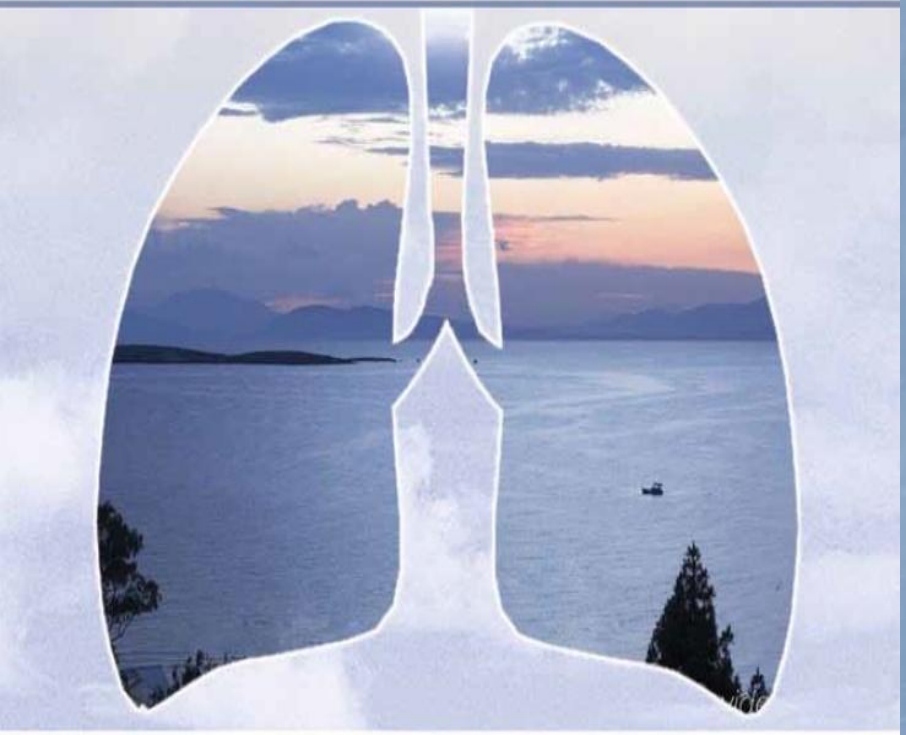
ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

14ο Εκπαιδευτικό Φροντιστήριο

ΕΚΠΑΙΔΕΥΣΗ ΣΤΗΝ ΠΝΕΥΜΟΝΟΛΟΓΙΑ

Συνδυάζοντας την τεκμηριωμένη θεωρία με την κλινική πρακτική

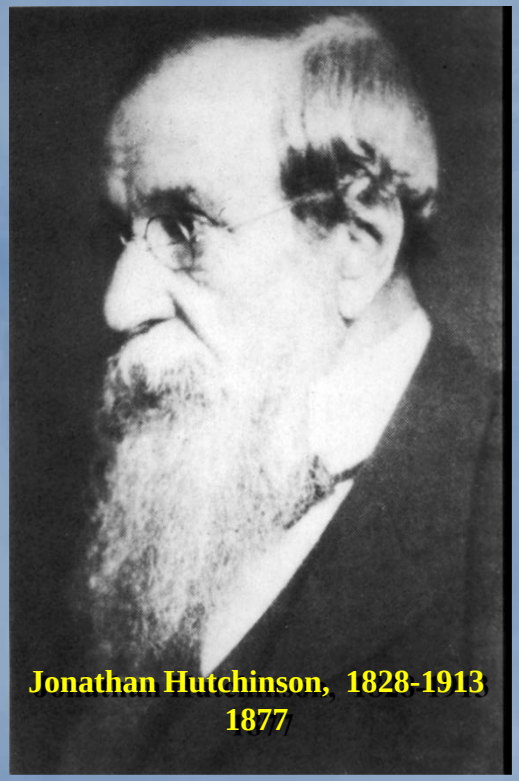


12-14 Οκτωβρίου 2018

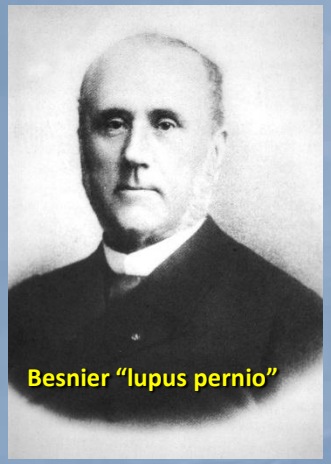
Amarilia Hotel, Αθήνα

Διάγνωση και θεραπευτική προσέγγιση Σαρκοείδωσης

Λυκούργος Κολιλέκας
Επιμελητής Α' ΕΣΥ
7η Πνευμονολογική Κλινική
ΝΝΘΑ '' Η ΣΩΤΗΡΙΑ''

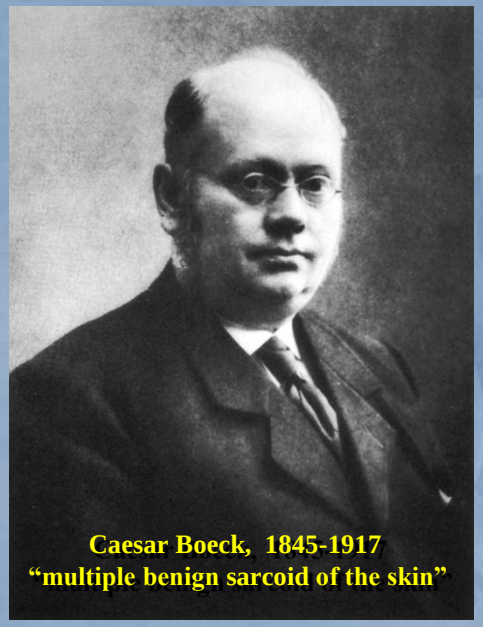


Jonathan Hutchinson, 1828-1913
1877

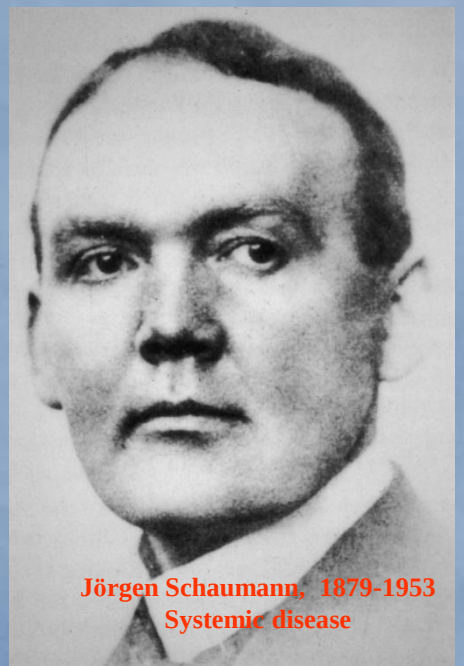


Besnier "lupus pernio"

FIGURE 1.2 The first patient with sarcoidosis described by J. Hutchinson had multiple, raised, dusty-red patches on his feet, fingers, and arms.



Caesar Boeck, 1845-1917
"multiple benign sarcoid of the skin"



Jörgen Schaumann, 1879-1953
Systemic disease

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).

It commonly affects young and middle-aged adults

Frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved.

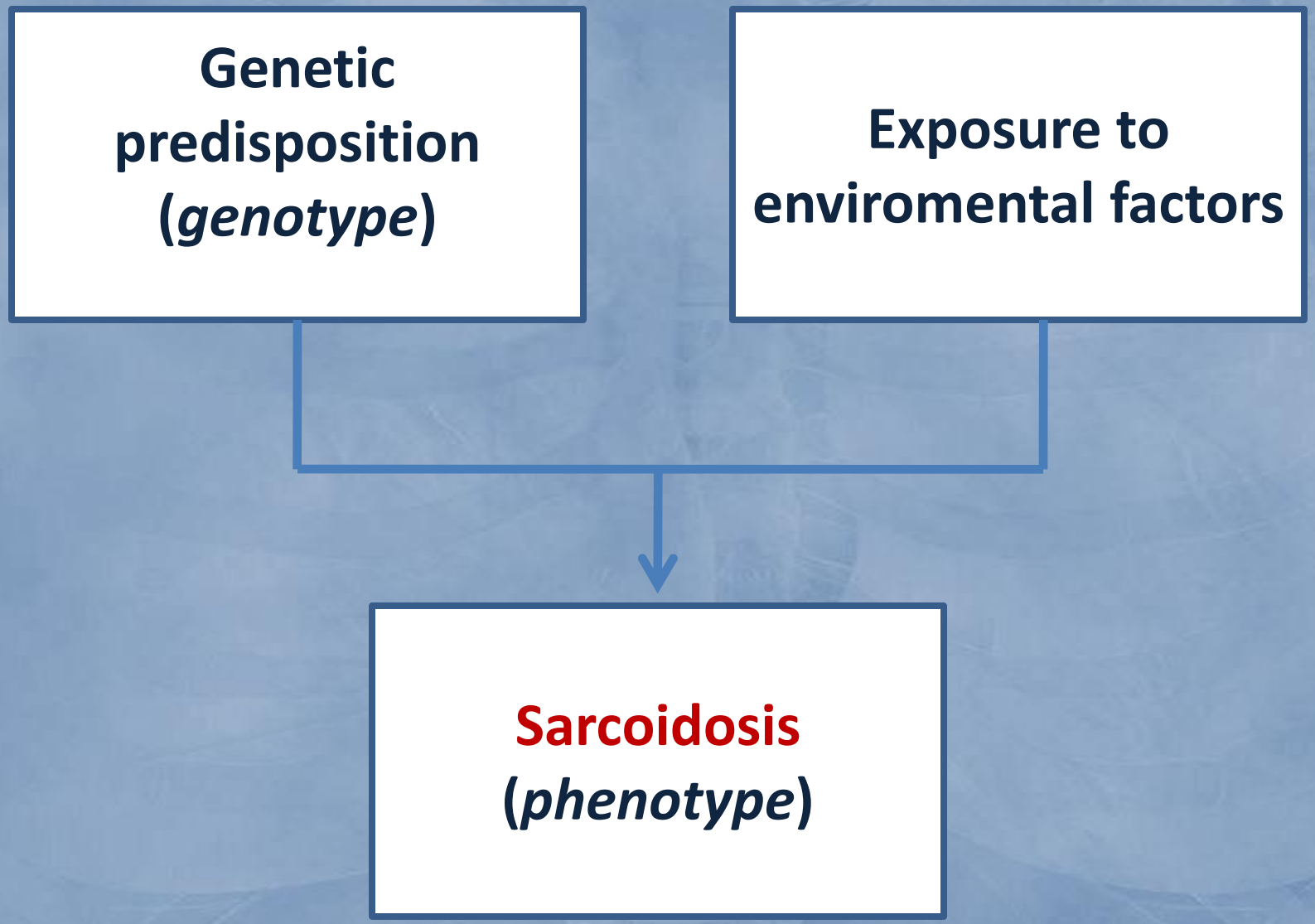
The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas.

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*

AETIOLOGY


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

GENETIC PREDISPOSITION

- There is a statistically significant increased risk for the disease among family members of sarcoidosis patients
- The disease differs in different ethnic groups.
- It is a genetically complex disease, with many genes contributing, both as risk factors but also with an influence on the disease course.
- The strongest genetic associations with sarcoidosis are found within human leukocyte antigen (HLA) - region on chromosome 6.

SUMMARY OF HLA ASSOCIATION STUDIES OF SARCOIDOSIS

HLA	Risk Alleles	Finding
HLA-A	A*1	Susceptibility
HLA-B	B*8	Susceptibility in several populations
HLA-DPB1	*0201	Not associated with sarcoidosis
HLA-DQB1	*0201	Protection, Löfgren's syndrome, mild disease in several populations
	*0602	Susceptibility/disease progression in several groups
HLA-DRB1	*0301	Acute onset/good prognosis in several groups
	*04	Protection in several populations
	*1101	Susceptibility in whites and African Americans. Stage II/III chest X-ray
HLA-DRB3	*1501	Associated with Löfgren's syndrome
	*0101	Susceptibility/disease progression in whites

Newman L, *et al. AJRCCM 2004*
Iannuzzi M, *et al. AJRCCM 2007*
Iannuzzi M, *Semin Respir Crit Care Med 2007*

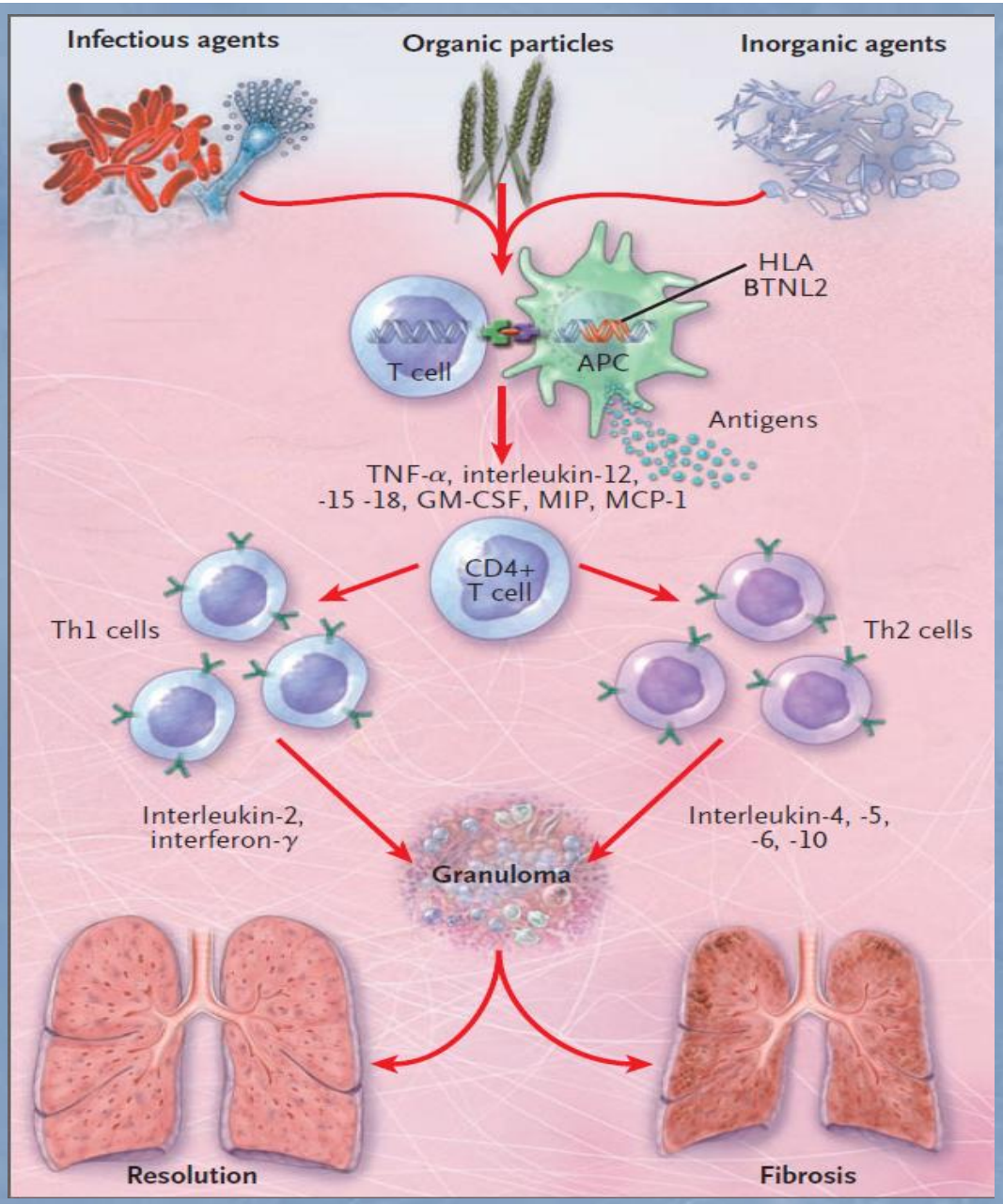
ENVIROMENTAL FACTORS

Table 2. – Potential infectious organisms or organic/inorganic substances triggering sarcoidosis

