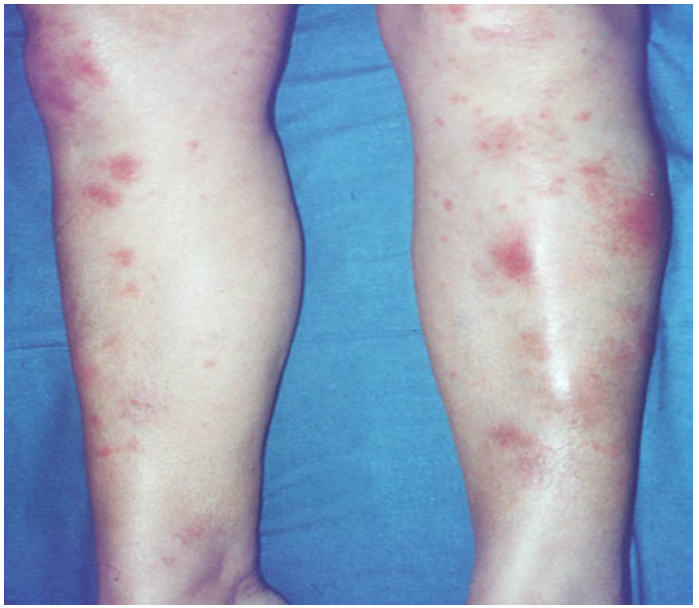
AJRCCM 1999

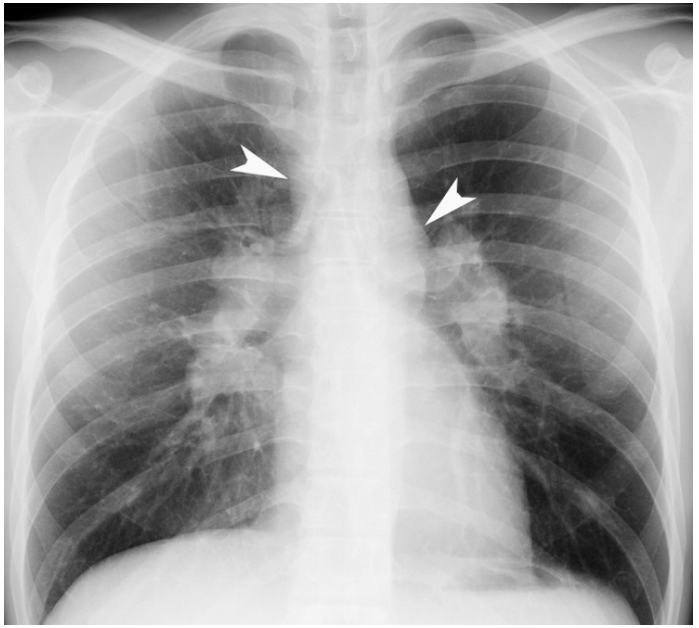
Löfgren's syndrome

An **acute presentation** consisting of:

- Fever
- Arthralgia
- Erythema nodosum
- Bilateral hilar adenopathy (BHL)

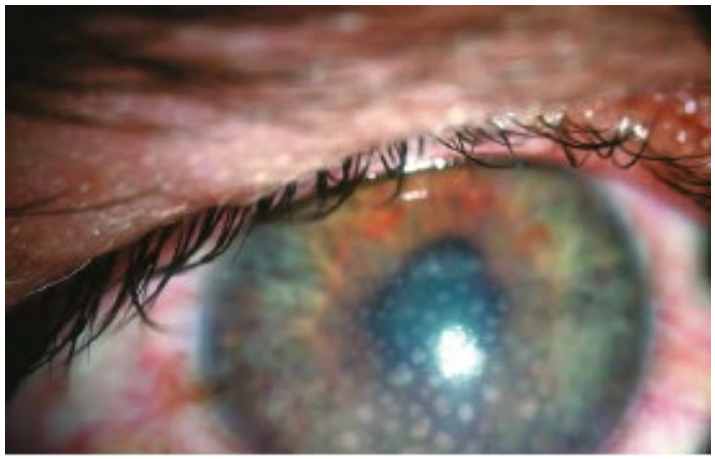
- Occurs in 9 to 34% of patients.

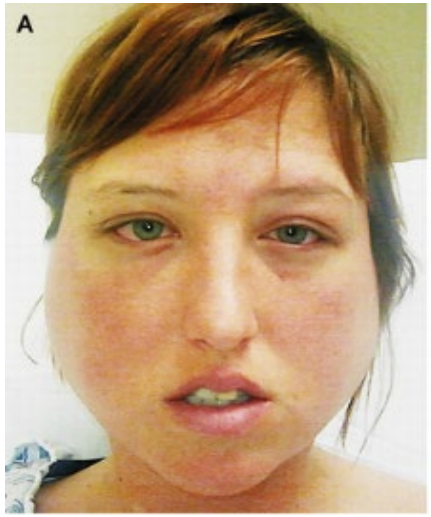


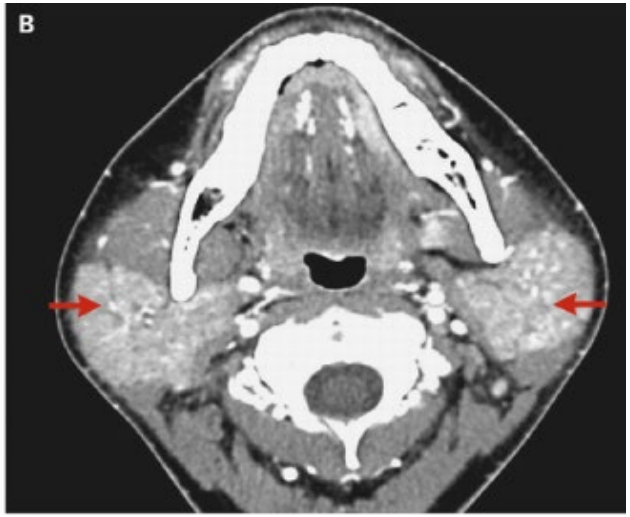


Heerford's syndrome

- Anterior Uveitis
- Fever (often)
- Parotid enlargement
- Facial palsy (often)







Sarcoidosis – multisystem disease

Ο ασθενής με τη νόσο
«προσεγγίζει και προσεγγίζεται»
(από) γιατρούς διαφόρων ειδικοτήτων

Sarcoidosis

The central role of pulmonary specialist

Since the intrathoracic manifestations are the most frequent, and the pulmonary specialist usually sees most of the patients

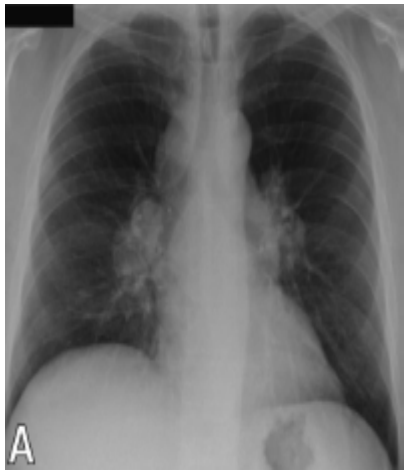
If there is a need for consultation of another organ specialist during the follow-up, the pulmonary physician will transfer the patient, but should keep the general management of the patient during the course of his disease

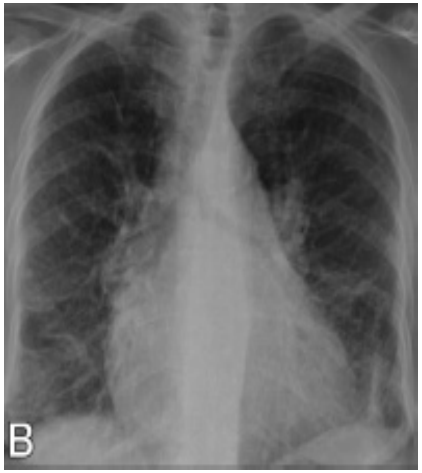
The management of patients with sarcoidosis requires a

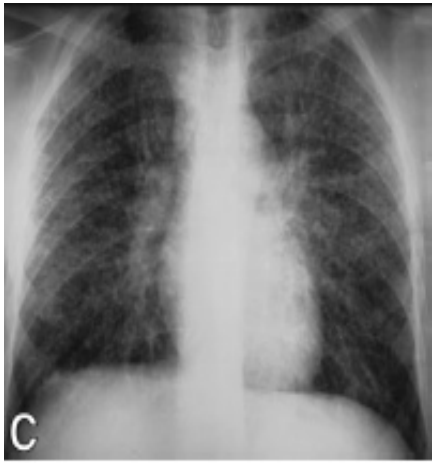
multidisciplinary approach

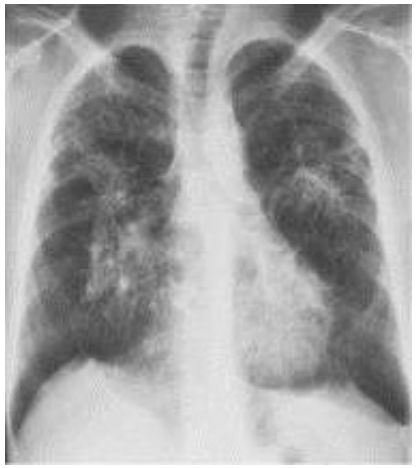
Staging of Sarcoidosis on the basis of Chest X-ray

Scadding staging







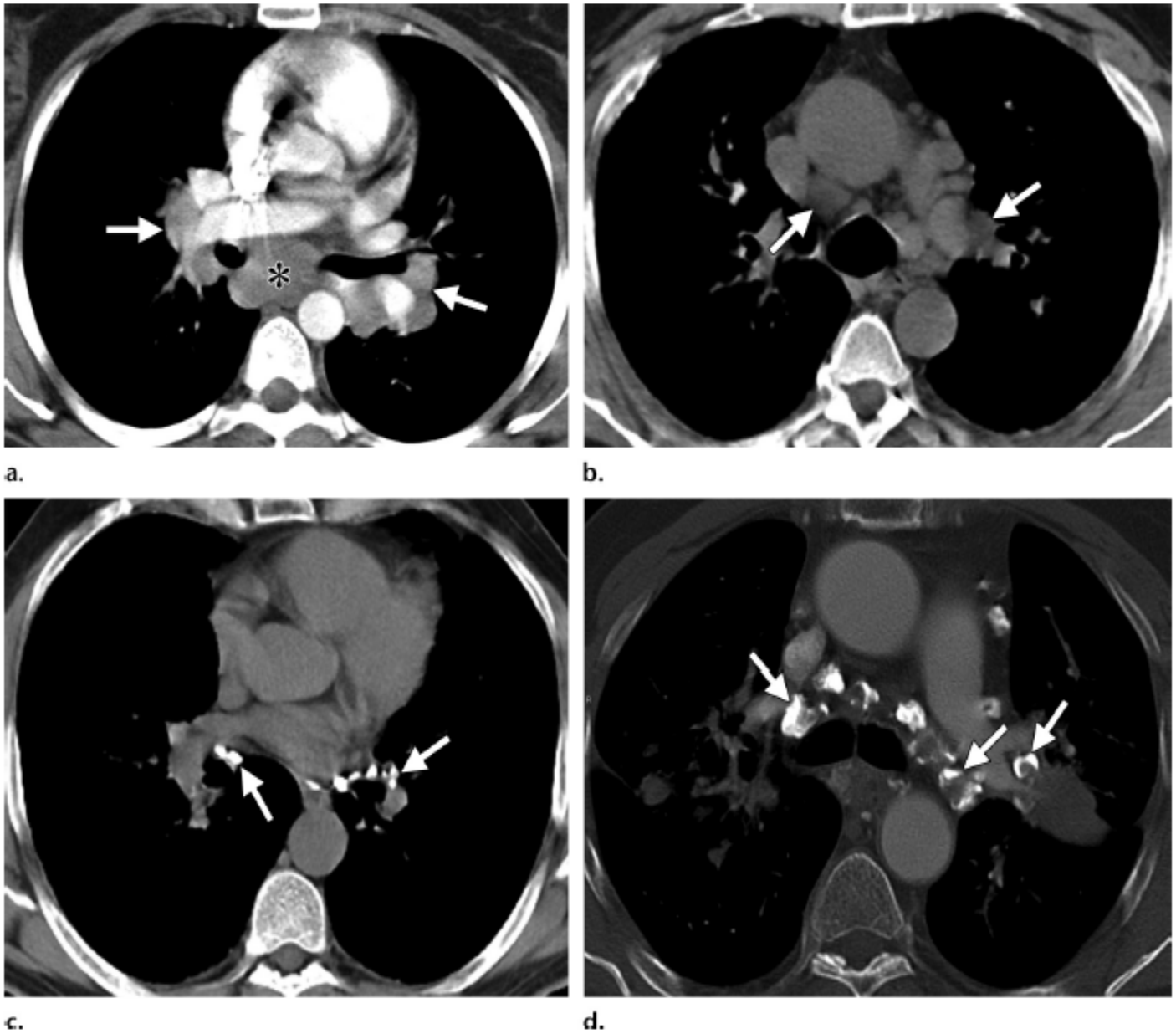


Radiographic stage	Chest X-ray	Frequency (%)	Resolution (%)
0	Normal	5–15	
I	BHL	25–65	60–90
II	BHL and pulmonary infiltrates	20–40	40–70
III	Pulmonary infiltrates without BHL	10–15	10–20
IV	Advanced pulmonary fibrosis	5	0