Category of trigger	Trigger
Infectious agents	*Mycobacterium tuberculosis*
	Atypical mycobacterial species
	Cell wall-deficient mycobacterial forms
	Propionibacterium acnes/granulosum
	Rickettsia helvetica
	Borrelia burgdorferi
	Mycoplasma spp.
	Viruses (*e.g.* human herpes viruses, Epstein–Barr)
Inorganic substances	Aluminium
	Zirconium
	Man-made mineral fibres
	Silica
	Silicone
	Clay
	Talc
Organic substances	Pine tree pollen
	Starch

Grutters J, *et al. Eur Respir Mon 2009*

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*

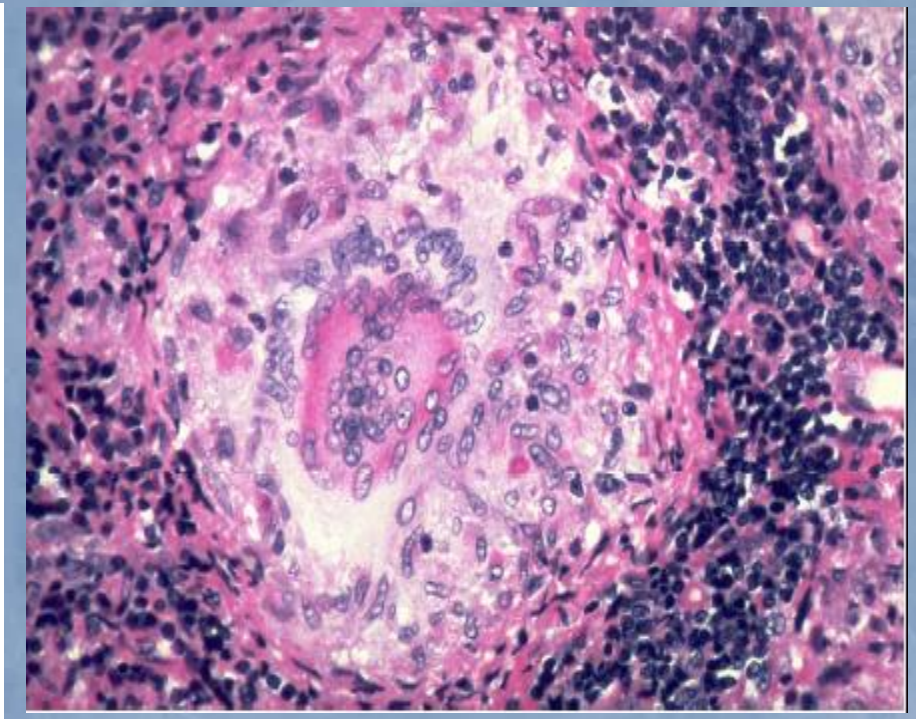
PATHOLOGOANATOMY-GRANULOMA

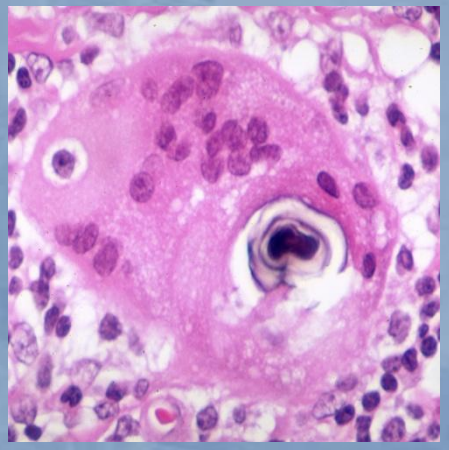
- The sarcoid granuloma usually consists of a compact (organized) collection of mononuclear phagocytes **(macrophages and epithelioid cells**).

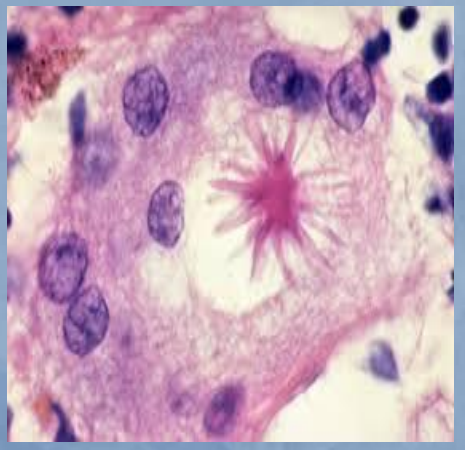
- **Typically, there is no necrosis within the sarcoid granuloma**; however, on occasion, there is a small to moderate amount of necrosis.

- Usually, 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** including asteroid bodies, Schaumann's bodies, birefringent crystals, and Hamazaki–Wesenberg bodies; however these inclusions are **not specific or diagnostic of sarcoidosis.**







ΣΑΡΚΟΕΙΔΩΣΗ

Συστηματική νόσος

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

General practitioner
Fever, anorexia, weight loss, lymphadenopathy, parotid enlargement, acute arthritis, nasal stuffiness, hoarseness

Dermatologist
Erythema nodosum
Lupus pernio
Maculopapular rash, scars, keloids, nodules

Cardiologist
Dyspnea, cardiac failure, heart block
Arrhythmias, abnormal ECG
Sudden death

Chest physician
Dyspnea, cough, wheezing, abnormal chest X ray, cor pulmonale, lung function impairment

Radiologist
Abnormal chest X-ray, bilateral hilar lymphadenopathy, interstitial fibrosis, bone cysts

Rheumatologist
Arthritis
Bone cysts

Nephrologist
Renal failure

Urologist
Hypercalciuria

Ophthalmologist
Iritis, choroiditis, keratoconjunctivitis, glaucoma, cataract, enlarged lacrimal glands, dry eye

Neurologist
Cranial nerve palsies, papilledema, meningitis, myopathy, peripheral neuropathy, space occupying lesions

Endocrinologist
Diabetes insipidus
Hypercalcemia
Hyperthyroidism

Hepatologist
Liver granuloma
Portal hypertension
Abnormal liver function tests

Hematologist
Anemia
Leucopenia
Thrombocytopenia
Hypersplenism

Otorhinolaryngologist
Parotid enlargement
Hoarseness
Nasal stuffiness

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

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

In this regard, the management of patients with sarcoidosis requires a **multidisciplinary approach**

ΣΑΡΚΟΕΙΔΩΣΗ

Συχνό πρόβλημα για το πνευμονολόγο

- **Η πλέον συνήθης διάχυτη πνευμονοπάθεια**
- **Ο πνεύμονας και οι λεμφαδένες νοσούν σχεδόν πάντα**
- **Η φτωχή πρόγνωση που παρατηρείται σε μειοψηφία ασθενών οφείλεται πρωταρχικά στη προοδευτικά εξελισσόμενη πορεία της πνευμονικής προσβολής, στην συμμετοχή καρδιάς και ΚΝΣ**

CLINICAL ASPECTS

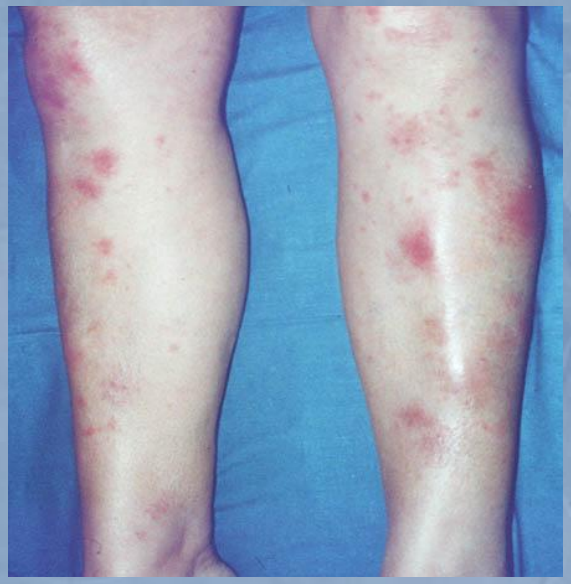
- Presentation depends on the extent and severity of the organ involved.
- Approximately 5% of cases are asymptomatic and incidentally detected by CXR.
- Systemic symptoms occur in 45% of cases such as:
  - Fever
  - Anorexia
  - Fatigue
  - Night sweats
  - Weight loss
- Dyspnea on exertion, cough,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

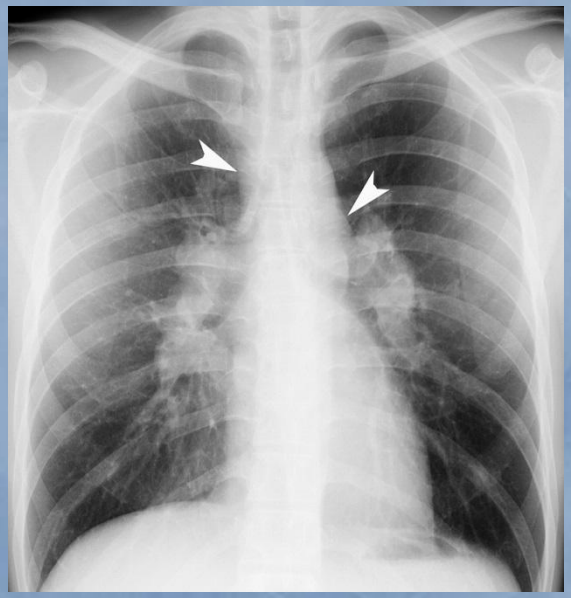
Löfgren's syndrome

An **acute presentation** consisting of:

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

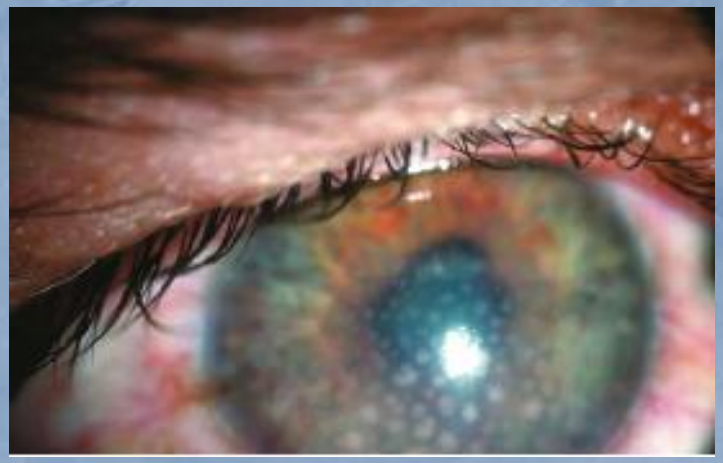
- Occurs in 9 to 34% of patients.

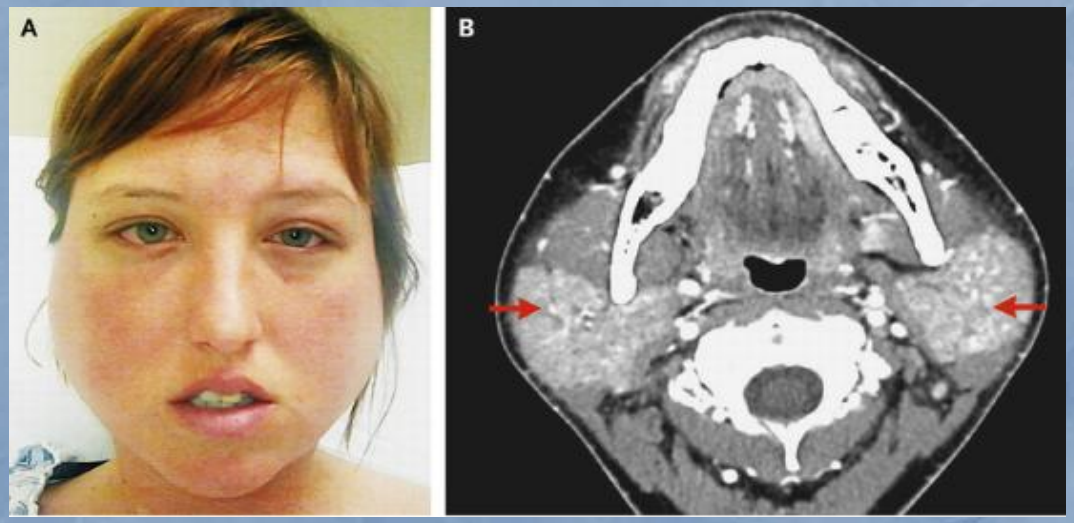


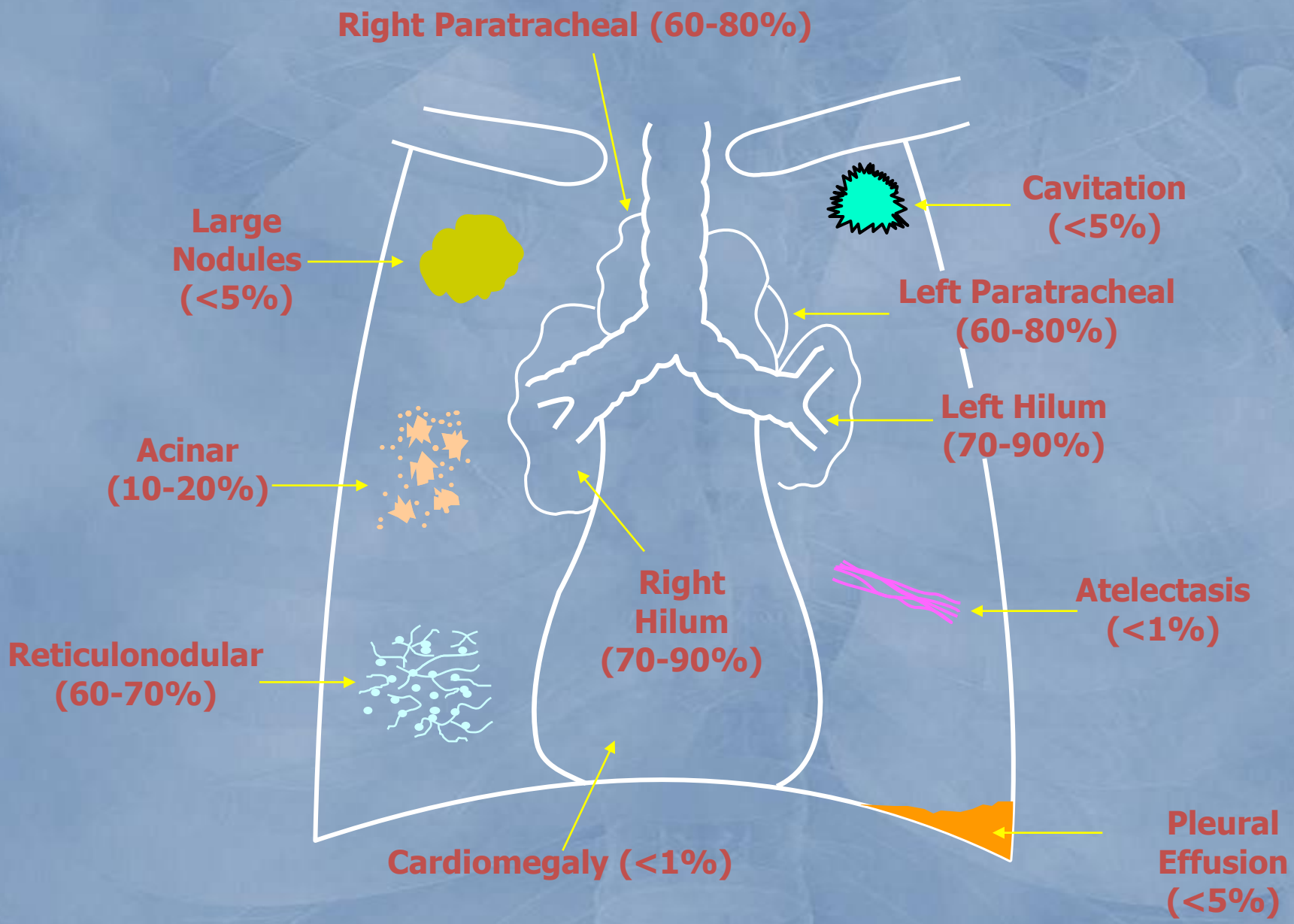


Heerford's syndrome

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

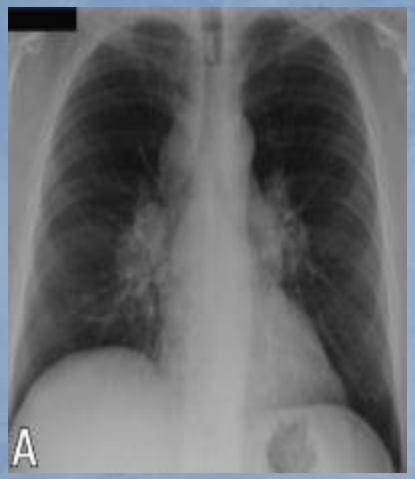


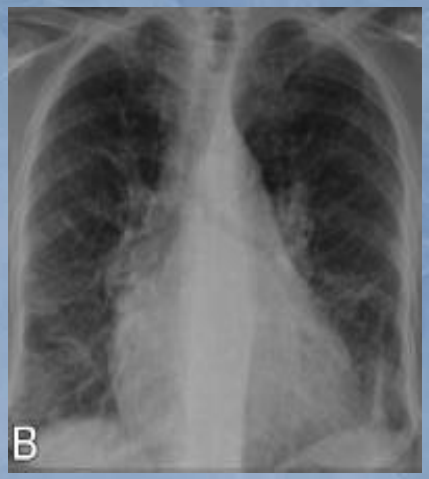


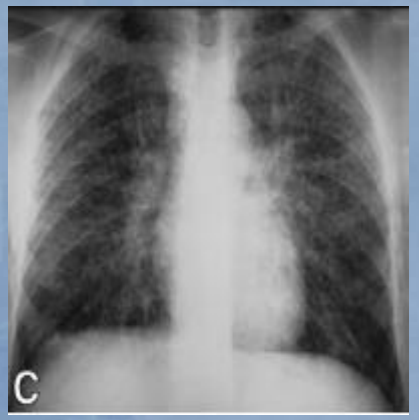

Right Paratracheal (60-80%)
Cavitation (<5%)
Large Nodules (<5%)
Left Paratracheal (60-80%)
Left Hilum (70-90%)
Acinar (10-20%)
Right Hilum (70-90%)
Atelectasis (<1%)
Reticulonodular (60-70%)
Cardiomegaly (<1%)
Pleural Effusion (<5%)

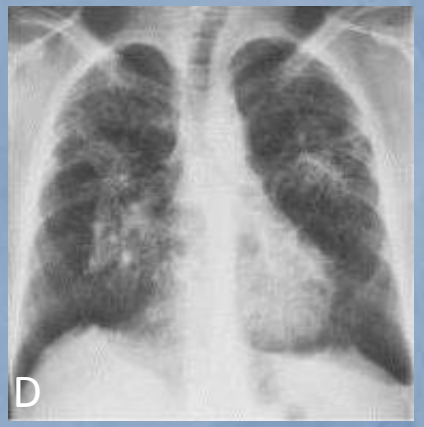
Staging of Sarcoidosis on the Basis of Chest Radiographs

STAGE 0	No abnormalities	5%–10%
STAGE 1	Lymphadenopathy (fig. A)	50%
STAGE 2	Lymphadenopathy + pulmonary infiltration (fig. B)	25%–30%
STAGE 3	Pulmonary infiltration (fig. C)	10%–12%
STAGE 4	Fibrosis	5% (up to 25% during the course of the disease)





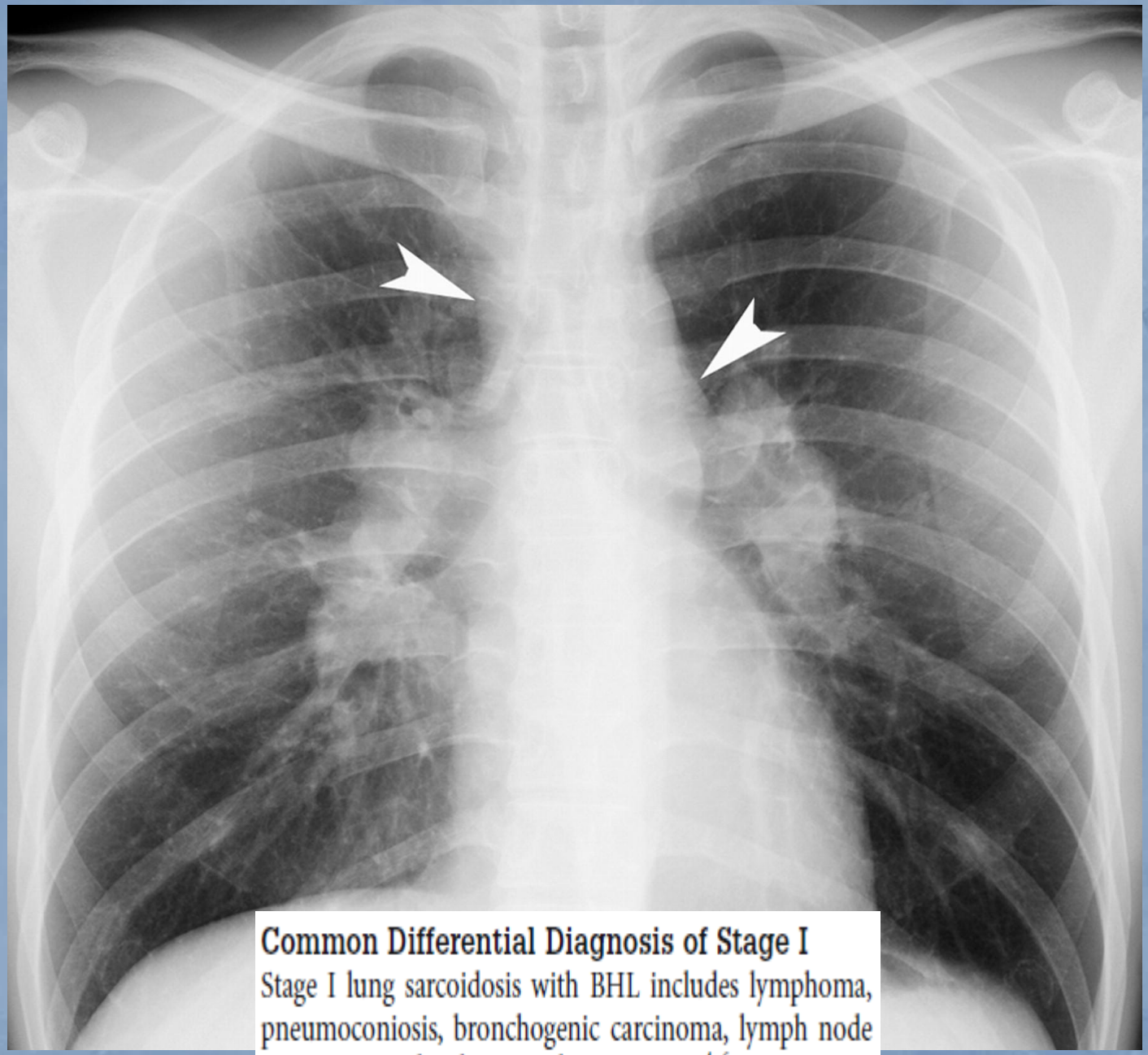




Radiographic stage	Chest X-ray	Frequency (%)	Resolution (%)
0	Normal	5–15	
I	BHL	25–65	60–90
II	BHL and pulmonary infiltrates	20–40	40–70
III	Pulmonary infiltrates without BHL	10–15	10–20
IV	Advanced pulmonary fibrosis	5	0