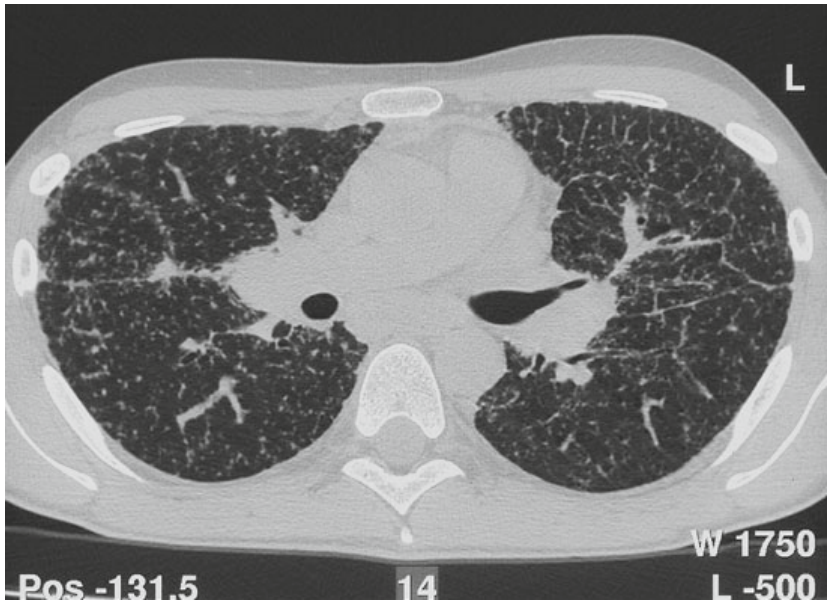
Prognostic information

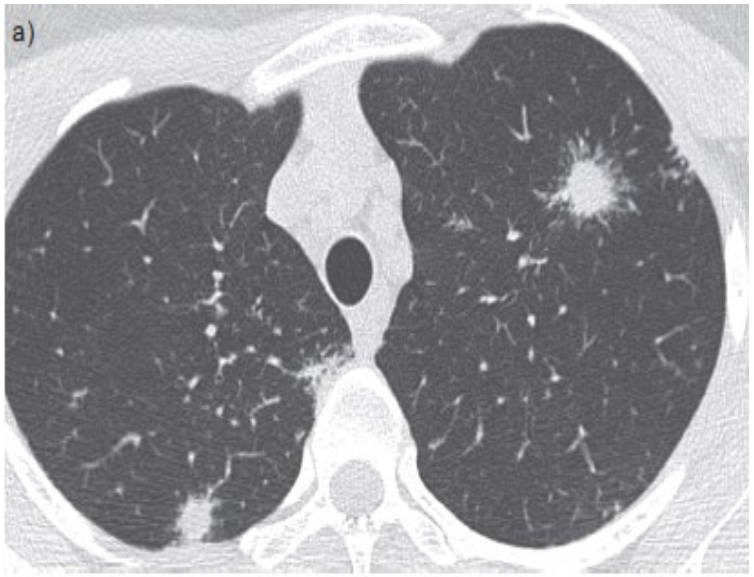
AJRCCM 1999

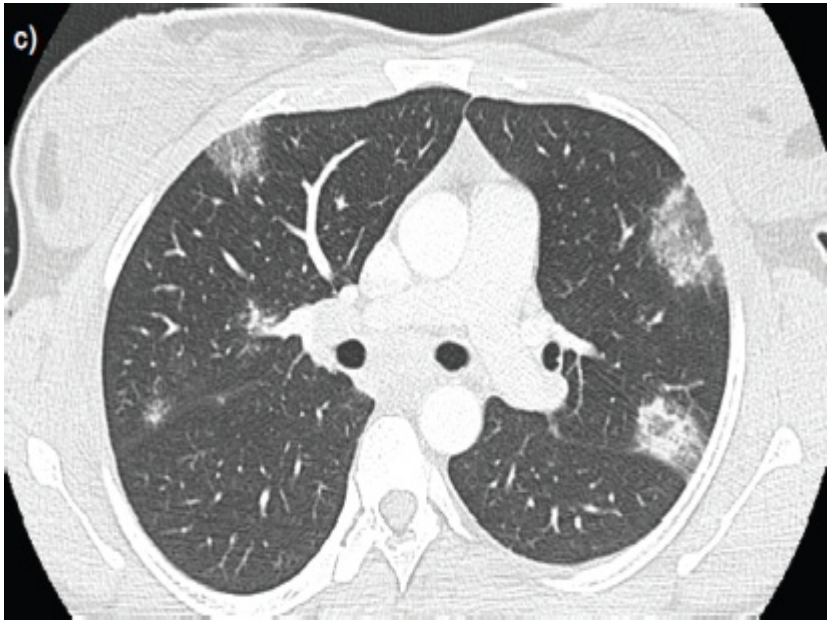
Sarcoidosis – Chest CT features

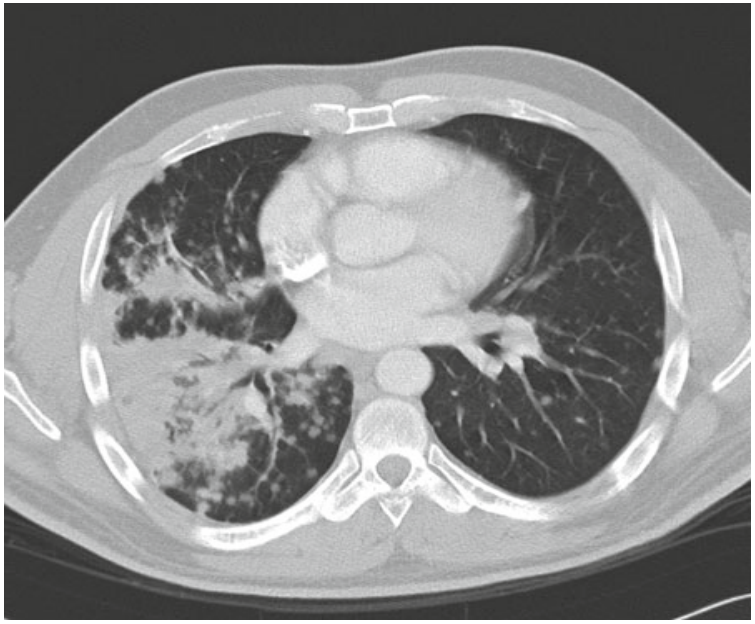


Sarcoidosis – Chest CT features

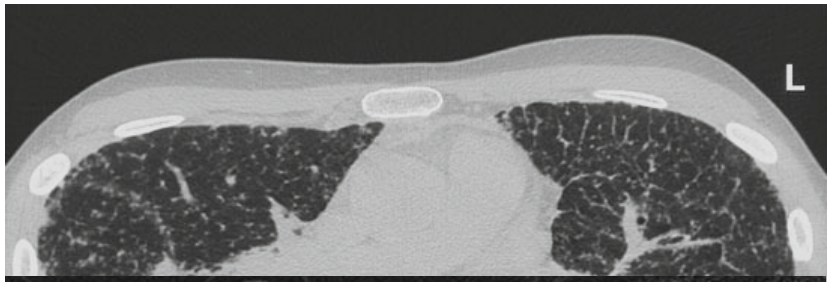


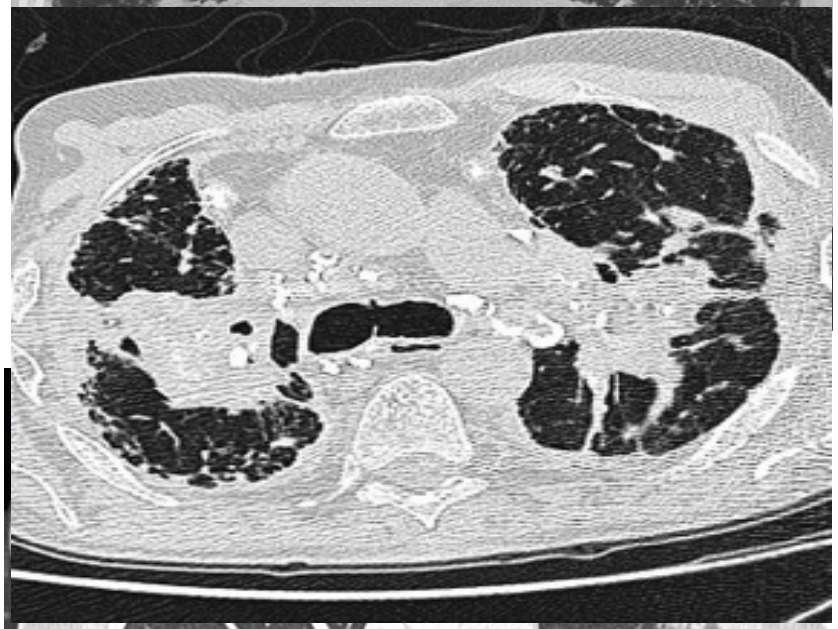


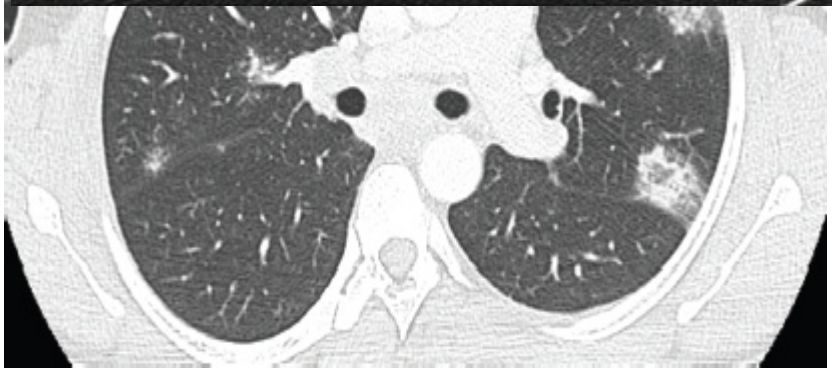


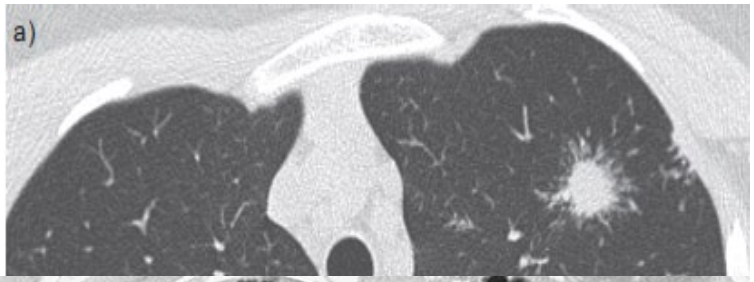


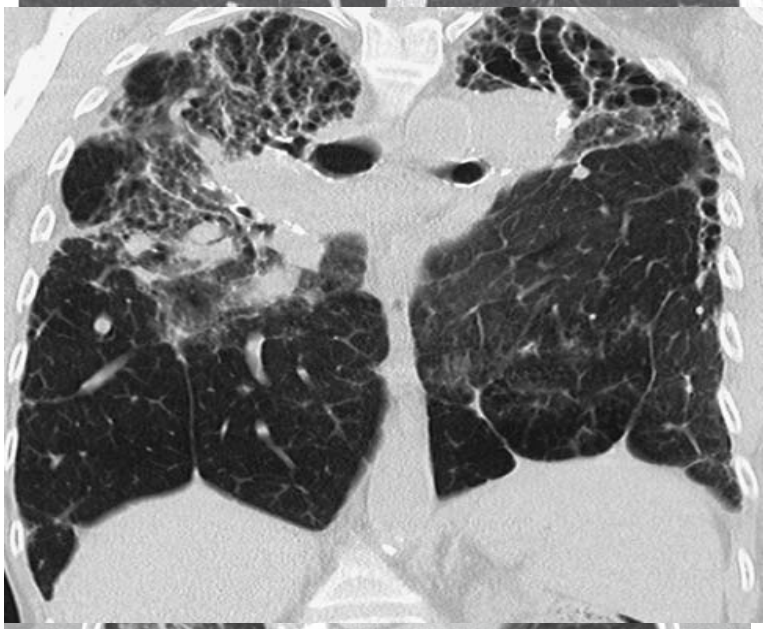
Sarcoidosis – Chest CT features

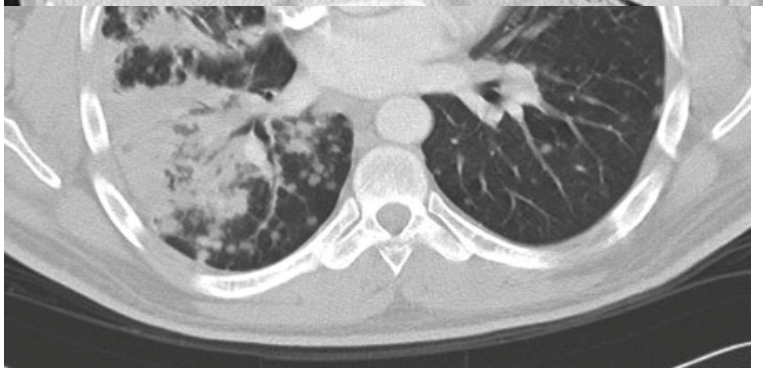




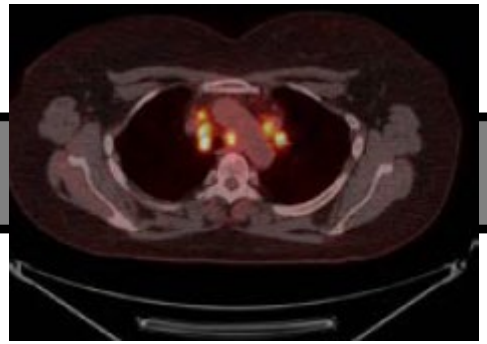








FDG PET for Gauging of Sarcoid Disease Activity



Indications for ^{18}F-FDG PET/CT in sarcoidosis
- Obtaining histological proof of sarcoidosis
- Determining the presence of active disease in symptomatic patients with normal conventional markers
- Assessing the presence of active cardiac sarcoidosis, combined with CMR
- Evaluating disease activity in symptomatic patients with longstanding sarcoidosis or stage IV disease

Lower radiation exposure (4mSv) - expensive – disponibility – false positives in Ca

When favoring an all-in-one or a so-called one-stop-shop examination of cardiac and extra-CS, FDG PET imaging is the modality of choice.

Adams H, *et al. Semin Respir Crit Care Med 2014*
Keijers R *et al. ERJ 2012*

Biomarkers

Serum markers
Serum amyloid A
Soluble interleukin-2 receptor
Lysozyme
Chitotriosidase
sACE
Krebs von den Lungen-6
Interferon gamma induced protein 10
Neopterin
B cell activating factor

Angiotensin converting enzyme,(sACE), produced by epithelioid cells is often used at diagnosis and for sarcoidosis monitoring

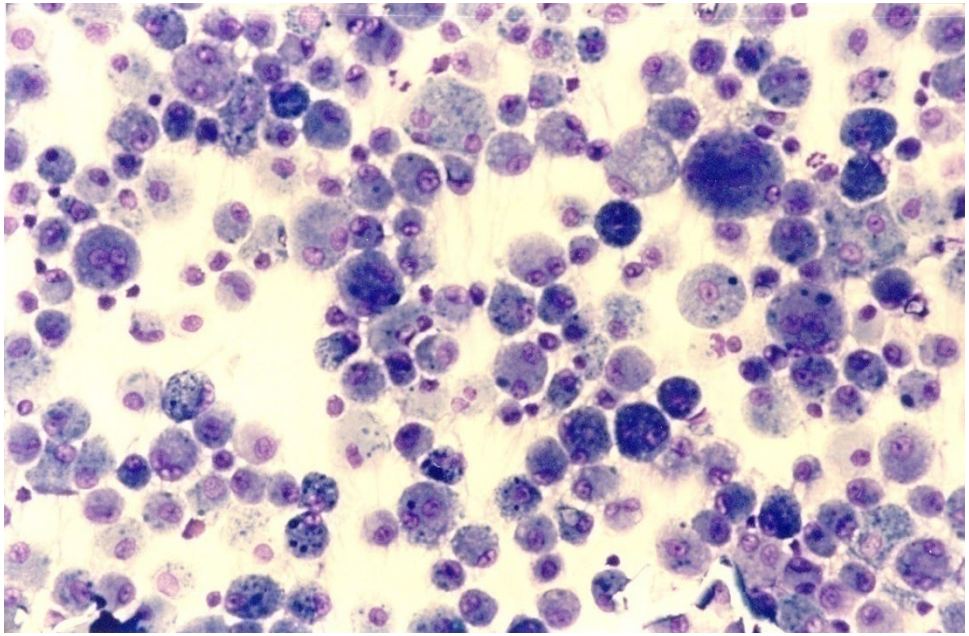
sACE is not accurate for diagnosing sarcoidosis because of a lack of both sensitivity and specificity, even after correction for a genetic insertion or deletion polymorphism that affects serum concentrations

The use of a sACE threshold level of 2N gives a specificity higher ~90% but with a poor sensitivity, ~55%

sACE can be increased in multiple conditions including those with clinical or pathological manifestations similar to sarcoidosis (e.g., tuberculosis, histoplasmosis, leprosy, lymphomas, asbestosis, Silicosis, diabetes mellitus, hyperthyroidism, LAM, Gaucher disease, or chronic beryllium disease, granulomatosis-associated common variable immune deficiency and drug-induced granulomatosis)

Valeyre D, *et al. Semin Respir Crit Care Med 2014*

Bronchoalveolar Lavage (BAL)



BAL lymphocytosis is not specific for sarcoidosis

Sarcoidosis
Granulomatous infectious diseases (mycobacteria, fungi)
Hypersensitivity pneumonitis
Viral pneumonitis
Drug-induced alveolitis
Lymphocytic interstitial pneumonitis (LIP)/lymphoma
Nonspecific interstitial pneumonitis (NSIP)
Cryptogenic organizing pneumonia (COP)
Chronic beryllium disease
Radiation pneumonitis

Drent et al.

20% Sarcoidosis $CD_4/CD_8 < 2$

12% EAA $CD_4/CD_8 > 3,5$

Sarcoidosis Vasc Diffuse Lung Dis 1997

Kantrow et al.

Sarcoidosis CD_4/CD_8 highly variable

ERJ 1997

Table 1 Predictive Value of CD4:CD8 Ratio in Bronchoalveolar Lavage

Study	CD4:CD8 Ratio	Sensitivity	Specif
Costabel et al 1988[14]	>3.5	53	93
	>5.0	47	98
Winterbauer et al 1993[15]	>3.0	67	89
	>4.0	59	96
Thomeer, Demedts 1997[16]	>3.0	64	89
	>4.0	55	94
Korosec et al 2010[17]	>3.3	70	88

Costabel U, *et al. Semin Respir Crit Care Med 2007*

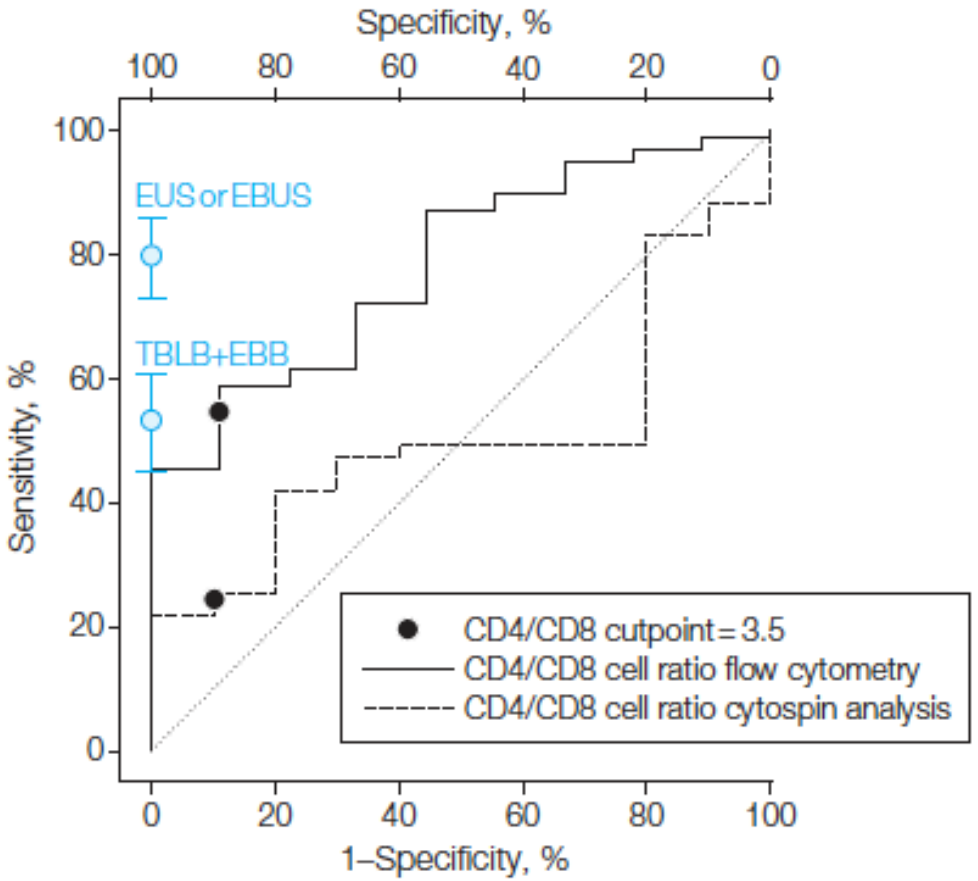
2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

Yield per stage

Stage I sarcoidosis Bronchoscopy **38%** Endosonography **84%**
Stage II sarcoidosis Bronchoscopy **66%** Endosonography **77%**



Diagnostic Approach

The diagnostic approach to sarcoidosis is a complex procedure

There is no single diagnostic test for this disease

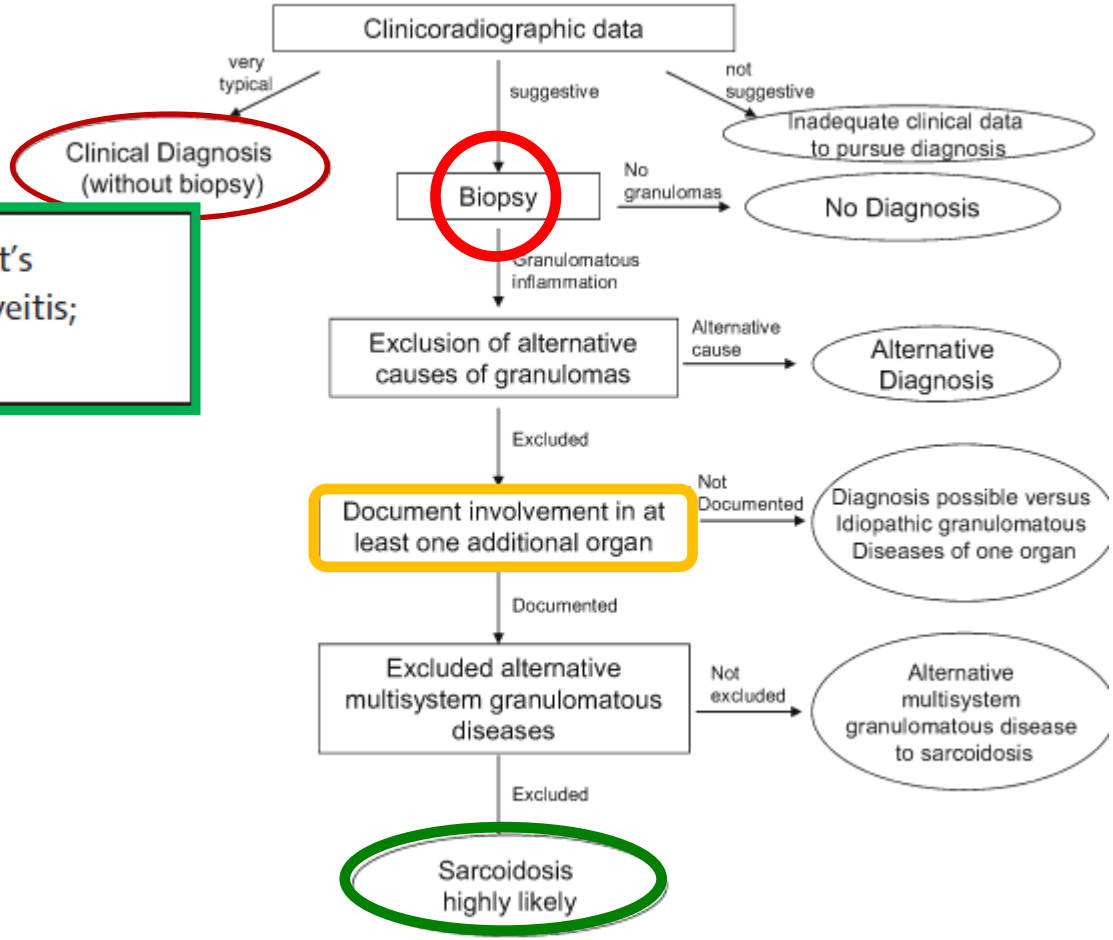
(e.g. the presence of non caseating granulomas in a single organ, such as skin, does not establish a diagnosis of sarcoidosis)

The diagnosis is based on three criteria:

- **A compatible clinical and/or radiological picture,**
- **Histological evidence of noncaseating granulomas,**
- **Exclusion of other diseases** that may produce a similar histological or clinical picture.

Judson MA. *Clin Chest Med 2008*
Cruser ED, et al. *AJRCCM 2020*
Thillai M, et al. *Thorax 2021*

Diagnostic Approach: multiple step process



Löfgren's and Heerfordt's syndromes; BHL and uveitis; asymptomatic BHL

Judson MA. *Clin Chest Med 2008*
Cruser ED, et al. *AJRCCM 2020*
Thillai M, et al. *Thorax 2021*

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 19-27

The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool

Table 1.6 Clinical criteria for extrapulmonary sarcoidosis organ involvement in patients with biopsy-confirmed sarcoidosis in another organ[a]

Organ	Definite	Probable	Possible
Lungs	1. Chest roentgenogram with one or more of the following • Bilateral hilar adenopathy • Diffuse infiltrates • Upper lobe fibrosis 2. Restriction on pulmonary function tests	1. Lymphocytic alveolitis by bronchoalveolar lavage (BAL) 2. Any pulmonary infiltrates 3. Isolated reduced diffusing capacity for carbon monoxide	1. Any other adenopathy 2. Obstructive pulmonary function tests
Skin	1. Lupus pernio 2. Annular lesion 3. Erythema nodosum	1. Macular/papular 2. New nodules	1. Keloids 2. Hypopigmentation
Eyes	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness 2. Positive in vivo confocal microscopy	1. Glaucoma 2. Cataract
Liver	1. Liver function tests > three times the upper limit of normal	1. Compatible computed tomography (CT) scan 2. Elevated alkaline phosphate	
Hypercalcemia/ hypercalciuria/ nephrolithiasis	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis—no stone analysis 2. Nephrolithiasis with negative family history for stones
Neurologic	1. Positive magnetic resonance imaging (MRI) with uptake in meninges or brainstem 2. Cerebrospinal fluid with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy 7. Positive positron emission tomography (PET) scan of CNS or spinal cord	1. Other abnormalities on magnetic resonance imaging (MRI) 2. Unexpected neuropathy 3. Positive electromyogram	1. Unexplained headaches 2. Peripheral nerve radiculopathy
Renal	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease

The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool

	Definite	Probable	Possible
Cardiac	1. Treatment responsive cardiomyopathy 2. Electrocardiogram showing intraventricular conduction defect or nodal block 3. Positive gallium scan of heart 4. Positive positron emission tomography (PET) scan of the heart	1. No other cardiac problem and either: • Ventricular arrhythmias • Cardiomyopathy 2. Positive thallium scan	1. In patient with diabetes and/or hypertension: • Cardiomyopathy • Ventricular arrhythmias
Non-thoracic lymph node		1. New palpable node above waist 2. Lymph node >2 cm by computed tomography (CT) scan	1. New palpable femoral lymph node
Bone marrow	1. Unexplained anemia 2. Leukopenia 3. Thrombocytopenia		1. Anemia with low mean corpuscular volume (MCV)
Spleen		1. Enlargement by: • Exam • Computed tomography (CT) scan • Radioisotope scan	
Bone/joints	1. Cystic changes on hand or feet radiographs	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
Ear/nose/throat		1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness
Parotid/salivary glands	1. Symmetrical parotitis with syndrome of mumps 2. Positive gallium scan (Panda sign)		1. Dry month
Muscles	1. Increased creatine phosphokinase (CK)/aldolase which decreases with treatment	1. Increased creatine phosphokinase (CK)/aldolase	1. Myalgias responding to treatment
Other organs			

[a]There can be no other explanation for the clinical findings in this table for these criteria to be valid. In addition, biopsy of each of these organs would constitute "definite" involvement. Adapted from [72] with permission

Initial Work-Up

- **History and Physical examination:** family sarcoidosis, environmental, and occupational exposure (beryllium, aluminum …)
- **Chest radiography**
- **Pulmonary function tests:** spirometry with bronchodilator, TLC and DLCO
- **Blood** cell counts, calcemia/calciuria, renal and liver function, urine analysis
- **Electrocardiogram (+ 24 hr Holter monitoring, echocardiography)**
- **Routine ophthalmologic examination** (slit-lamp, tonometric/funduscopic examination)
- **Tuberculin skin test**
- **Others**[a]

[a]According to clinical presentation, diagnosis issues, and assessment of disease activity.

Valeyre D, *et al. Semin Respir Crit Care Med 2014*
Baughman et al. *ERJ 2021*

The decision to treat

- Progressive disease
- Functional impairment
- Respiratory failure
- Death

- Cough
- Dyspnea

Baughman RP et al. *Sarcoidosis Vasc Diffuse Lung Dis 2018*

PFTs

"With no other disease did pulmonary physiologists have so much fun as with sarcoidosis."