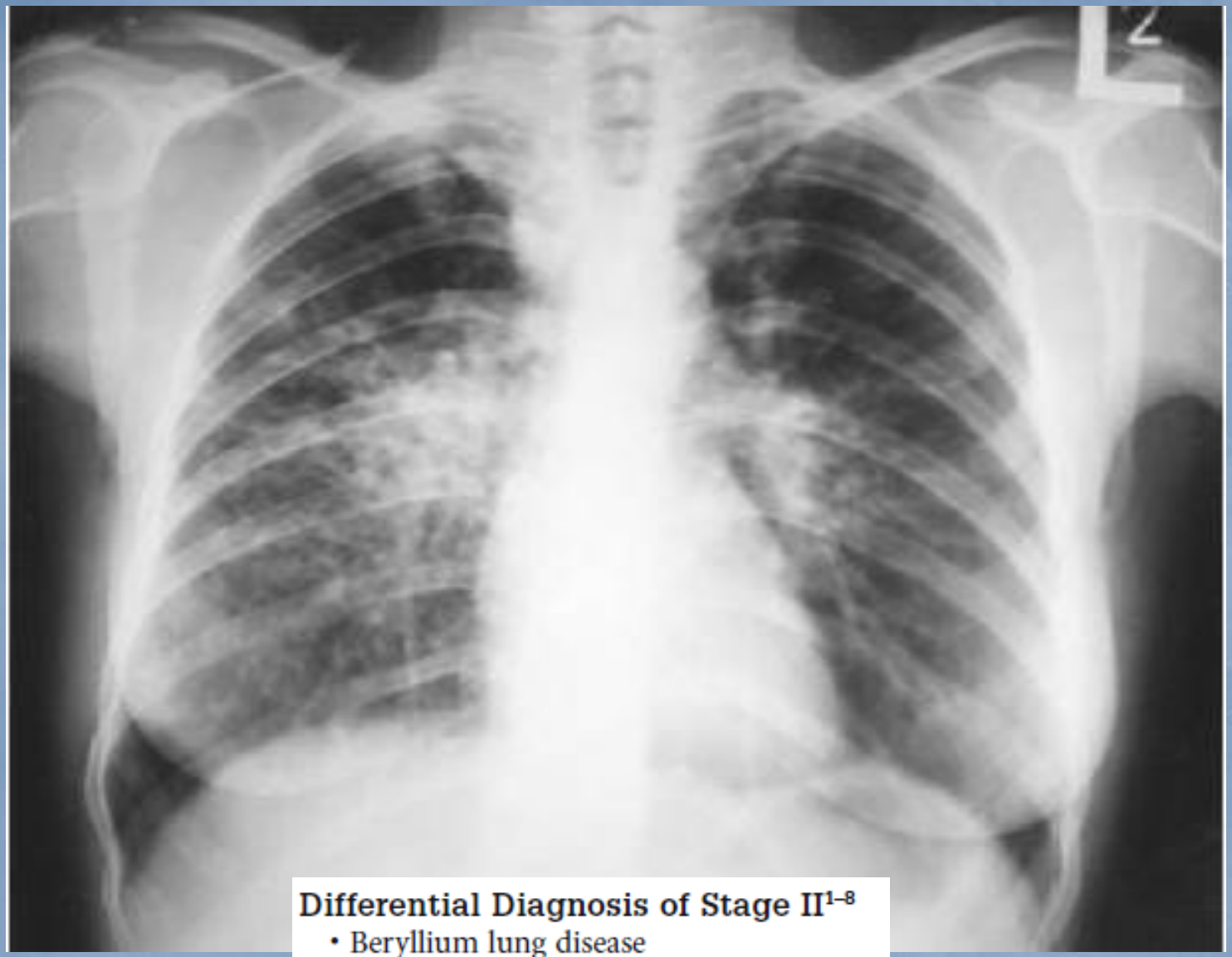
Prognostic information

Great interobserver variability



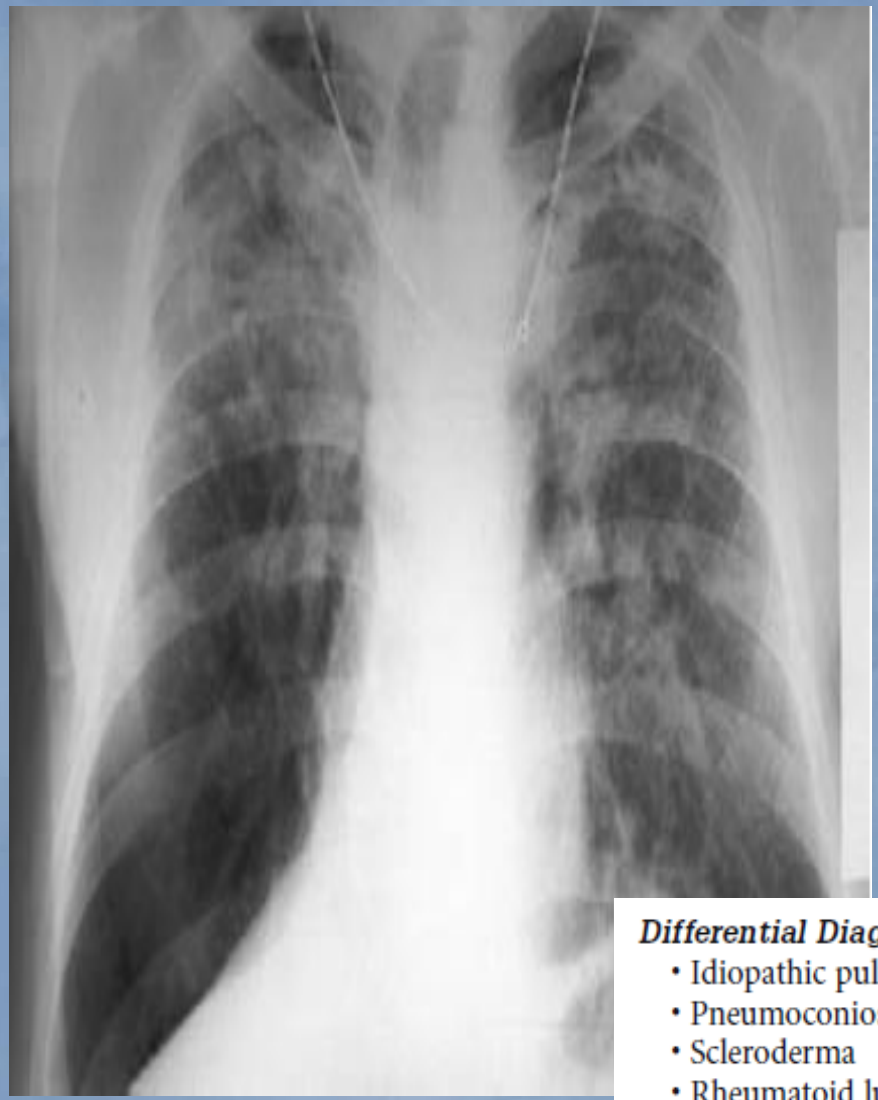
Common Differential Diagnosis of Stage I

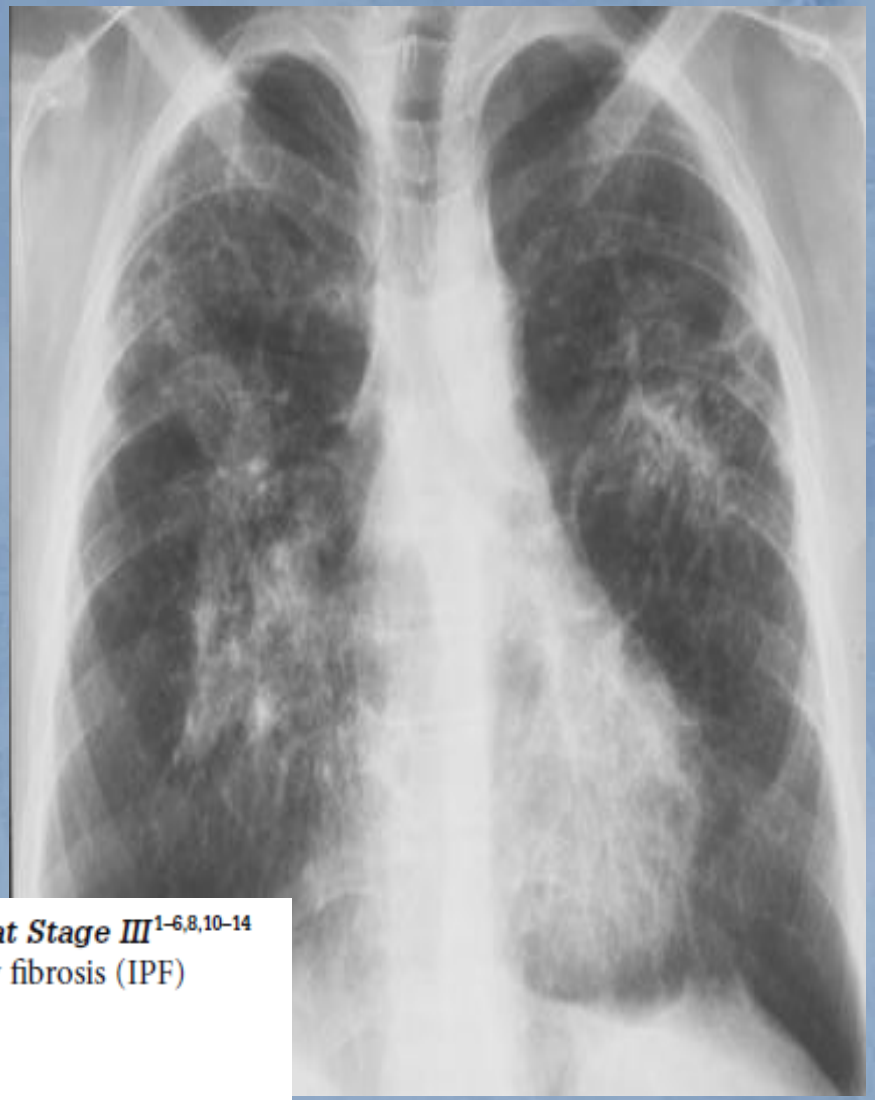
Stage I lung sarcoidosis with BHL includes lymphoma, pneumoconiosis, bronchogenic carcinoma, lymph node metastasis, and pulmonary hypertension.[4–6]



Differential Diagnosis of Stage II[1–8]

- Beryllium lung disease
- Silicosis
- Tuberculosis
- Lymphangitic carcinoma
- Coccidioidomycosis
- Brucellosis





Differential Diagnosis at Stage III[1–6,8,10–14]

- Idiopathic pulmonary fibrosis (IPF)
- Pneumoconiosis
- Scleroderma
- Rheumatoid lung
- Lupus erythematosus, lung involvement

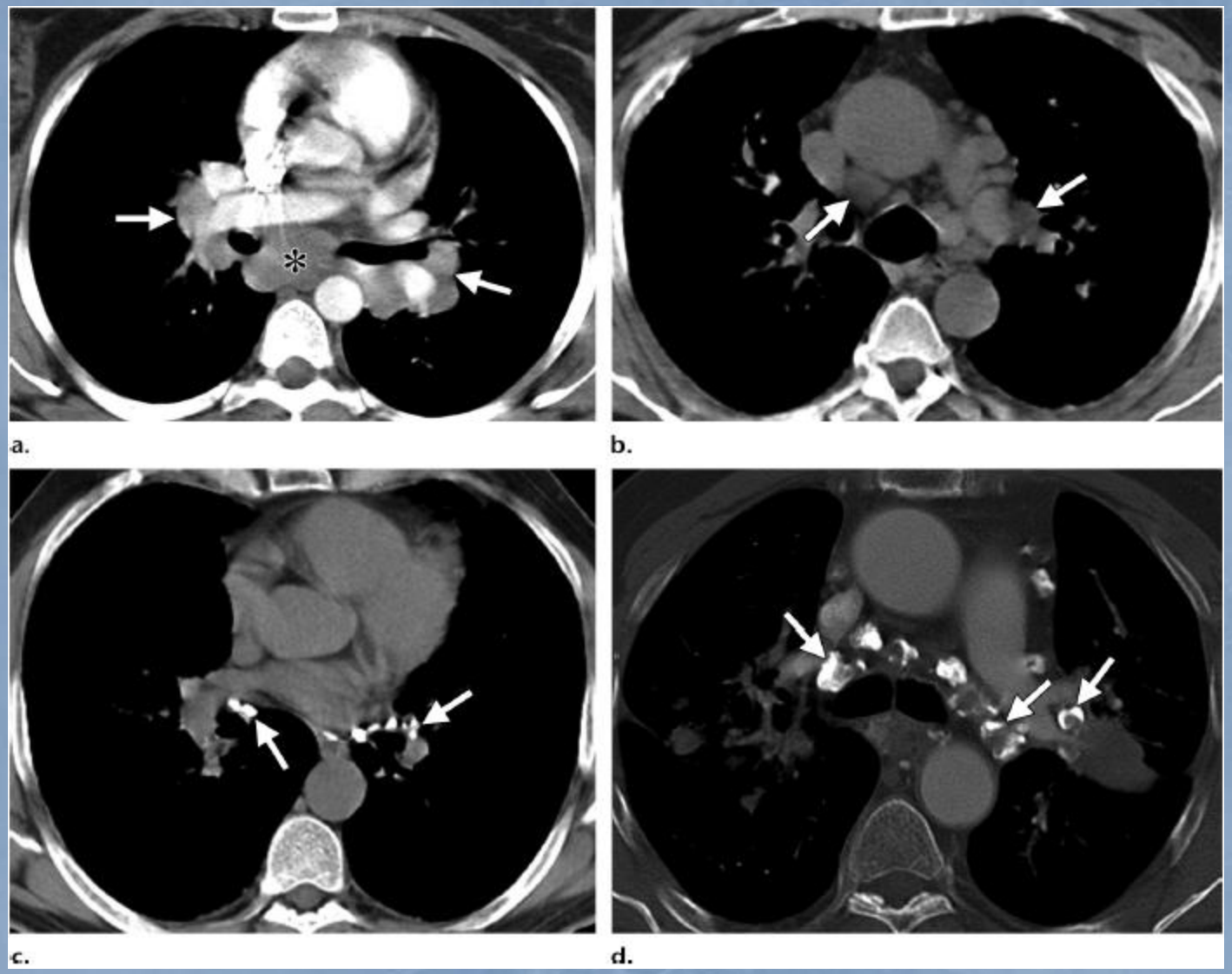
- Extrinsic alveolitis
- Lymphangitic carcinomatosis
- Tuberculosis (upper lobe localization)
- Eosinophilic granuloma
- Hemosiderosis
- Drug reaction

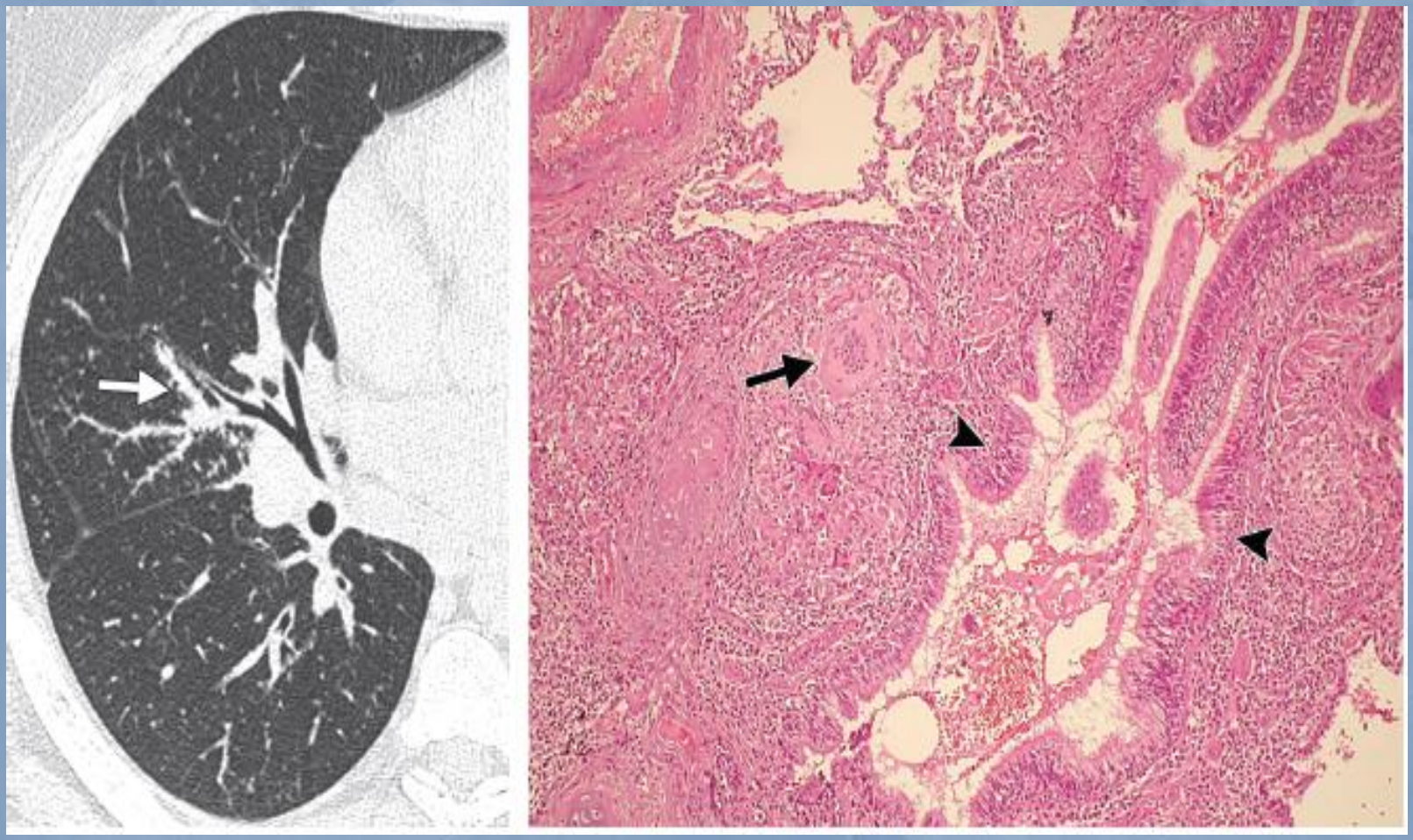
CHEST HRCT FINDINGS

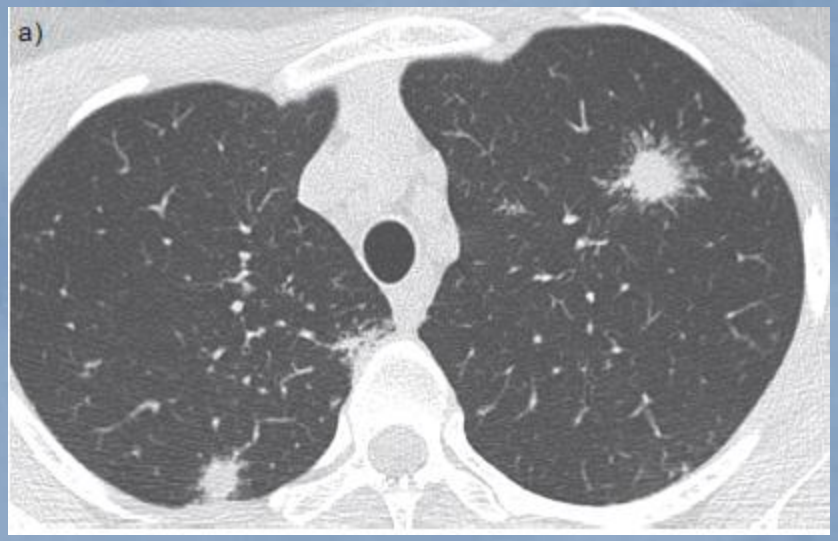
Table 1
Typical and Atypical Features of Pulmonary Sarcoidosis at High-Resolution CT