Om P. Sharma

All varieties of abnormalities in pulmonary function tests can be seen in sarcoidosis

- A decreased diffusion capacity and a restrictive ventilatory defect are most often seen
- Almost 30 % of patients also have obstructive airway disease
- Bronchial hyper responsiveness is seen in up to 20 % of patients and is associated with the presence of microscopic non-necrotizing granulomas in the endobronchial mucosa

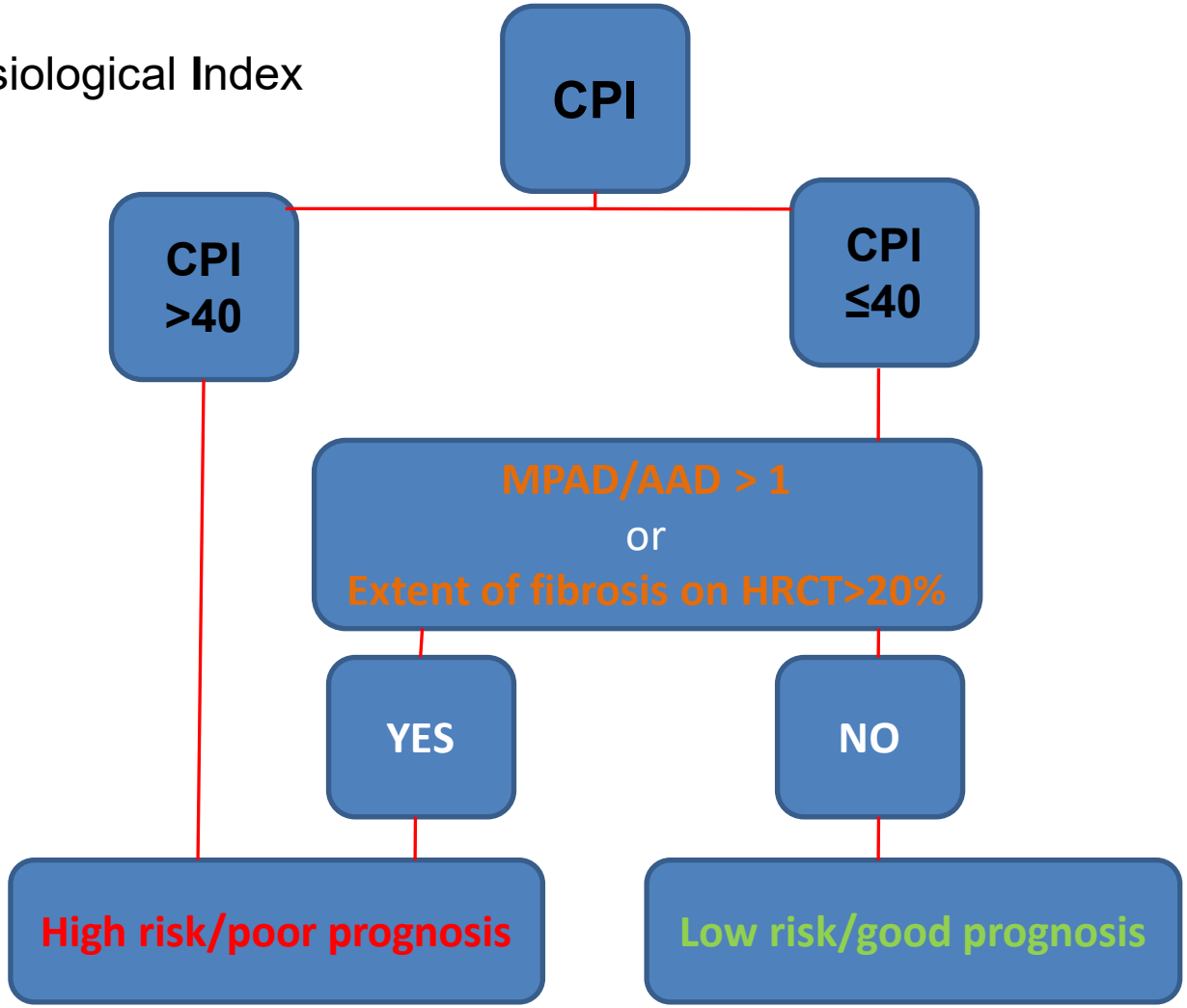
Baughman, *et al. AJRCCM 2001*

An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study

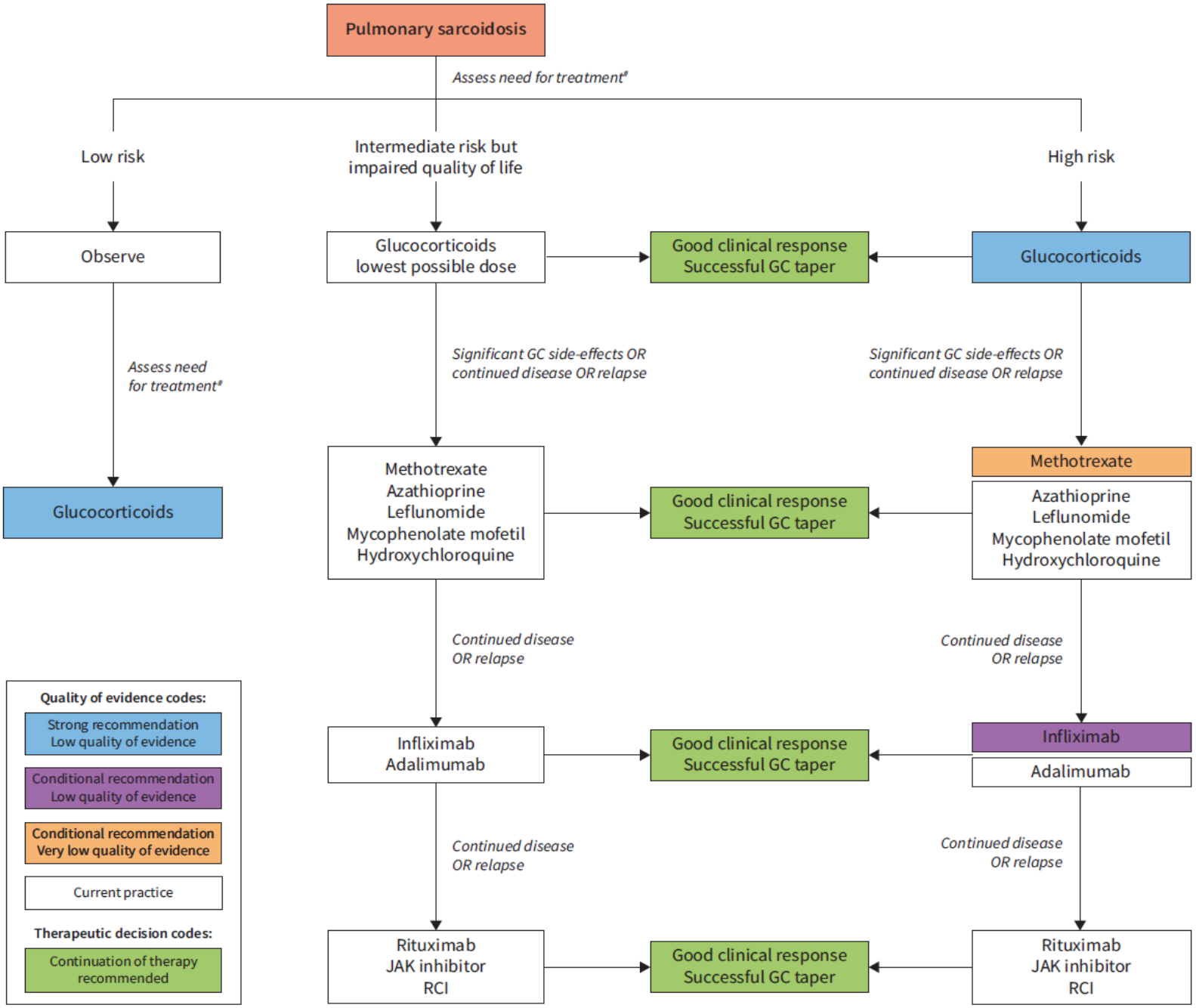
Simon LF Walsh, Athol U Wells, Nicola Sverzellati, Gregory J Keir, Lucio Calandriello, Katerina M Antoniou, Susan J Copley, Anand Devaraj, Toby M Maher, Elizabetta Renzoni, Andrew G Nicholson, David M Hansell

Lancet Respir Med 2014

Composite **P**hysiological **I**ndex

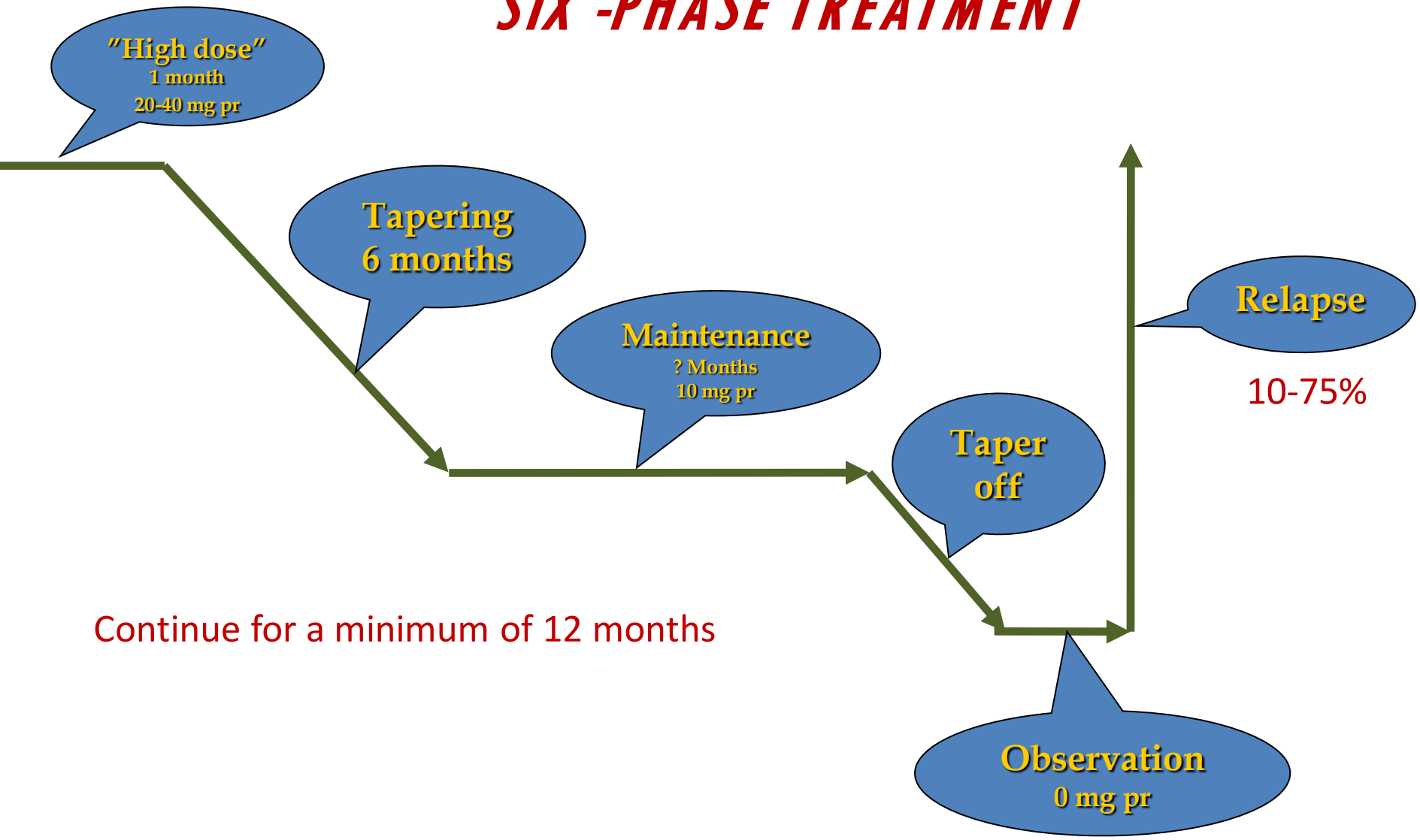


CPI=91.0-(0.65*percent predicted DLCO)-(0.53*percent predicted FVC)+(0.34*percent predicted FEV_1)



Baughman RP, et al. *Eur Respir J 2021*

SIX -PHASE TREATMENT



Continue for a minimum of 12 months

Judson MA. *Respir Med 2012*

Follow-Up

- **Stage I disease:** every 6 months
- **Other stages:** every 3 to 6 months
- **Follow-up for a minimum of 3 years after therapy is discontinued**
- **If radiograph has normalized for 3 years, subsequent follow-up is not routinely required**
- **Note:** Follow-up needs to be more vigilant after corticosteroid-induced remissions than after spontaneous remissions

ATS/WASOG Statement on Sarcoidosis. *AJRCCM 1999*
Grutters *et al. ERJ 2006*
Thillai *et al. Thorax 2021*

Adverse and Favourable Prognostic Factors in Sarcoidosis

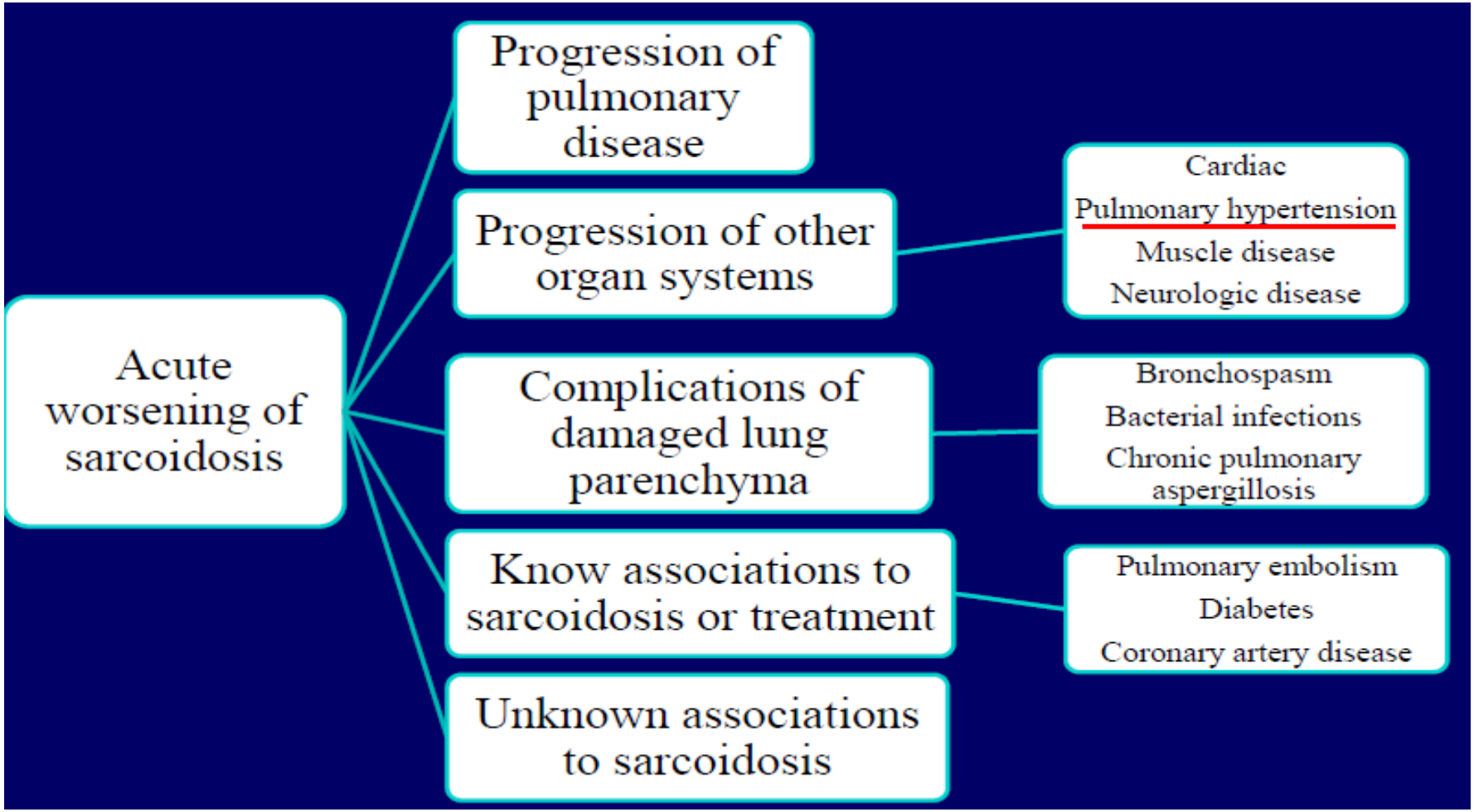
Variable	Adverse Prognostic Factors†	Favorable Prognostic Factors
Demographic characteristics	Age ≥40 yr at onset[10] Black race[11] Black race and female sex Lower income[4,11]	Age <40 yr at onset[10]
Pulmonary involvement[12,13]	Scadding stage III (absence of lymphadenopathy) or stage IV (signs of fibrosis) on chest radiography‡ Severe dyspnea or hypoxemia with minimal exertion at presentation[13] Clinically significant lung functional impairment Pulmonary hypertension[13]	Asymptomatic Scadding stage I or II (presence of lymphadenopathy) on chest radiography‡
Bronchoalveolar lavage fluid	Neutrophilia at presentation[14] Elevated metalloproteinases (MMP12)	Lymphocytosis without increased eosinophils or neutrophils or both[15] Increased CD4:CD8 ratio[15]
Extrapulmonary involvement	Lupus pernio: nasal mucosal involvement[10] Vitiligo Chronic uveitis[10] Cardiac involvement Hepatomegaly Splenomegaly Neurologic involvement Osseous involvement[10] Hypercalcemia[10] Nephrolithiasis or nephrocalcinosis[10] Small-fiber neuropathy–associated symptoms[16,17]	Acute inflammatory manifestations (e.g., Löfgren's syndrome: acute onset with fever, erythema nodosum, bilateral ankle arthritis, and bilateral hilar lymphadenopathy)[1] Isolated cranial-nerve palsy
Requirement for treatment	Risk of disease progression and organ failure or death[12]	No risk of disease progression or organ failure
Associated genetic variants§	*HLA-DRB1*14*, *HLA-DRB1*15*+[1] Presence of a *TNF-α* rs1800629 G/A variant allele¶ Presence of a *BTNL2* rs2076530 G/A variant allele[18]¶ Presence of an *ANXA11* rs1049550 C/T variant allele	*HLA-DRB1*03*+, *HLA-DQB1*0201* Absence of a *TNF-α* variant allele Absence of a *BTNL2* variant allele Absence of an *ANXA11* variant allele

Drent M, et al. *NEJM 2021*

Worsening of pulmonary sarcoidosis

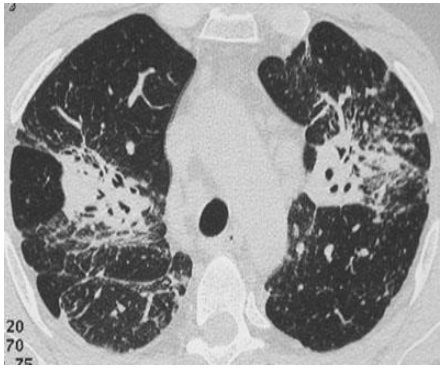
Marc A. Judson[a] and Robert P. Baughman[b]

2014

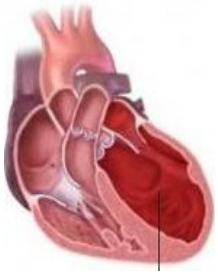


Pathogenesis SAPH: Multifactorial mechanisms

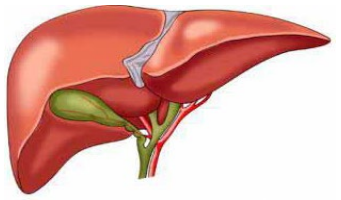
Hypoxic vasocostrinction
Pulmonary vascular rarefaction



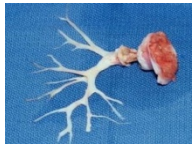
Left heart disease



Portal hypertension



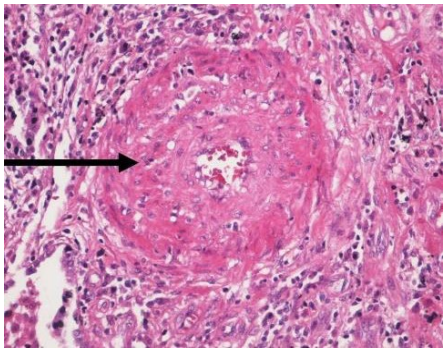
CTEPH



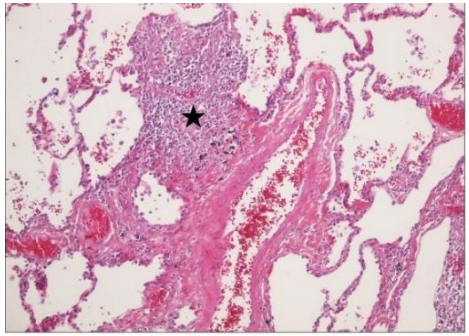
OSAS

SAPH

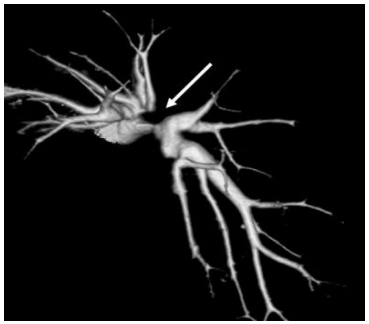
Vascular remodelling



'PVOD'