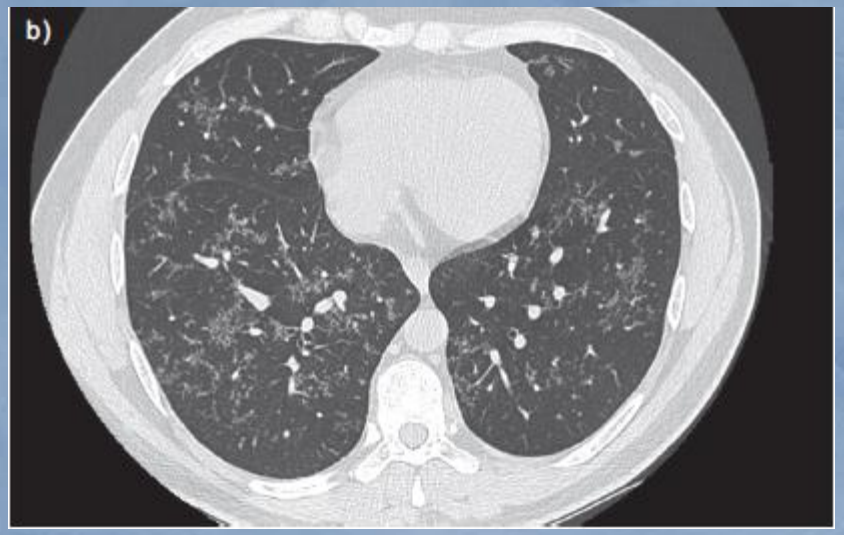
Typical features
Lymphadenopathy: hilar, mediastinal (right paratracheal), bilateral, symmetric, and well defined
Nodules: micronodules (2–4 mm in diameter; well defined, bilateral); macronodules (≥5 mm in diameter, coalescing)
Lymphangitic spread: peribronchovascular, subpleural, interlobular septal
Fibrotic changes: reticular opacities, architectural distortion, traction bronchiectasis, bronchiolectasis, volume loss
Bilateral perihilar opacities
Predominant upper- and middle-zone locations of parenchymal abnormalities
Atypical features
Lymphadenopathy: unilateral, isolated, anterior and posterior mediastinal
Airspace consolidation: masslike opacities, conglomerate masses, solitary pulmonary nodules, confluent alveolar opacities (alveolar sarcoid pattern)
Ground-glass opacities
Linear opacities: interlobular septal thickening, intralobular linear opacities
Fibrocystic changes: cysts, bullae, blebs, emphysema, honeycomb-like opacities with upper- and middle-zone predominance
Miliary opacities
Airway involvement: mosaic attenuation pattern, tracheobronchial abnormalities, atelectasis
Pleural disease: effusion, chylothorax, hemothorax, pneumothorax, pleural thickening, calcification
Pleural plaquelike opacities
Mycetoma, aspergilloma

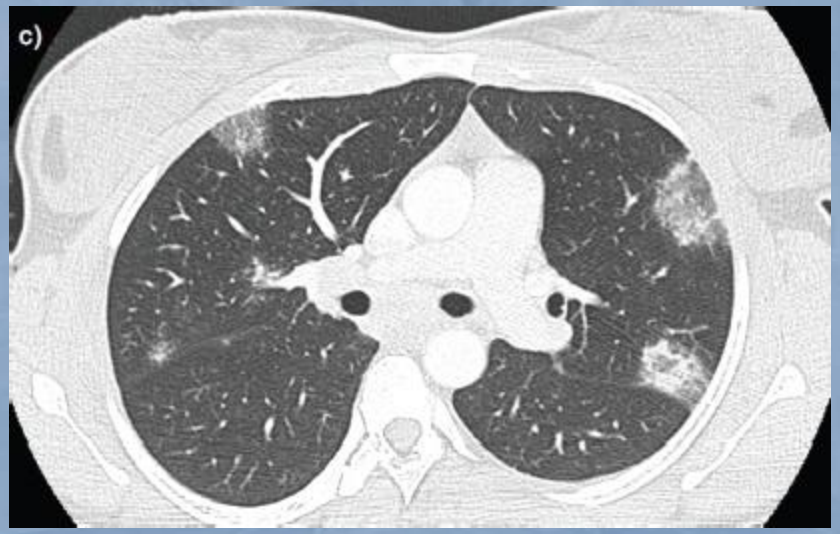
Radiographics 2010

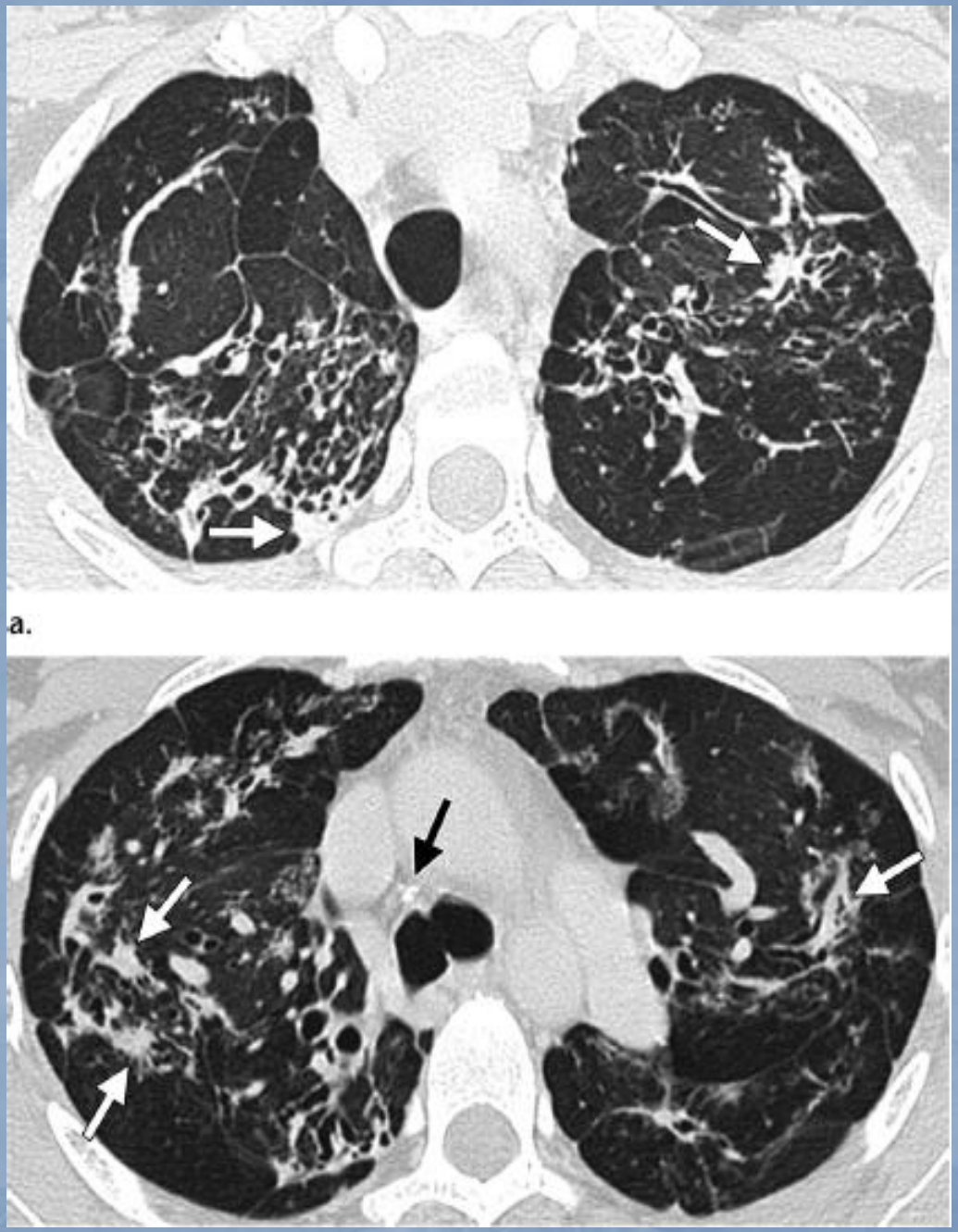

a.
b.
c.
d.



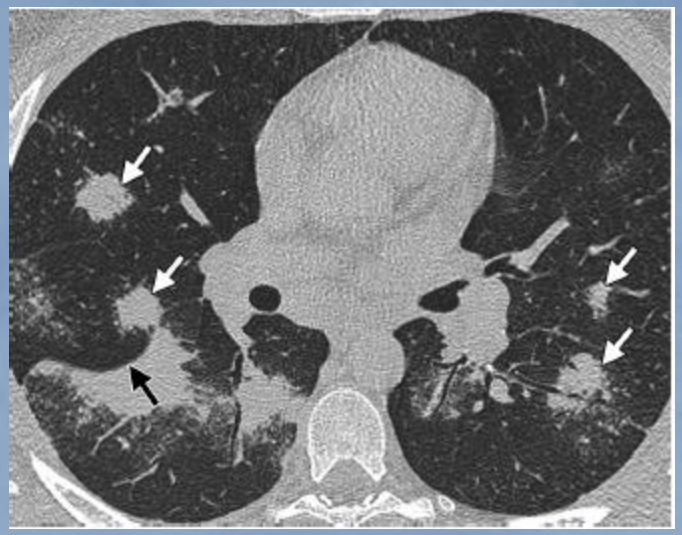

a)

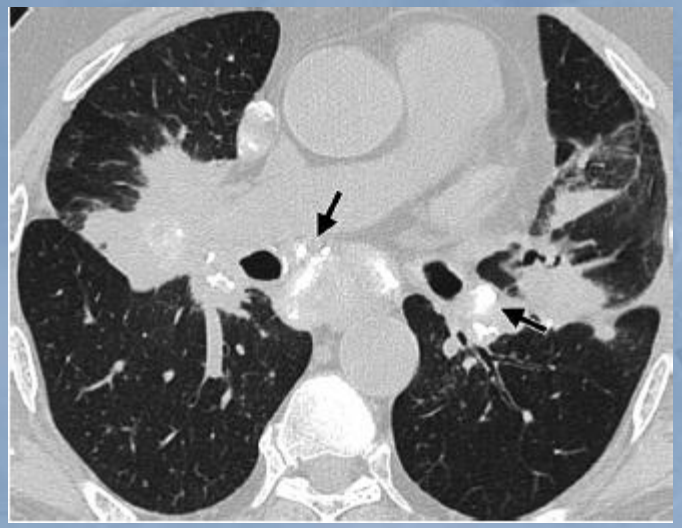

b)

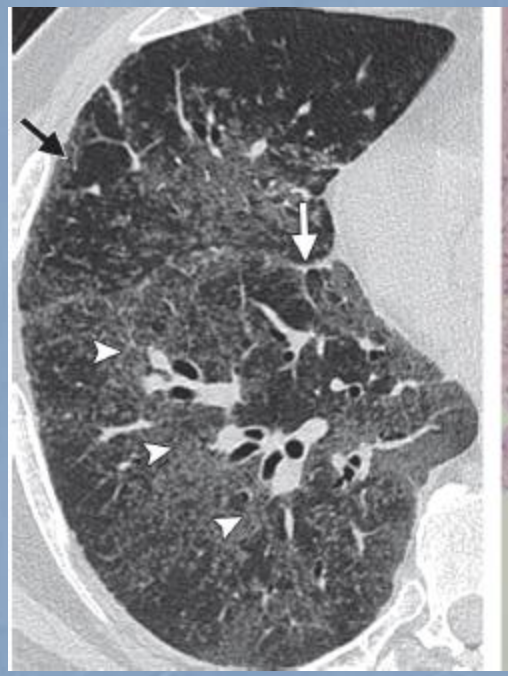

c)

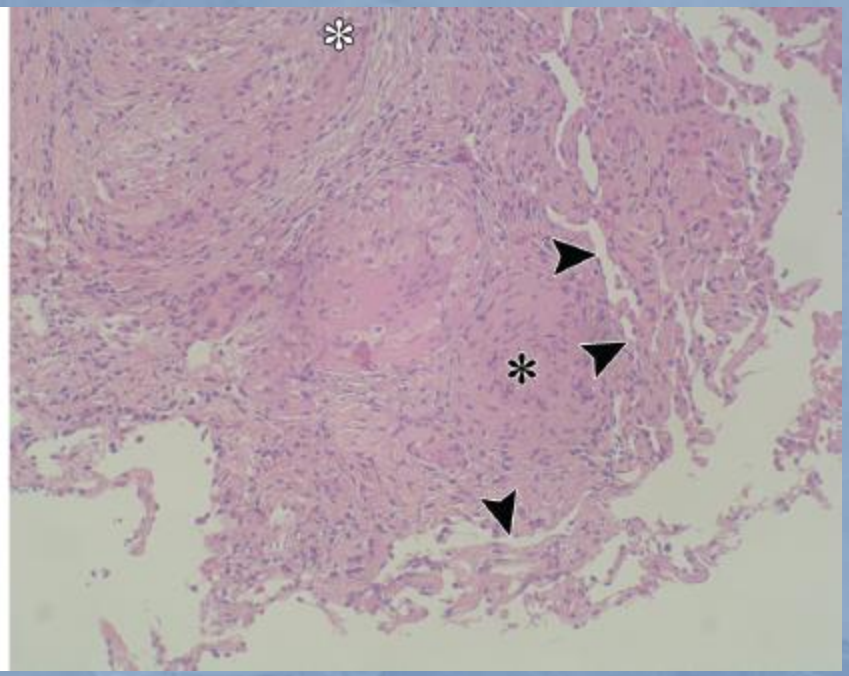


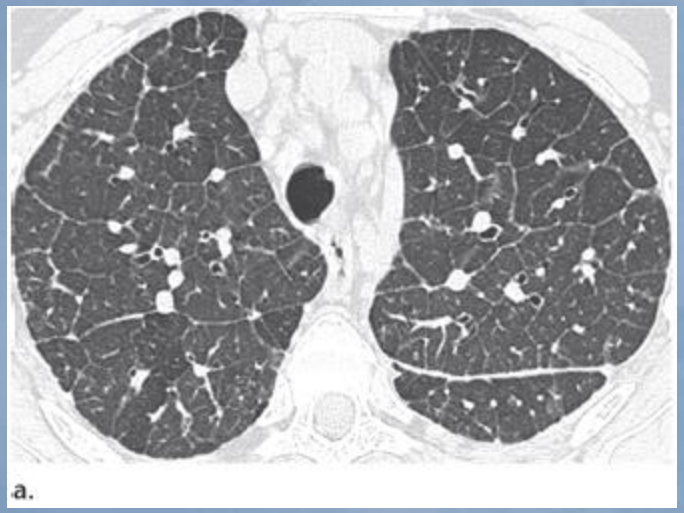
a.