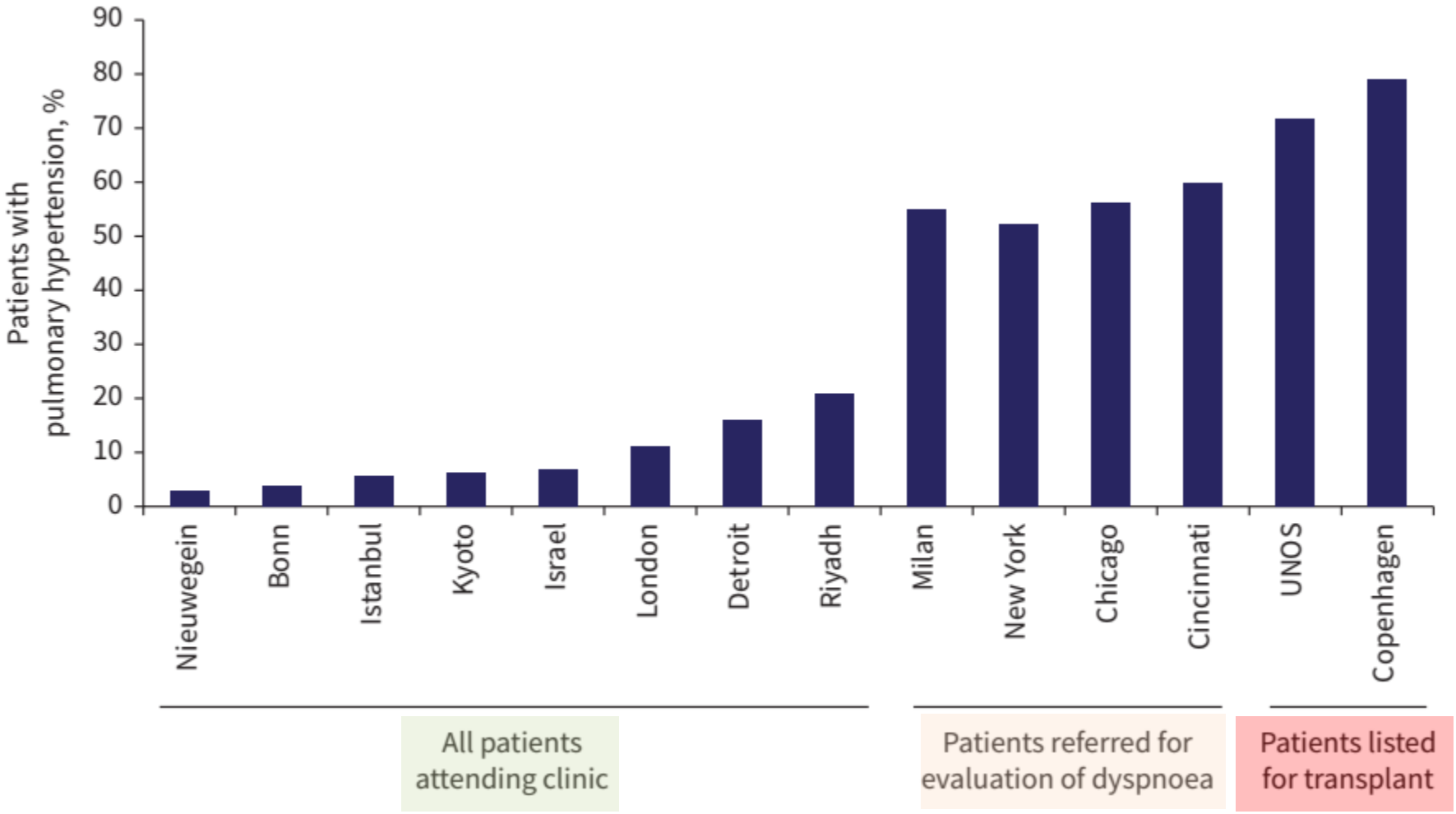


Compression of LNs or Fibrosing mediastinitis



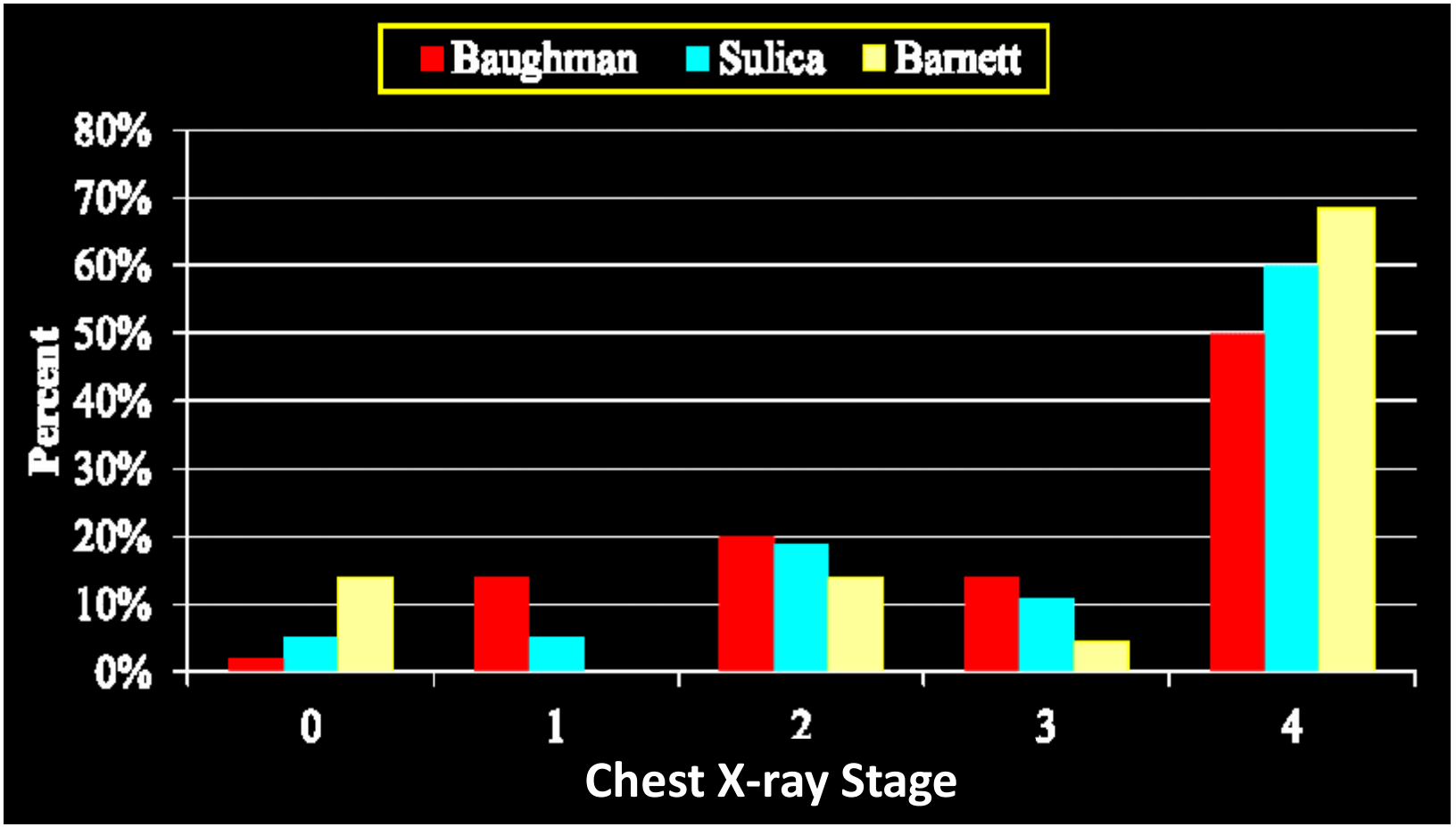
Nunes H. *Eur Respir Monogr* 2012

Prevalence of PH in Sarcoidosis: 5-73%



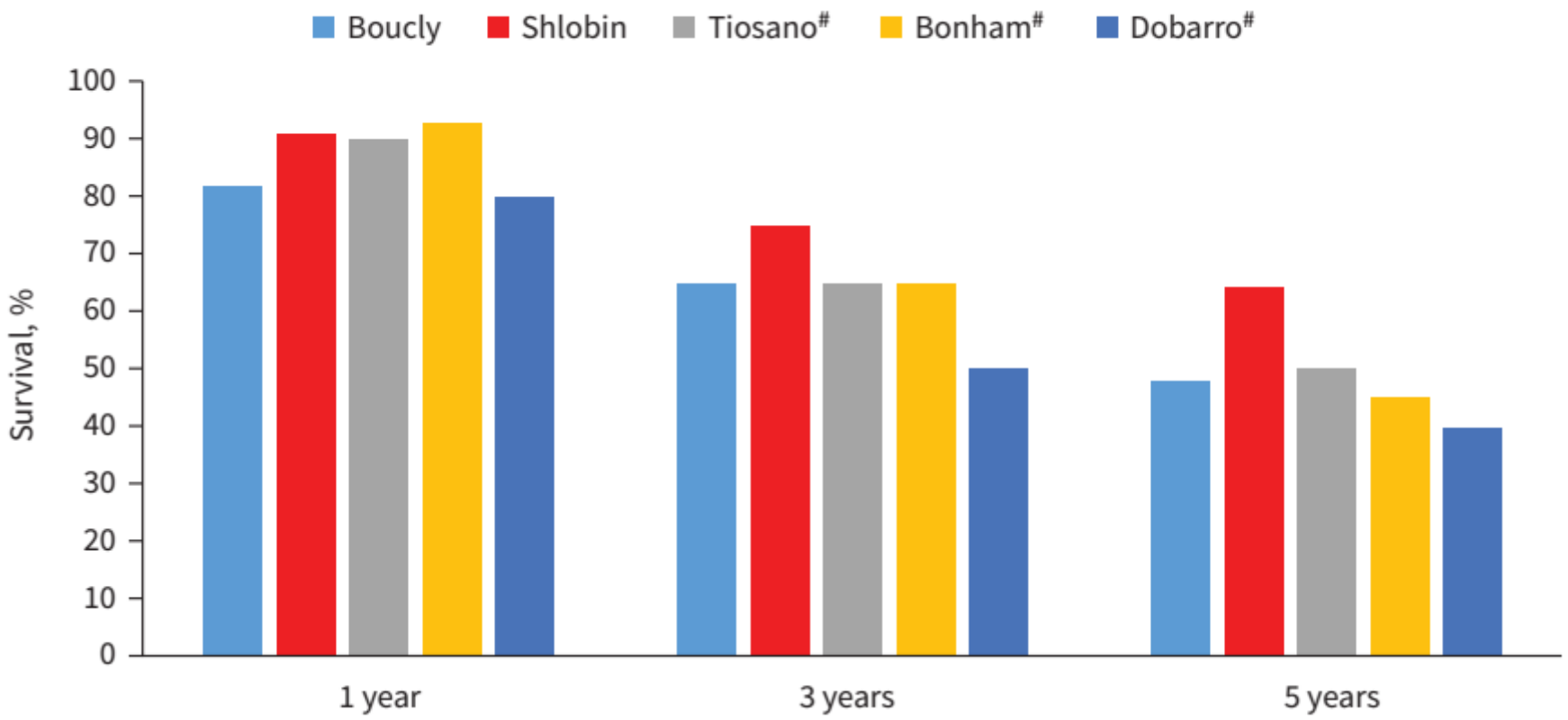
Savale L. *Eur Respir Rev* 2022

Prevalence of PH in Sarcoidosis



Baughman RP. *Chest* 2010
Sulica R. Chest 2005
Burnett CF. Chest 2009

Pulmonary hypertension is an independent predictor of mortality in patients with sarcoidosis



Savale L. *Eur Respir Rev* 2022

CHEST

Original Research

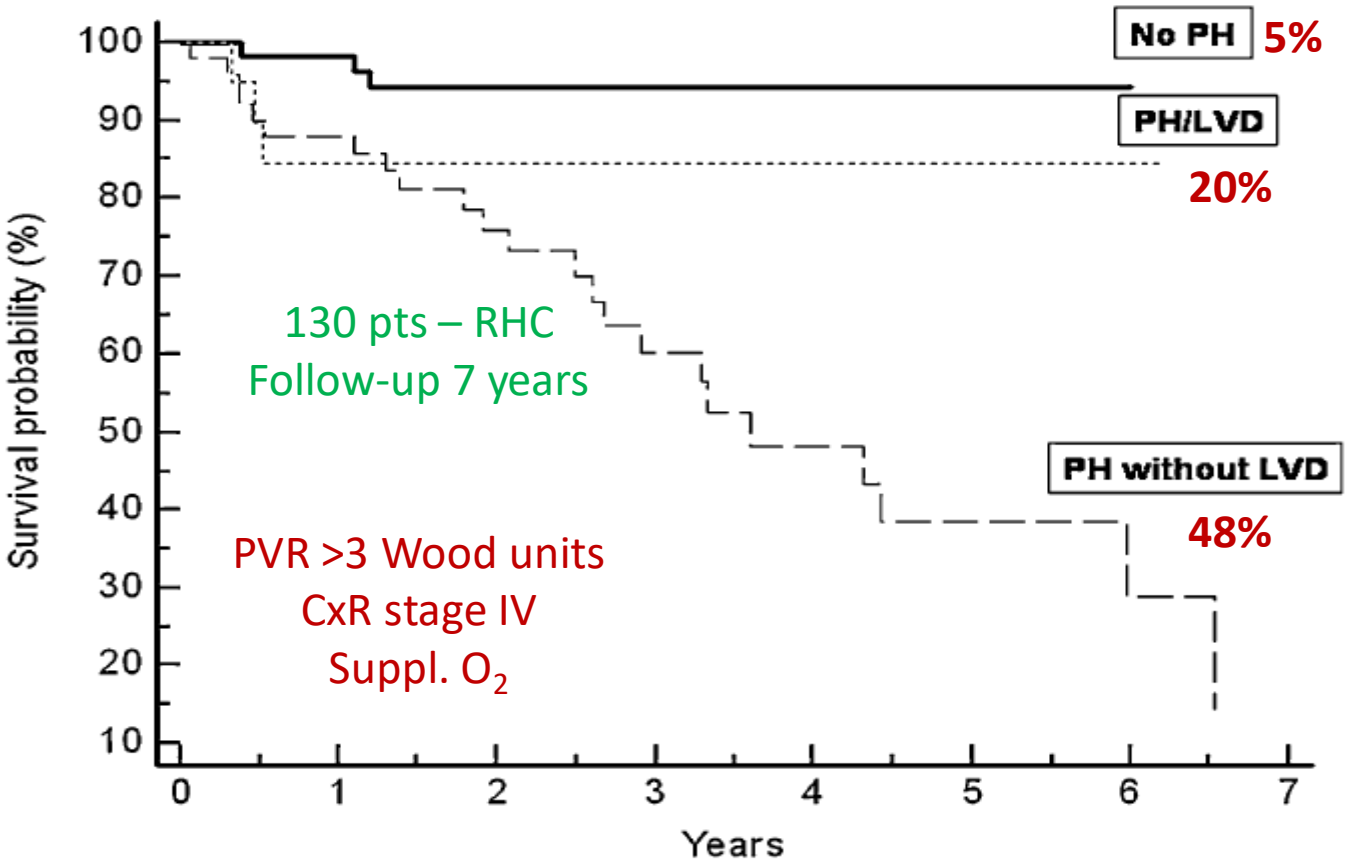
PULMONARY HYPERTENSION

Survival in Sarcoidosis-Associated Pulmonary Hypertension

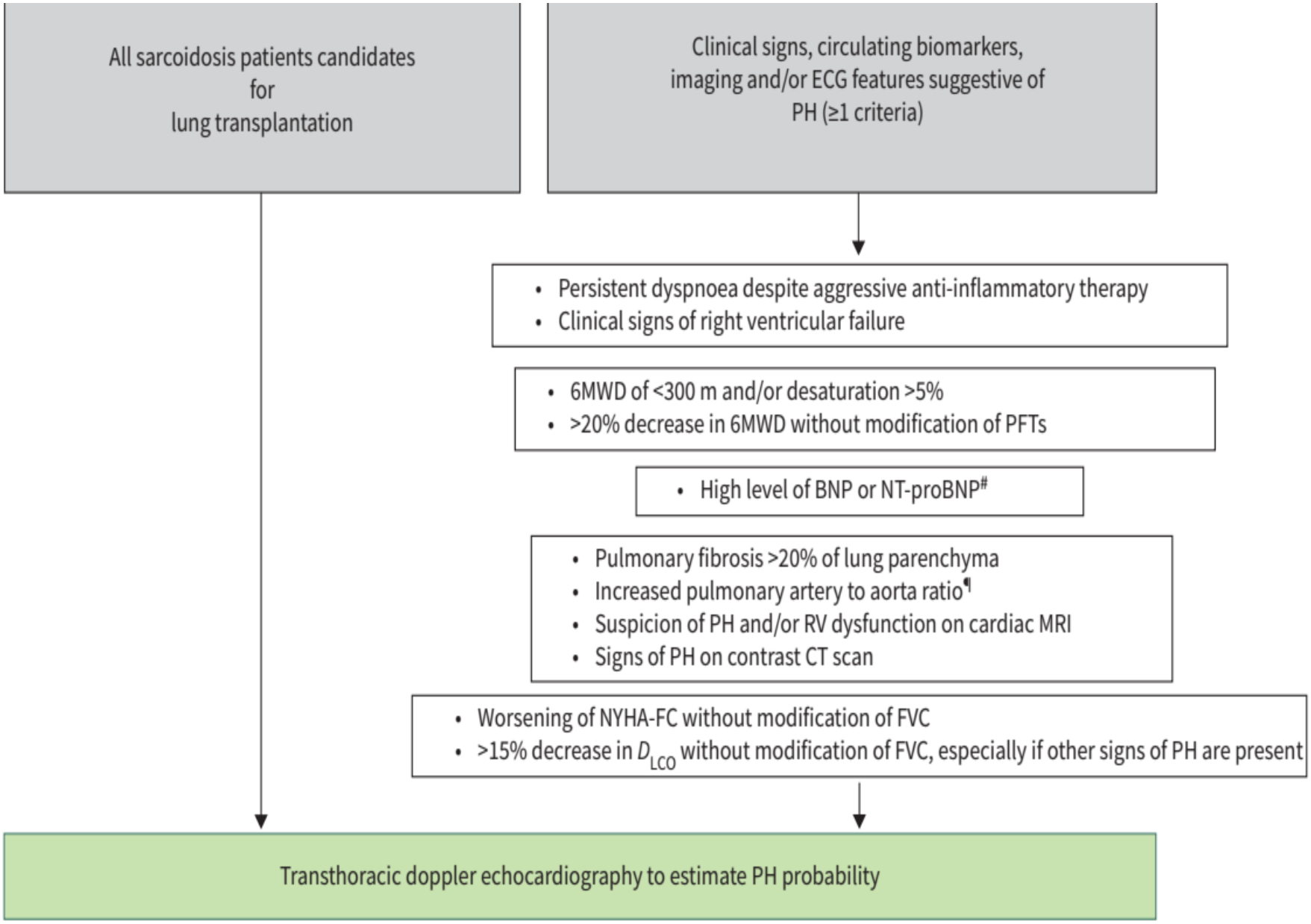
The Importance of Hemodynamic Evaluation

2010

Robert P. Baughman, MD, FCCP; Peter J. Engel, MD; Lisa Taylor, BA, RN; and Elyse E. Lower, MD

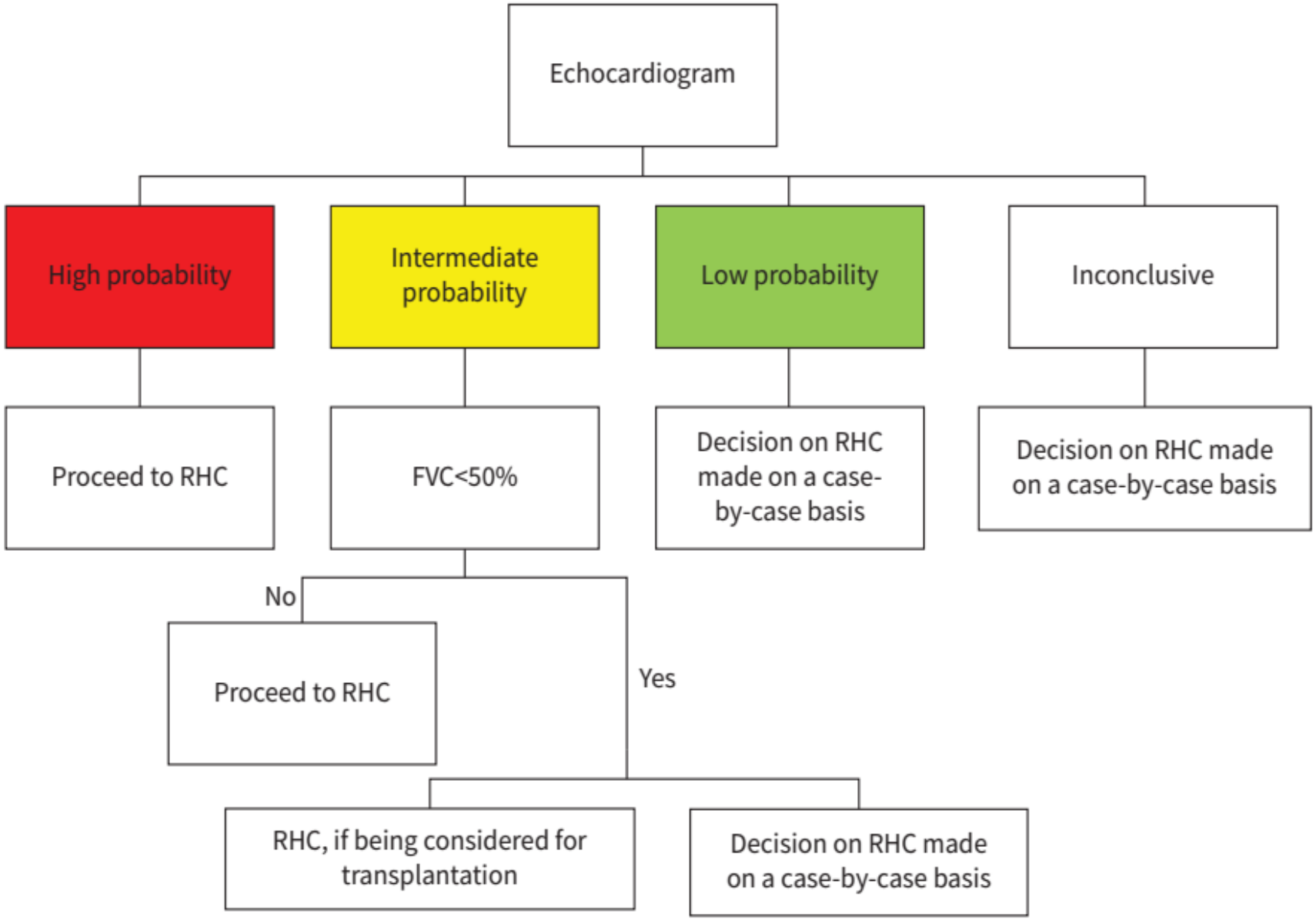


Diagnostic approach



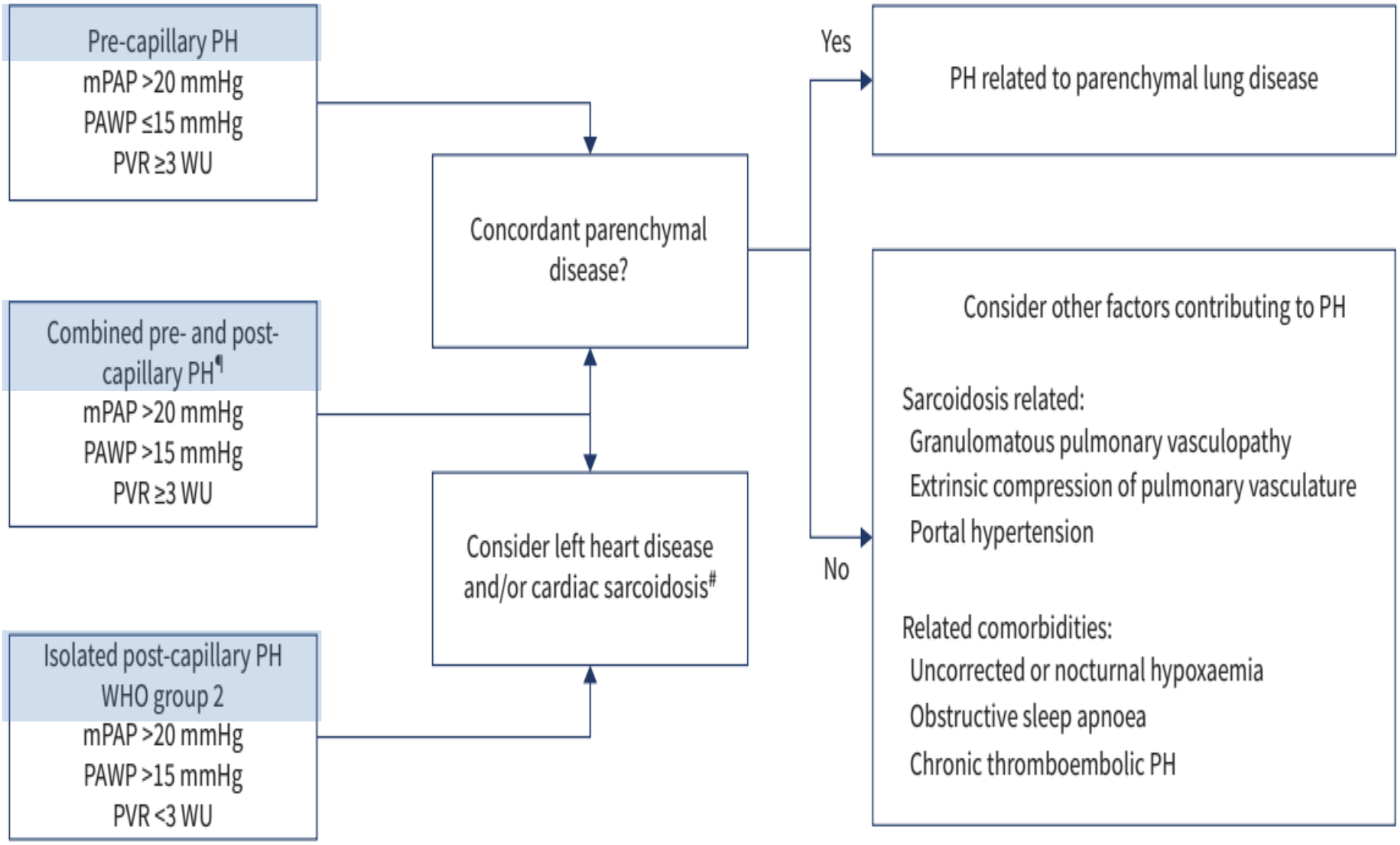
Savale L. *Eur Respir Rev* 2022

Diagnostic approach



Savale L. *Eur Respir Rev* 2022

Diagnostic approach



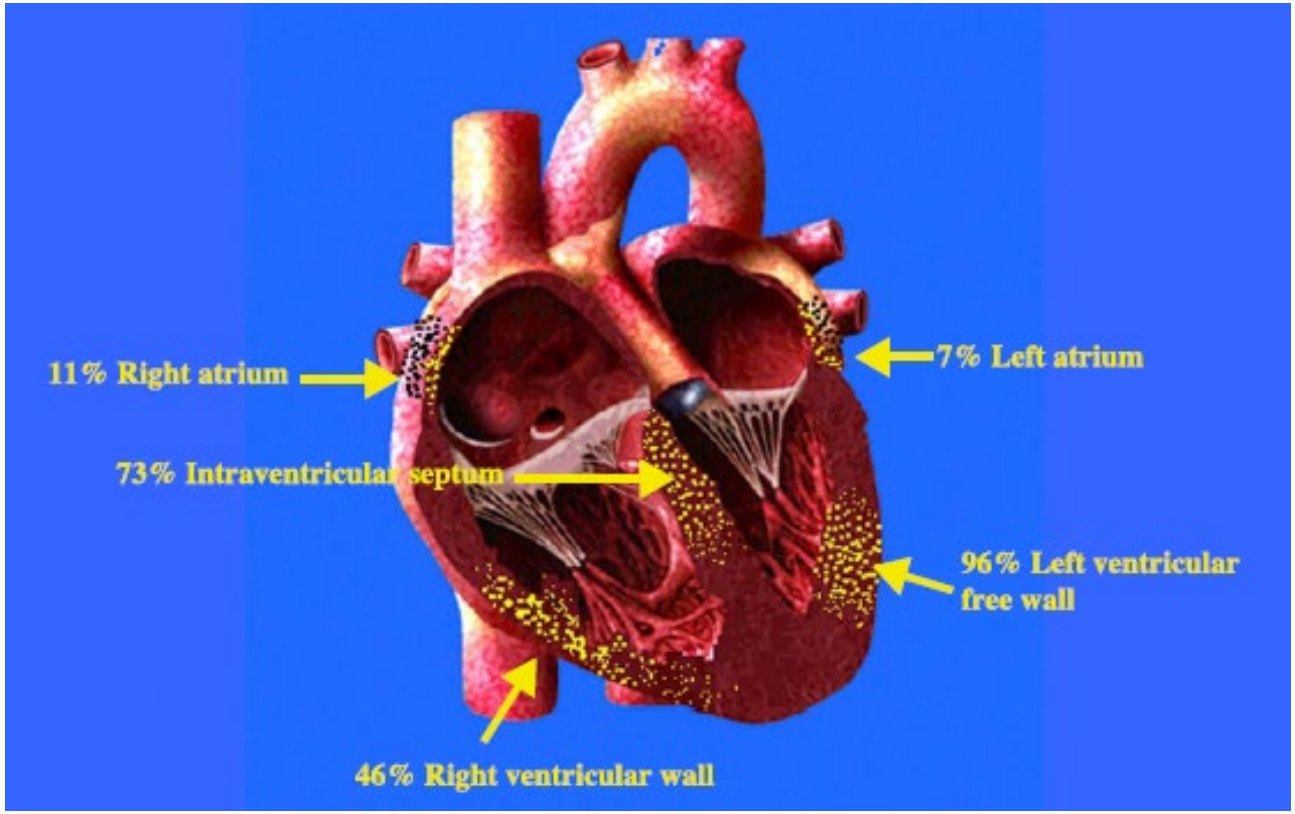
Savale L. *Eur Respir Rev* 2022

Frequency of Organ Involvement

Lung - 90%
Lymph nodes - 75-90%
Pleura - 1-5%
Skin - 25%
Eye - 25%
Nasal mucosa - 20%
Larynx - 5%
Bone marrow - 15-40%
Spleen -50-60%
Liver -60-90%
Kidney - Rare
Calcium disorder - 11%
CNS - 5%
Bones - 5%
Joints - 25-50%
Heart - 5%
Endocrine glands - Rare
Parotid gland - 10%
GI tract - Rare

Cardiac Involvement in Sarcoidosis

Cardiac involvement occurs in 20–27% of sarcoid patients in the United States and may be as high as 58% in Japan. The majority of these patients are asymptomatic; clinical evidence of cardiac sarcoidosis is present in ~5% of patients with sarcoidosis, but occult involvement is much higher (> 20%).



Lynch JP III, *et al. Semin Respir Crit Care Med 2014*

Clinical manifestations in cardiac sarcoidosis

Author	Year	*N*	AV block (%)	BBB (%)	SVT/V-Tach (%)	CHF (%)	SD (%)
Matsui [9]	1976	42	62	48	14	10	41
Roberts [12]	1977	26	27	12	35	30	65
Fleming [14]	1981	300	26	61	73	24	26
Yazaki [15]	1998	95	45	NA	18	26	12

N, number of patients; AV, atrioventricular; BBB, bundle branch block; SVT, supraventricular tachycardia; V-Tach, ventricular tachycardia; CHF, congestive heart failure; SD, sudden death.

Cardiac involvement may occur at any point during the course of sarcoidosis and may occur in the absence of pulmonary or systemic involvement.

Prognosis of CS is related to extent and site(s) of involvement. Most deaths due to CS are due to arrhythmias or conduction defects

The yield of endomyocardial biopsies is low

Currently, 18F-FDG PET-CT and gadolinium-enhanced MRI (cMRI) are the key imaging modalities to diagnose CS

Lynch JP III, *et al. Semin Respir Crit Care Med 2014*

HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis

*Expert Consensus Recommendations on **Criteria for the Diagnosis of CS***

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological Diagnosis from Myocardial Tissue
   CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
2. Clinical Diagnosis from Invasive and Non-Invasive Studies:
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis
   and
   b) One or more of following is present
   - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
   - Unexplained reduced LVEF (<40%)
   - Unexplained sustained (spontaneous or induced) VT
   - Mobitz type II 2nd degree heart block or 3rd degree heart block
   - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
   - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
   - Positive gallium uptake (in a pattern consistent with CS)

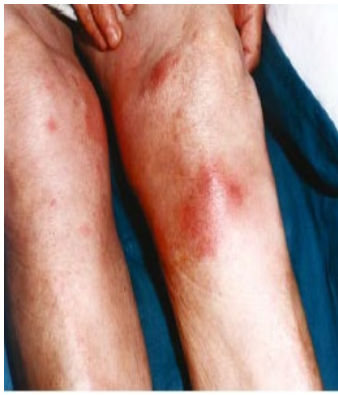
   and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded

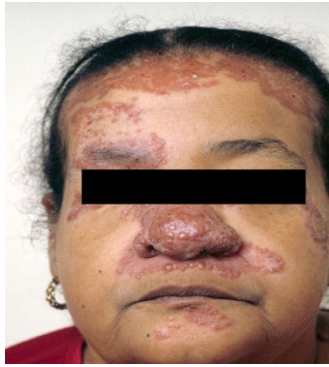
*In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.[33]

Birnie DH, *et al. Heart Rhythm 2014*

Cutaneous Involvement

Although not life-threatening, but can be emotionally devastating and are divided into two categories: specific and nonspecific.





- **Erythema nodosum** may occur.
- **Lupus pernio** is the most specific associated cutaneous lesion.
- **Violaceous rash** is often seen on the cheeks or nose.
- **Maculopapular plaques**

- **Lupus pernio** is more common in women than in men and is associated with chronic disease and extrapulmonary involvement.

- **Erythema nodosum** occurs in about 10% of patients with sarcoidosis and usually lasts for about 3 weeks.

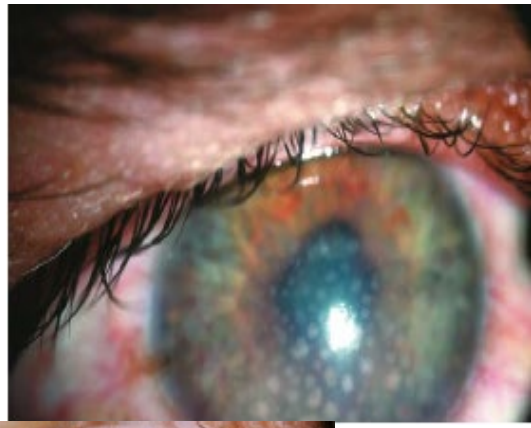
- **Biopsy specimens of erythema nodosum lesions** show nonspecific septal panniculitis (NOT BX erythema nodosum lesions).

Marchell RM, *et al. Semin Respir Crit Care Med 2010*

Ophthalmologic Complications

- The eye and adnexa are involved in 25 -80%
- Anterior or posterior granulomatous uveitis, Optic neuritis.
- Conjunctival lesions and scleral plaques may also be noted.
- Ocular involvement may lead to blindness if untreated.

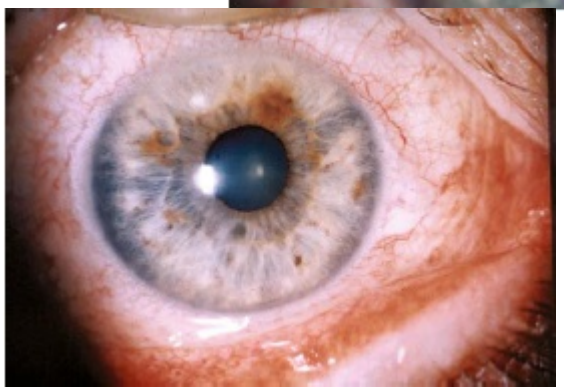
This necessitating routine slit-lamp and funduscopic examination



- **Anterior uveitis**

Is the most common manifestation

Chronic anterior uveitis, with insidious symptoms leading to glaucoma and vision loss, is more common than **acute anterior uveitis**.



- **Posterior uveitis:**

If suspected fluorescence angiography

Baughman RP, *et al. Semin Respir Crit Care Med* 2010

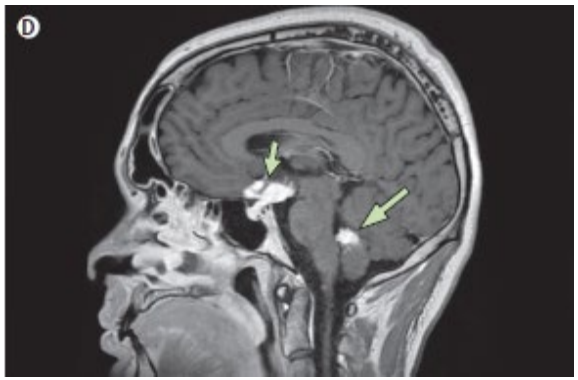
Neurologic Involvement

CNS is involved in up to 25% of patients with sarcoidosis who undergo autopsy, but only 10% of all patients with sarcoidosis present with neurologic symptoms.