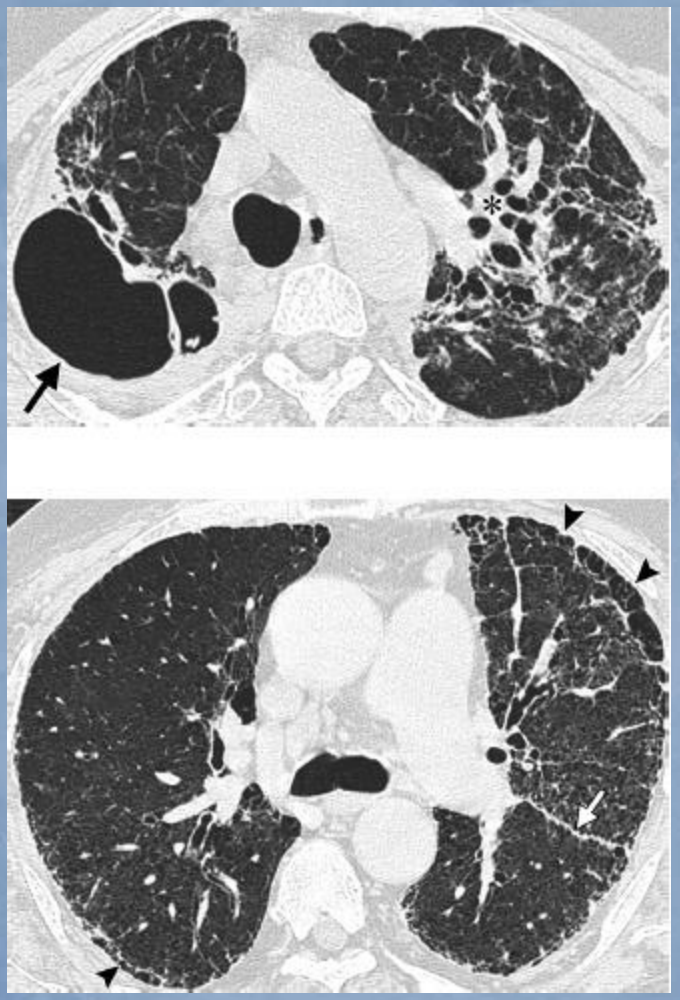









a.



Clinical Radiology 65 (2010) 642–650

Contents lists available at ScienceDirect

Clinical Radiology

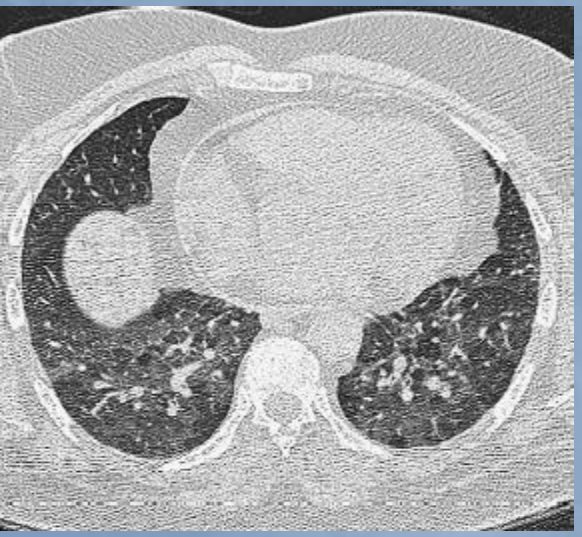
journal homepage: www.elsevierhealth.com/journals/crad

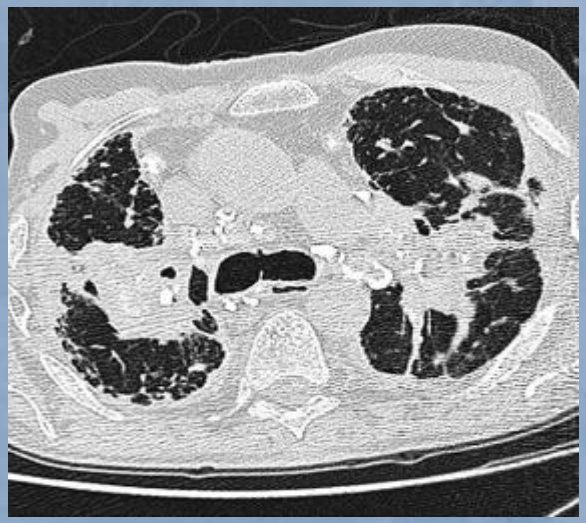
Pictorial Review

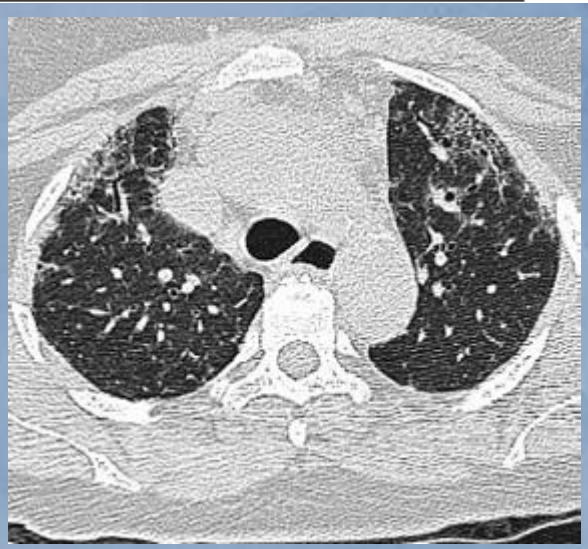
Pulmonary sarcoidosis: the 'Great Pretender'

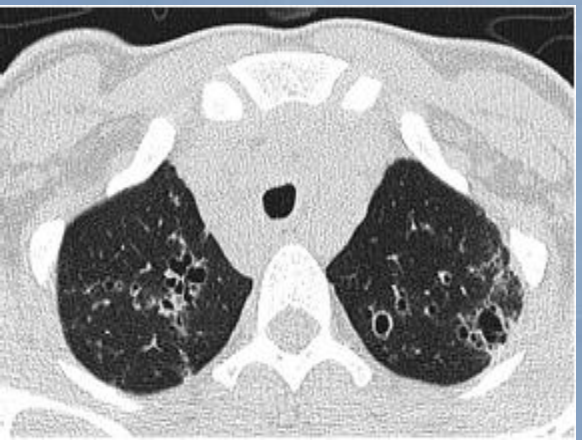
K.E. Hawtin [a,*], M.E. Roddie [a], F.A. Mauri [b], S.J. Copley [a]

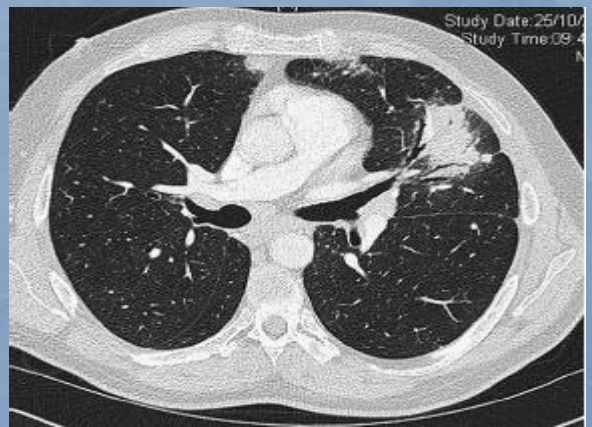
[a] Department of Radiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
[b] Department of Histopathology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK











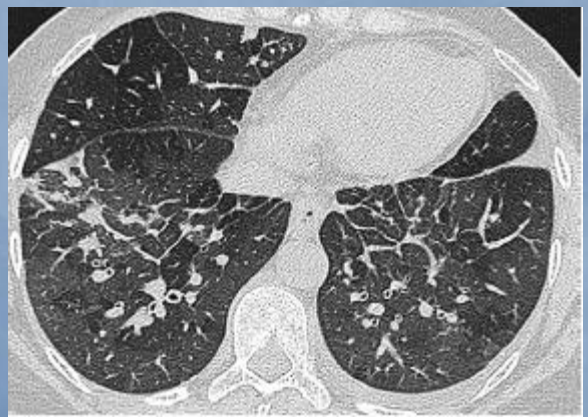


TABLE 3 Reversibility of sarcoidosis features observed on computed tomography (spontaneously or under therapy)

Reversible features	Irreversible features	Variable reversibility
Micronodules	Architectural distortion	Consolidation[#]
Nodules	Bronchial distortion	Ground-glass opacification[¶]
Peribronchovascular thickening	Honeycombing	Linear opacities[+]
	Bullae	

[#]: consolidations are wholly or partially reversible in most cases, in particular those with surrounding micronodules, representing coalescent granulomas. [¶]: a coarse texture or concomitant traction bronchiectasis increases the likelihood of underlying fibrosis. [+]: irregular distorted lines are more likely to be fibrotic.

Nunes H *et al. ERJ 2012*

ΣΑΡΚΟΕΙΔΩΣΗ
Αξονική τομογραφία

Είναι κοινή κακή πρακτική η κατάχρηση της ΑΤ τόσο στην αρχική εκτίμηση της νόσου όσο και κατά τη διάρκεια της παρακολούθησης

1. Άτυπα κλινικά ή ακτινολογικά ευρήματα
2. Ανίχνευση νόσου επί εδάφους φυσιολογικής Ro θώρακος
3. Ανίχνευση επιπλοκών (βρογχιεκτασίες, ίνωση, εμφύσημα, ασπεργίλλωμα)
4. Λοίμωξη ή νεοπλασία

BRONCHOSCOPY

- Bronchoscopy
  (TBLB/ TBNA/ EBB/ BAL)

  EBB: diagnostic 40-60%

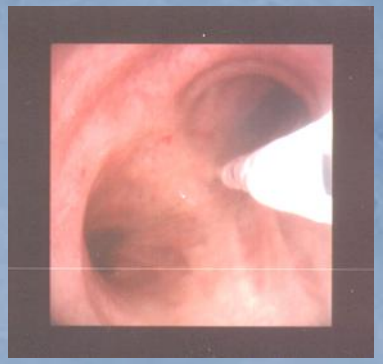
  TBLB: diagnostic ~70% (40-78%)

  TBNA: diagnostic 62%

Meta analysis, 15 studies

- Endosonography
  (EBUS- TBNA and EUS-FNA)

  EBUS-TBNA: diagnostic 79%



Agarwal R, *et al. Respir Med 2012*

ORIGINAL CONTRIBUTION

2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

- RCT: (TBLB + EBB vs. EBUS/EUS)

  + BAL was additionally performed in all patients

- Suspected sarcoidosis stage I/II
  need for tissue verification

- 14 hospitals across Europe (2009-2011)