Sarcoidosis can affect any part of the neuroaxis
Neurosarcoidosis may appear in an acute explosive fashion or as a slow chronic illness

Most common presentations

- cranial nerve palsies
- brain and spinal cord intraparenchymal lesions
- leptomeningeal infiltration
- peripheral neuropathies

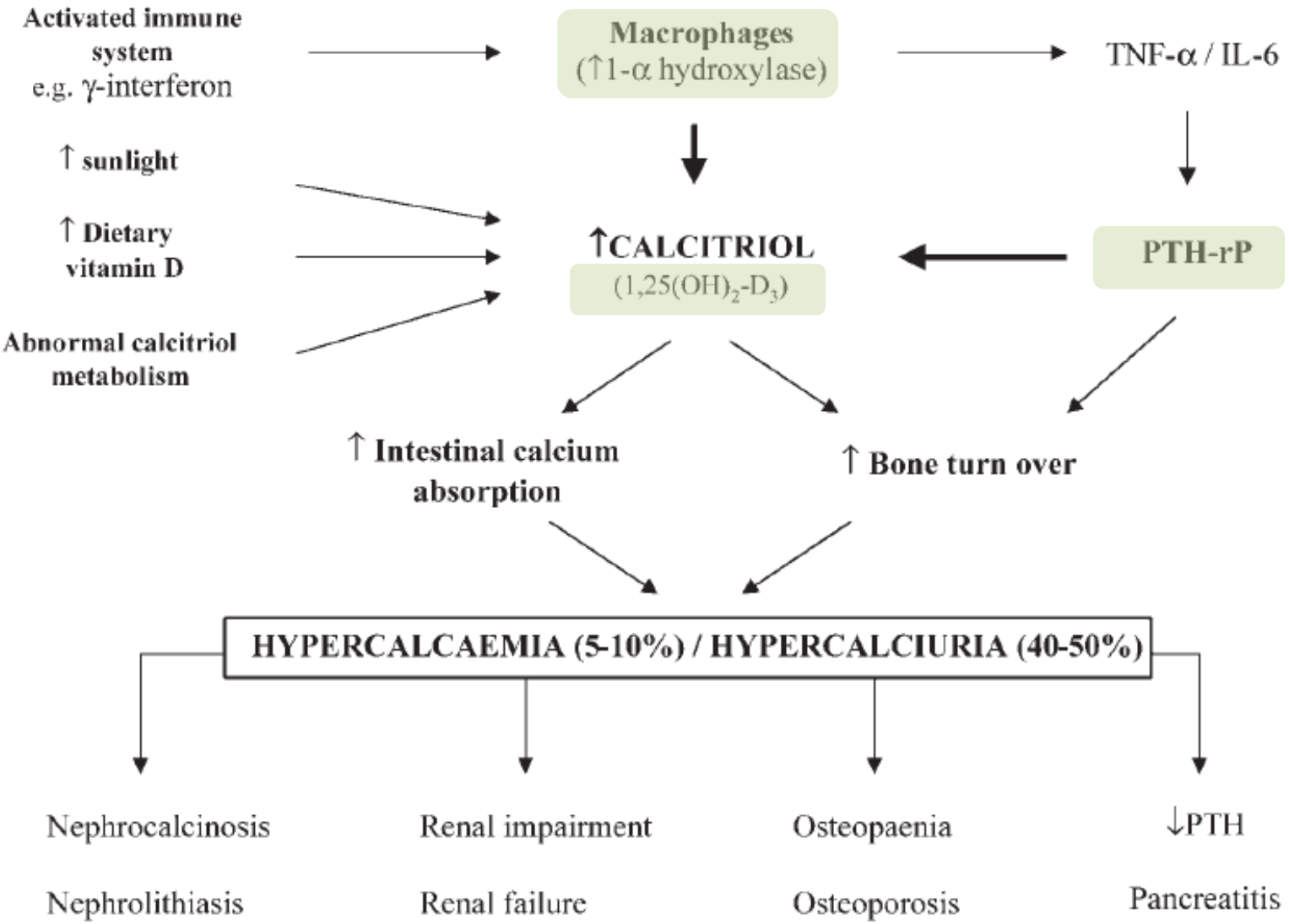


Depending on the location of the granulomas in the neuroaxis, the symptomatology reflects the neuroanatomical structures compromised. This means that potentially any neurological symptom and sign can be seen in patients with neurosarcoidosis.

- Magnetic resonance imaging (MRI), FDG-PET
- CSF analysis important in excluding TB/fungal infections – CSF ACE ↑ but not spec.
- May ultimately require a tissue biopsy to reach a definitive conclusion

Vargas DL, *et al. Semin Respir Crit Care Med 2010*

Calcium and Vitamin D in Sarcoidosis: How to Assess and Manage



Burke RR, *et al. Semin Respir Crit Care Med 2010*

Other Manifestations

Kidneys

- more commonly renal failure related to hypercalcemia and nephrocalcinosis
- rarely interstitial nephritis by granulomas

Hematological abnormalities

anemia: 4-20%; hemolytic anemia: rare

leukopenia: up to 40%, rarely severe;

bone marrow involvement: rare

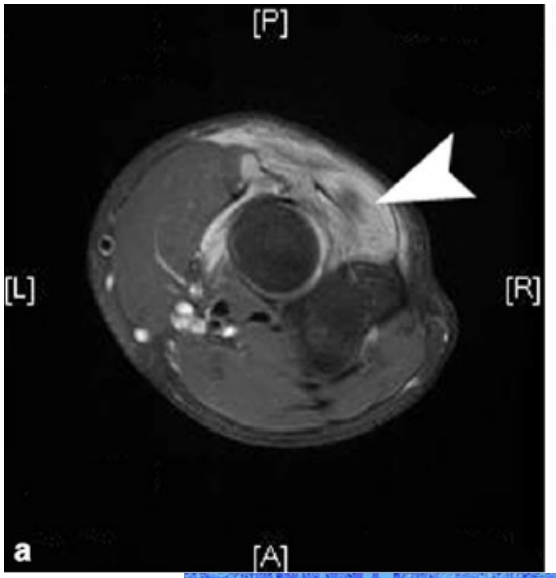
Rheumatol Int
DOI 10.1007/s00296-009-0989-1

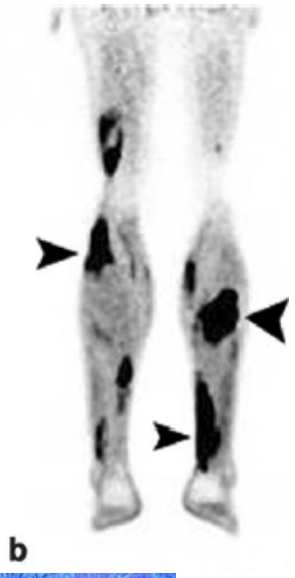
SHORT COMMUNICATION

The many faces of sarcoidosis: asymptomatic muscle mass mimicking giant-cell tumor

Likurgos Kolilekas · Christina Triantafillidou · Effrosyni Manali · Dimitra Rontogianni · Sophia Chatziioannou · Spyros Papiris

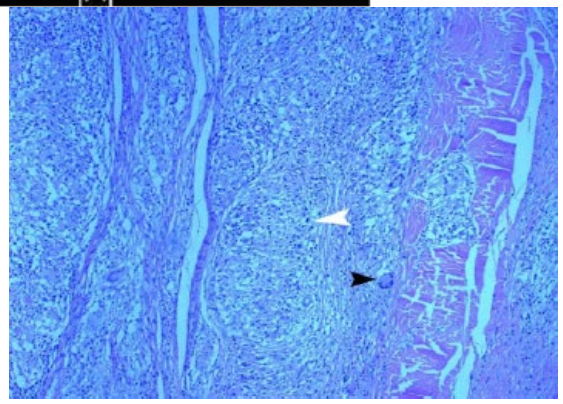
Although symptomatic sarcoid myositis is rarely encountered (<5%), muscle involvement is common in sarcoidosis and muscle biopsy in asymptomatic patients reveals granulomas in 50–80% of cases.



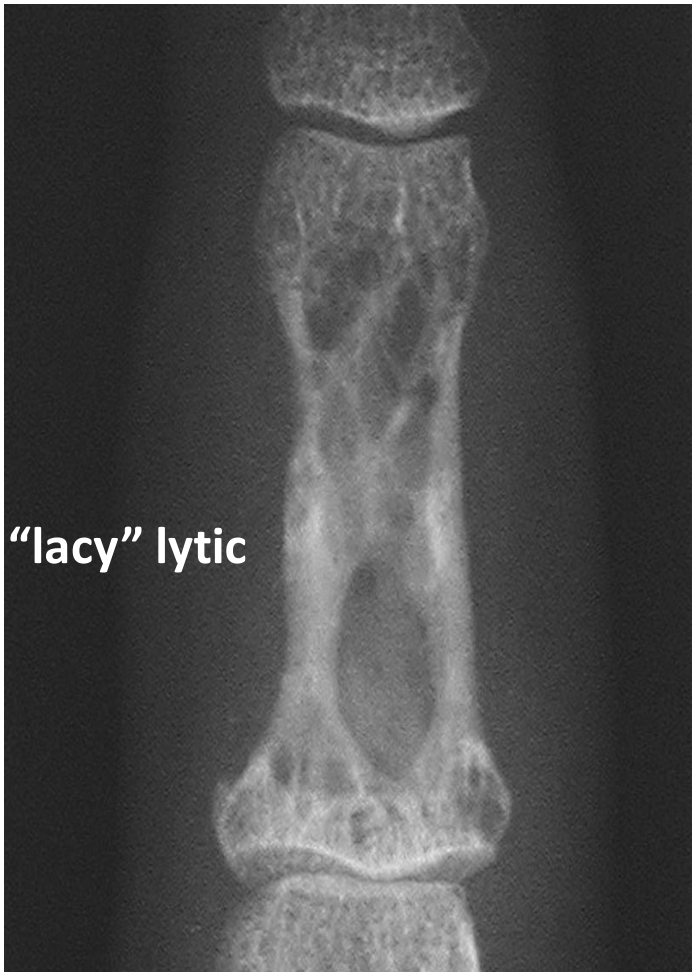


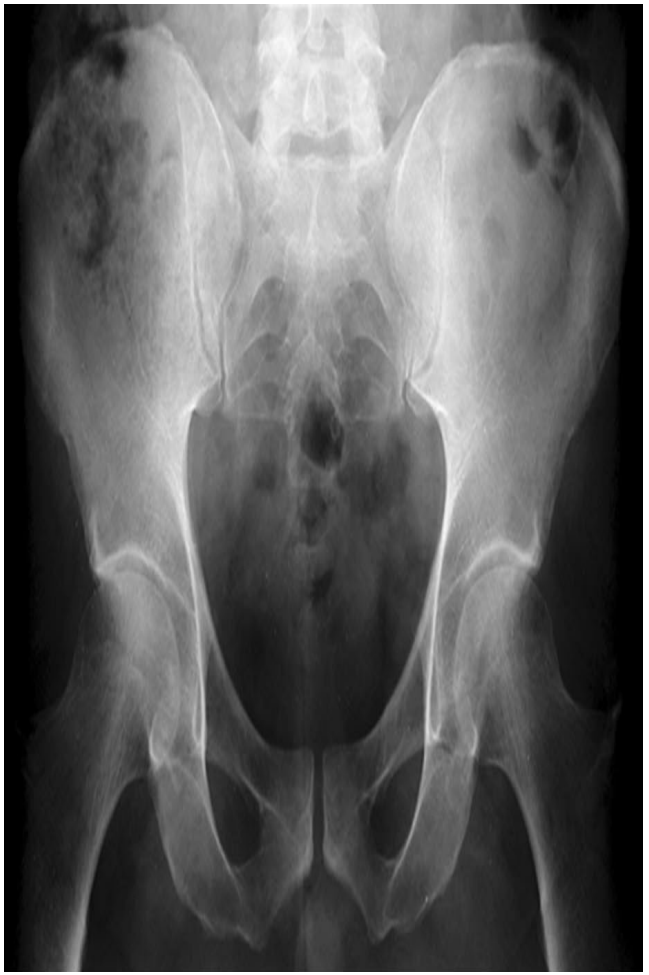
Three types of muscle sarcoidosis:

- **chronic myopathy**
- **acute myositis**
- **nodular or tumorous type**



Bone Involvement



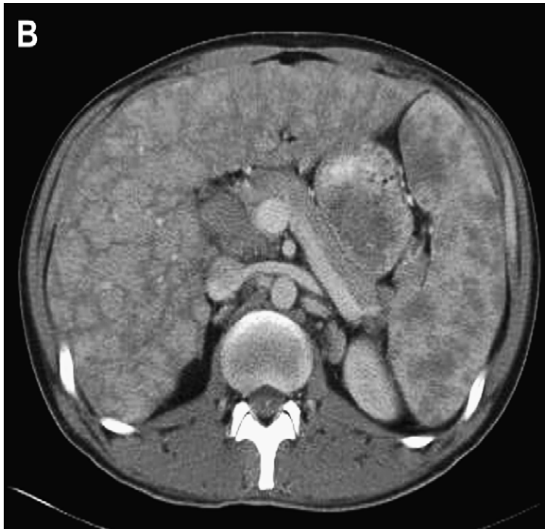


- **Small and large bones,** painfull or asymptomatic
- **Cystic, lytic or sclerotic lesions** (d.d.: Ca, TB, fungal infections)
- **Sarcoid athropathy**

Moore SE, *et al. RadioGraphics 2003*

Liver and Spleen Involvement

- 10% of all patients with sarcoidosis have elevated serum aminotransferase and alkaline phosphatase levels
- Detection of hepatic and splenic lesions on CT is described in 5% and 15% of patients.



- A cholestatic syndrome characterized by pruritus and jaundice, hepatic failure, or portal hypertension can develop (liver involvement is usually clinically silent)
- 60% of patients with hepatic manifestations have constitutional symptoms such as fever, night sweats, anorexia, and weight loss.
- Portal hypertension and cirrhosis leading to liver failure occur in only 1% of patients with sarcoidosis.

Ebert E, *et al. Am J Gastroenterol 2008*

Sarcoidosis associated fatigue

- **Alternative causes must be excluded**
  (anaemia, vitamin D deficiency, iron deficiency, thyroid dysfunction, hypercalcemia, sleep disorders, depression, DM, CHF, small fiber neuropathy or CS myopathy)

- **No established therapy**

- **If there is unacceptable loss of quality of life:**
  - Short trial of steroids (prednisone 5-10 mg/d +/- MTX/hydroxychloroquine)
  - Methylphenidate (10-30mg/bd) or modafinil (100-200mg/bd) (off label)
  - Rehabilitation programmes
  - Natural remedies (*Ginkgo biloba 120mg/d*)

Thillai M, *et al. Thorax 2021*
Baughman RP, *et al. ERJ 2021*