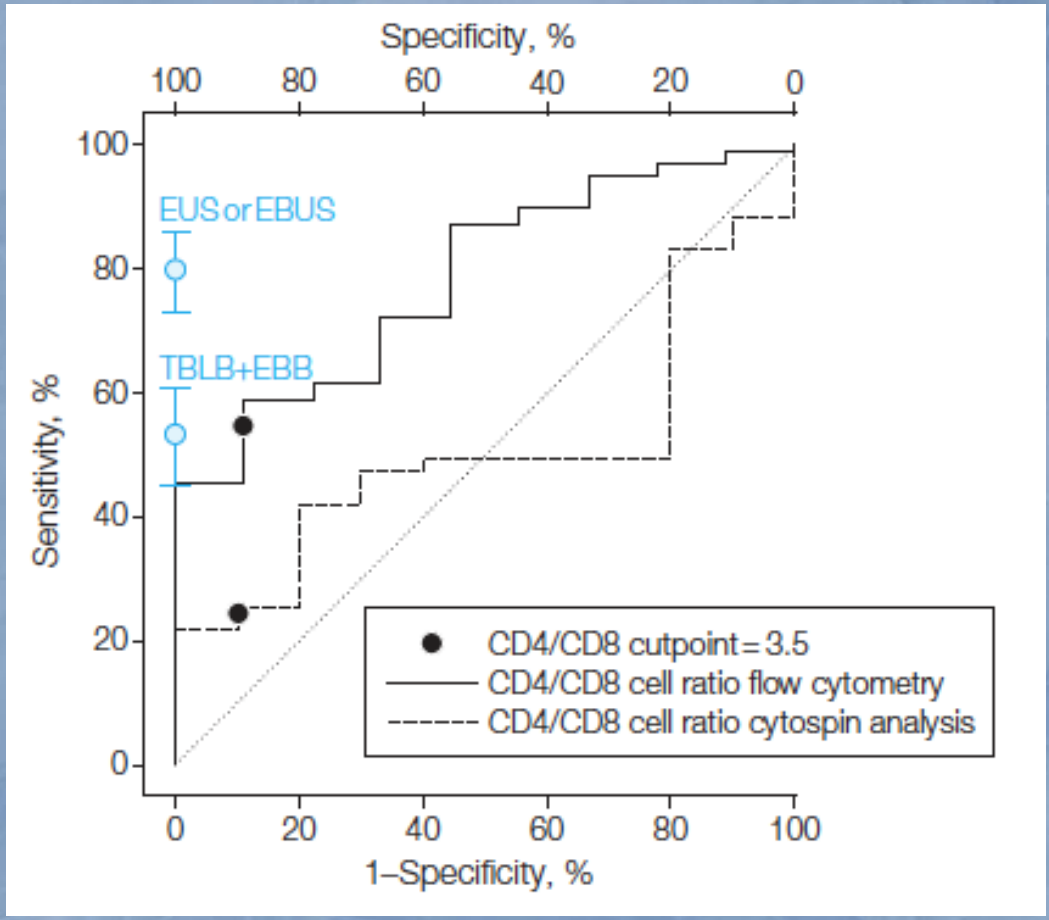
2013

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%**	



ORIGINAL CONTRIBUTION

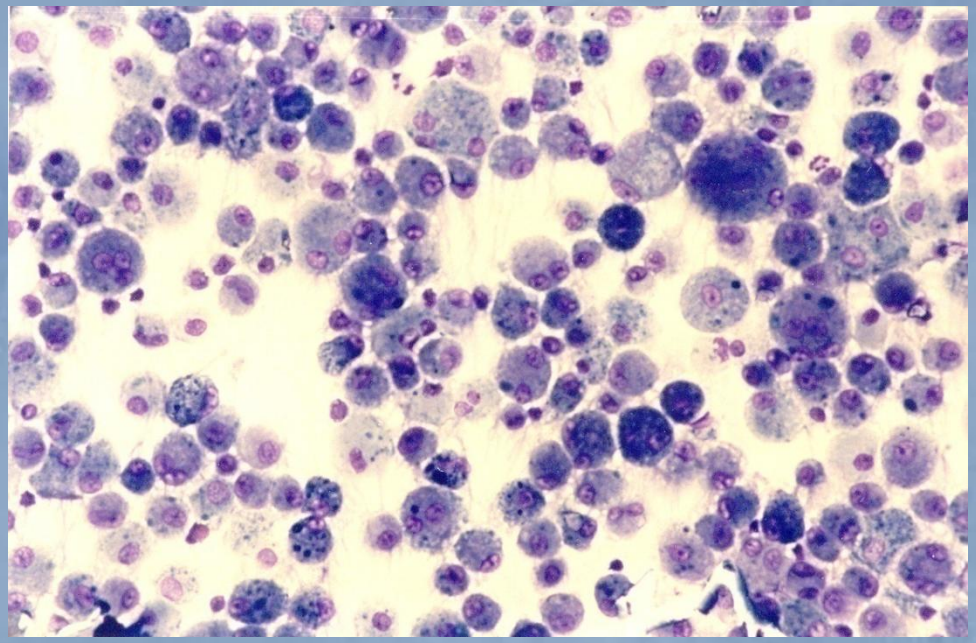
2013

Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

- Endosonography has higher diagnostic yield (**80% vs 53%**) in comparison with bronchoscopy (TBLB+EBB) for patients with stage I/II sarcoidosis
- Serious adverse events related to endosonography and bronchoscopy were rare
- The value of BAL in diagnosing sarcoidosis is limited
- (In case EBUS is not available, blind TBNA with onsite cytology + TBLB seems a good alternative)

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*

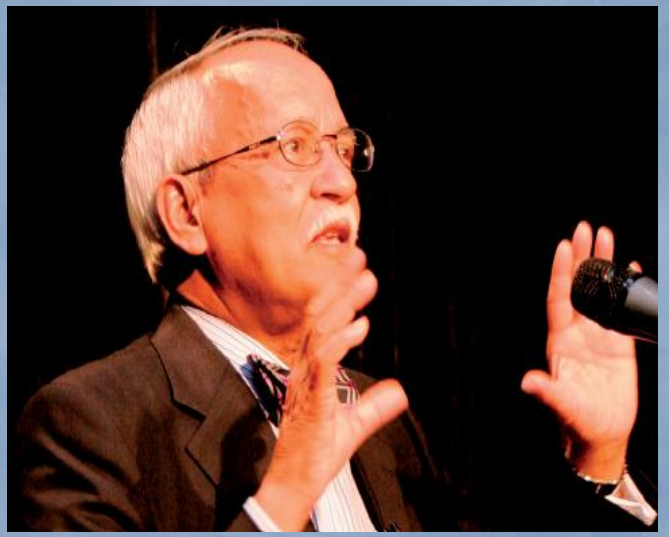
PFTs

"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*

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).

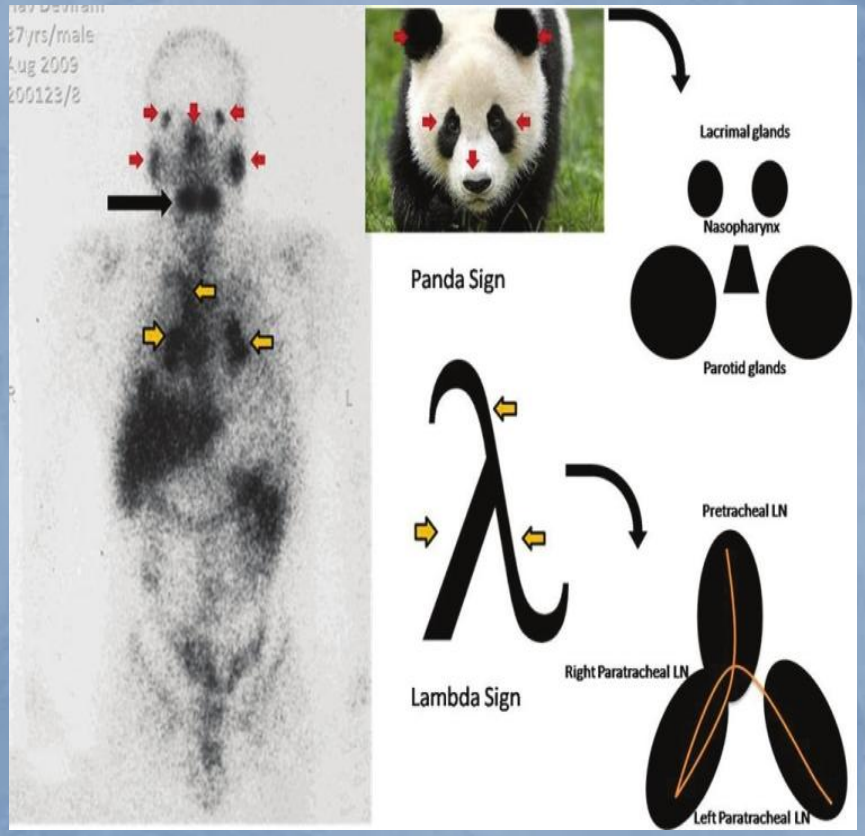
Valeyre D, *et al. Semin Respir Crit Care Med 2014*

Gallium Scintigraphy—An Obsolete Technique?

Some features can be suggestive of the disease such as the so-called “panda sign” or “lambda sign,”

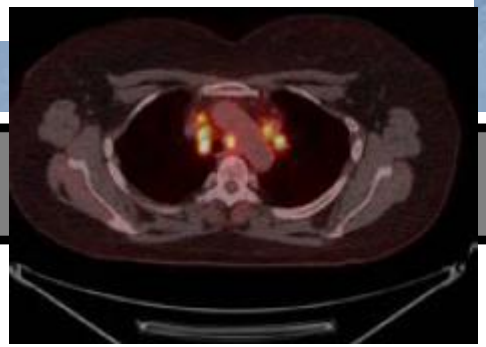
it is however not specific for sarcoidosis

higher radiation exposure (15mSv)



Adams H, *et al. Semin Respir Crit Care Med 2014*

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*

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.**

DIAGNOSTIC APPROACH

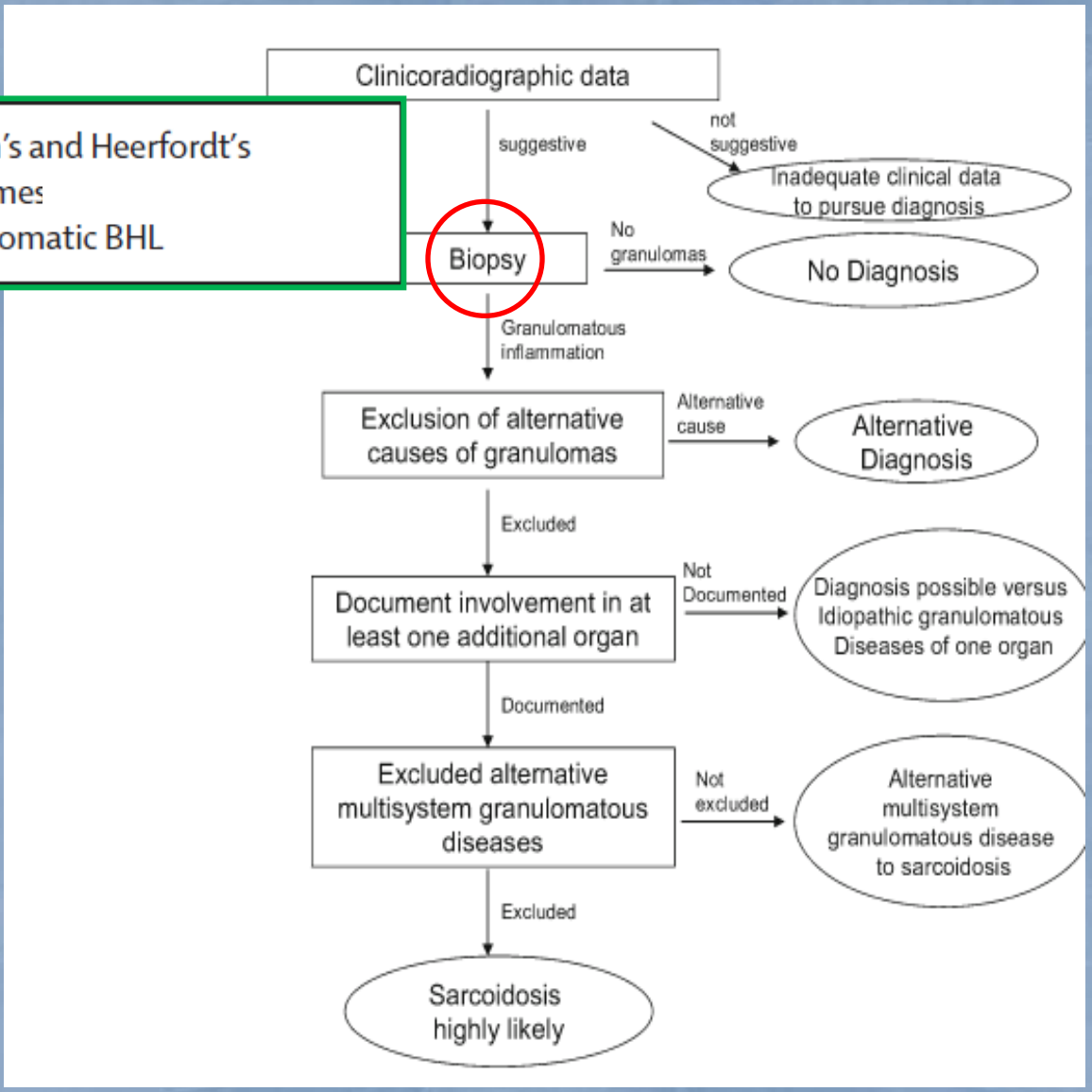
The diagnostic procedures should accomplish the following goals:

- **Provide histological confirmation of the disease;**
  Biopsies can be obtained from easily accessable organs
- **Evaluate the extent and severity of organ involvement;**
- **Assess whether the disease is stable or likely to progress;**
- **Determine if the patient will benefit from treatment.**

Costabel U. *ERS Monograph 2005*

DIAGNOSTIC APPROACH: multistep process

Löfgren's and Heerfordt's syndromes
asymptomatic BHL



Judson MA. *Clin Chest Med 2008*

Major pathologic Differential Diagnosis of Sarcoidosis at Biopsy

LUNG

- Tuberculosis
- Atypical mycobacteriosis
- Fungi
- Pneumocystis carinii
- Mycoplasma
- Hypersensitivity pneumonitis
- Pneumoconiosis: Beryllium (chronic beryllium disease), Titanium, Aluminum
- Drug reactions
- Aspiration of foreign materials
- Wegener's granulomatosis (Sarcoid-type granulomas are rare)
- Necrotizing sarcoid granulomatosis (NSG)

LYMPH NODE

- Tuberculosis
- Atypical mycobacteriosis
- Brucellosis
- Toxoplasmosis
- Granulomatous histiocytic necrotizing lymphademitis (Kikuchi's disease)
- Cat-scratch disease
- Sarcoid reaction in regional lymph nodes to carcinoma
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- Granulomatous lesions of unknown significance (the GLUS syndrome)

SKIN

- Tuberculosis
- Atypical mycobacteriosis
- Fungi
- Reaction to foreign bodies: beryllium, zirconium, tattooing, paraffin, etc.
- Rheumatoid nodules

LIVER

- Tuberculosis
- Brucellosis
- Schistosomiasis
- Primary biliary cirrhosis
- Crohn's disease
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- GLUS syndrome

BONE MARROW

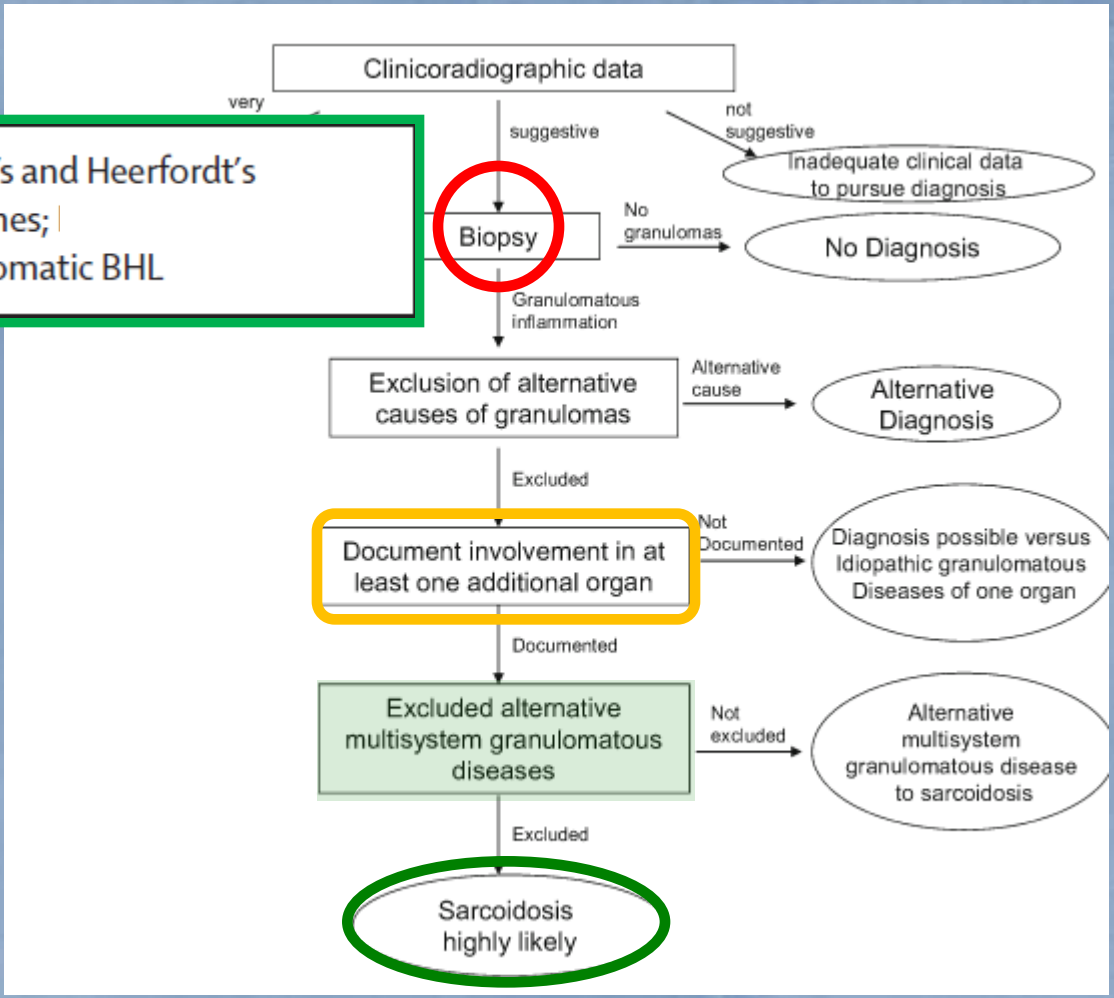
- Tuberculosis
- Histoplasmosis
- Infectious mononucleosis
- Cytomegalovirus
- Hodgkin's disease
- Non-Hodgkin's lymphomas
- Drugs
- GLUS syndrome

OTHER BIOPSY SITES

- Tuberculosis
- Brucellosis
- Other infections
- Crohn's disease
- Giant cell myocarditis
- GLUS syndrome

ATS/WASOG Statement. *AJRCCM 1999*

DIAGNOSTIC APPROACH: multistep process



Löfgren's and Heerfordt's syndromes; asymptomatic BHL

The presence of granulomatous inflammation in an isolated organ is not diagnostic of sarcoidosis, as, by definition, multiple organs should be involved

Judson MA. *Clin Chest Med 2008*

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

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

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

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. .

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
  Serum protein electrophoresis

- **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.

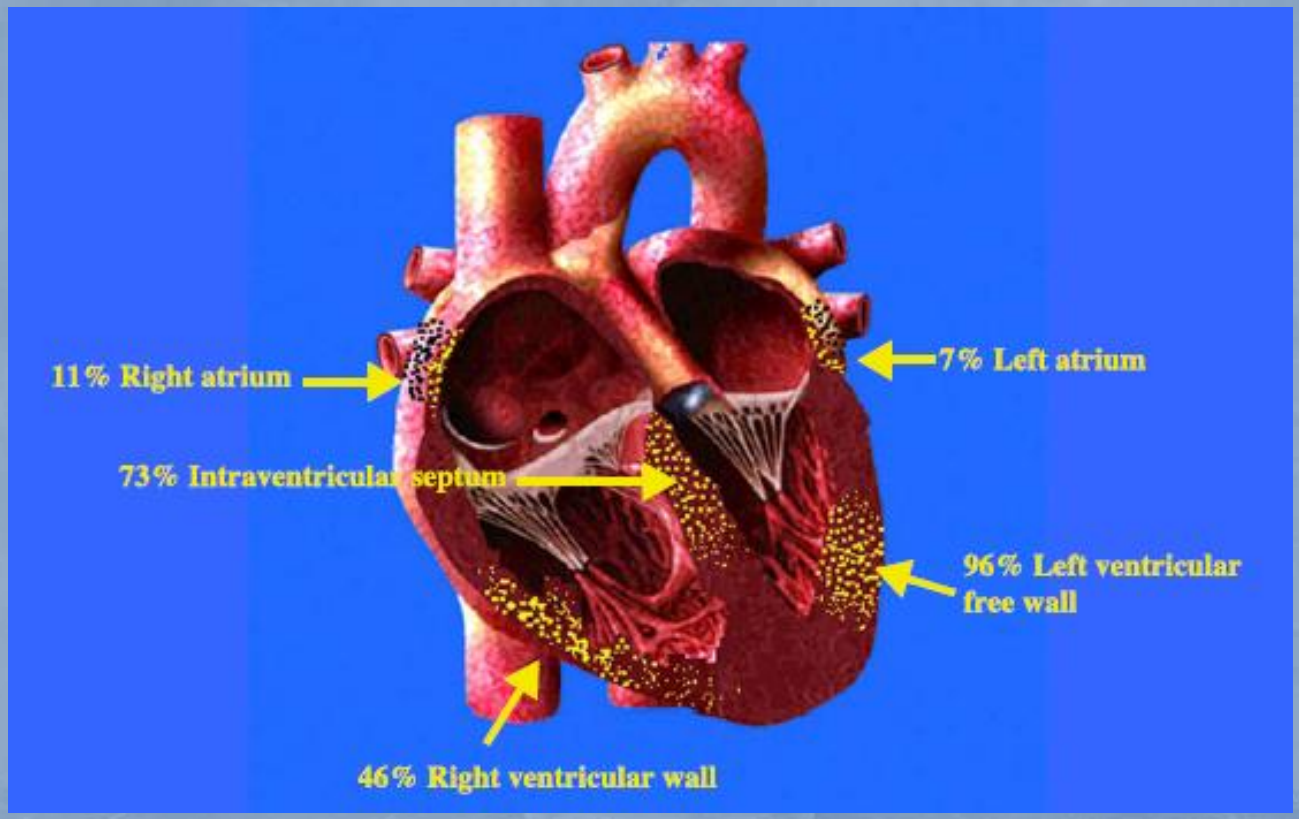
Valeyre D, *et al. Semin Respir Crit Care Med 2014*

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*

The 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

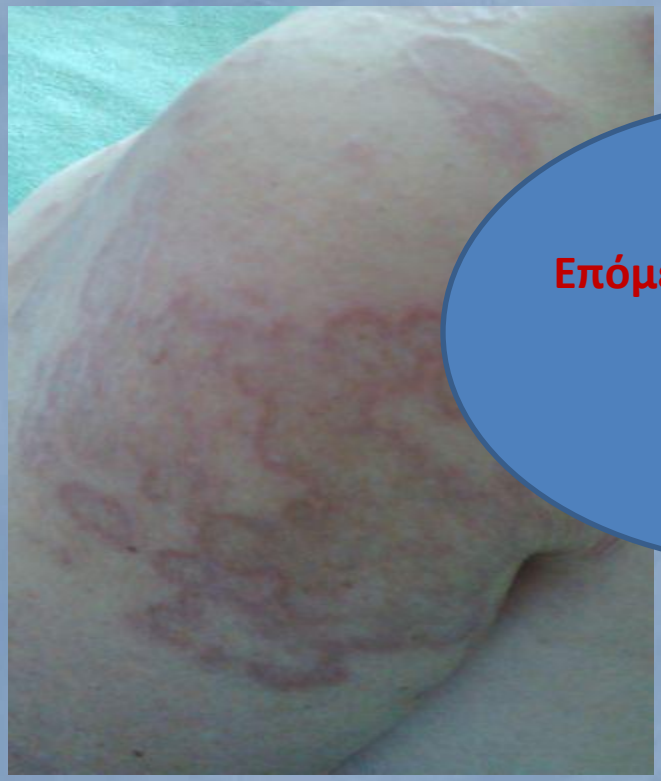
The yield of endomyocardial biopsies is low

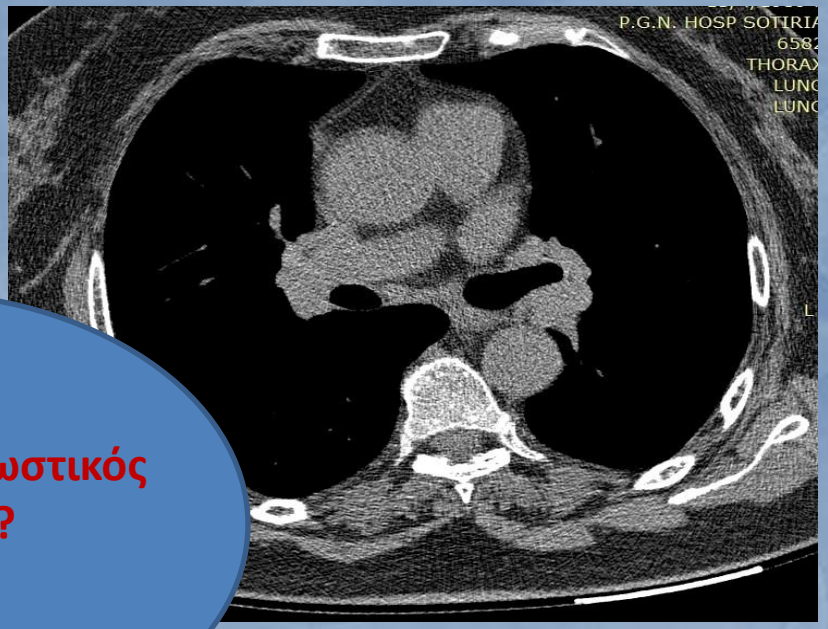
Currently, 18F-fluorodeoxyglucose positron emission tomography/computed tomography and gadolinium-enhanced magnetic resonance imaging scans are the key imaging modalities to diagnose CS

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

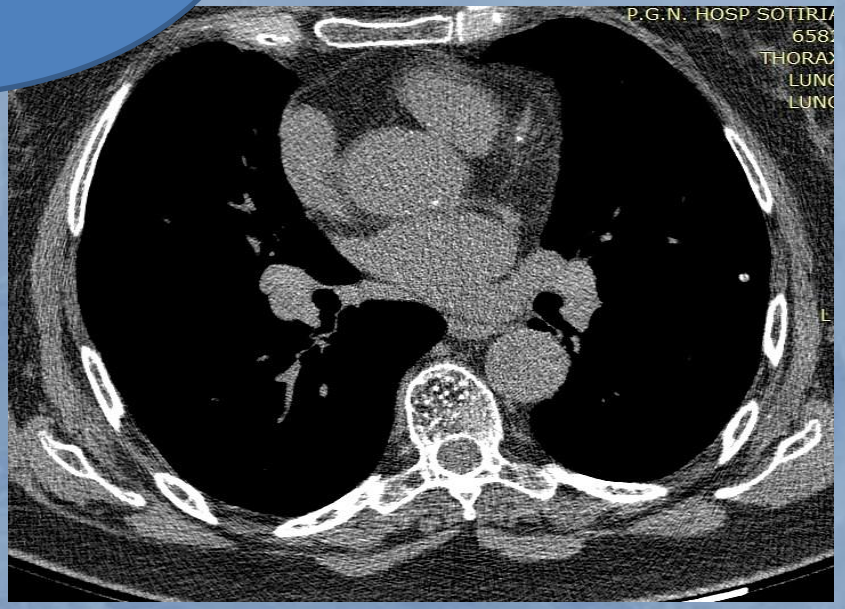
CASE #1

Θήλυ, 60 ετών, μη καπνίστρια,
βήχας, δεκατική πυρετική κίνηση,
απώλεια ΣΒ





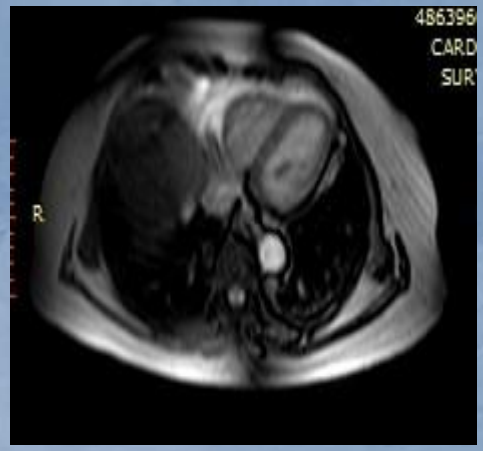
Επόμενος διαγνωστικός χειρισμός?



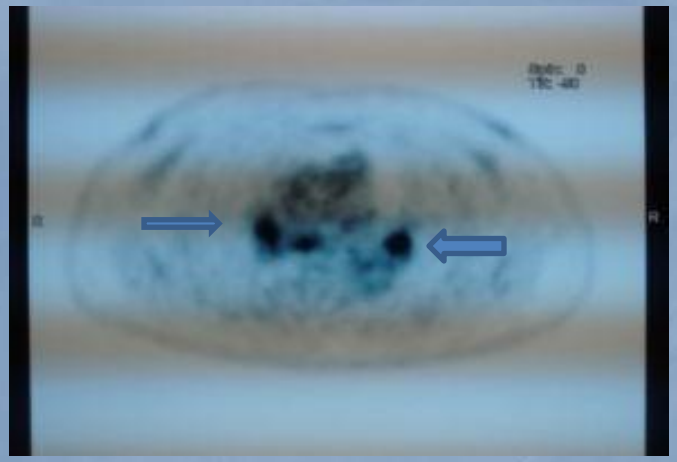
Βιοψία : σαρκοειδικού τύπου κοκκίωμα

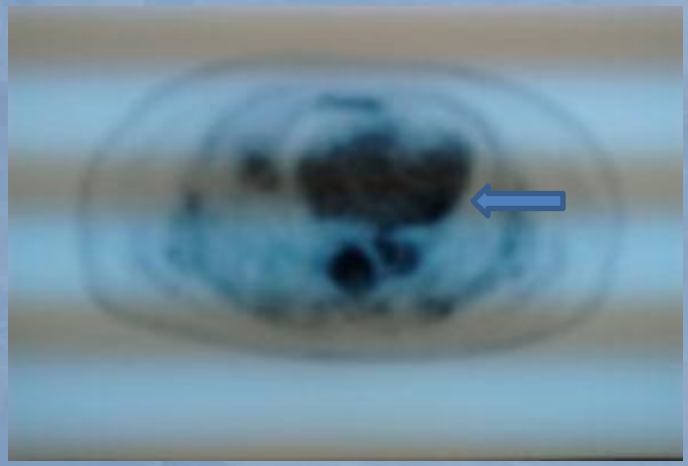
BAL: L 30%, CD4/CD8:4.59
PFTs normal, ΗΚΓ SR
U/S καρδίας: ήπια υποκινησία αρ κοιλίας

MRI καρδίας: οίδημα μυοκαρδίου αρ κοιλίας



PET-CT: Αυξημένη πρόσληψη ρ/φ στις πνευμονικές πύλες άμφω (SUVmax 7.1), δε παρατραχειακό λεμφαδένα (4.3) και στο βασικό τμήμα του κατώτερου -πλάγιου τοιχώματος της αρ κοιλίας





Δοκιμασία κόπωσης με SC έλεγχο με Tc99m-Sestamibi: αρνητική για ισχαιμία μυοκαρδίου

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***

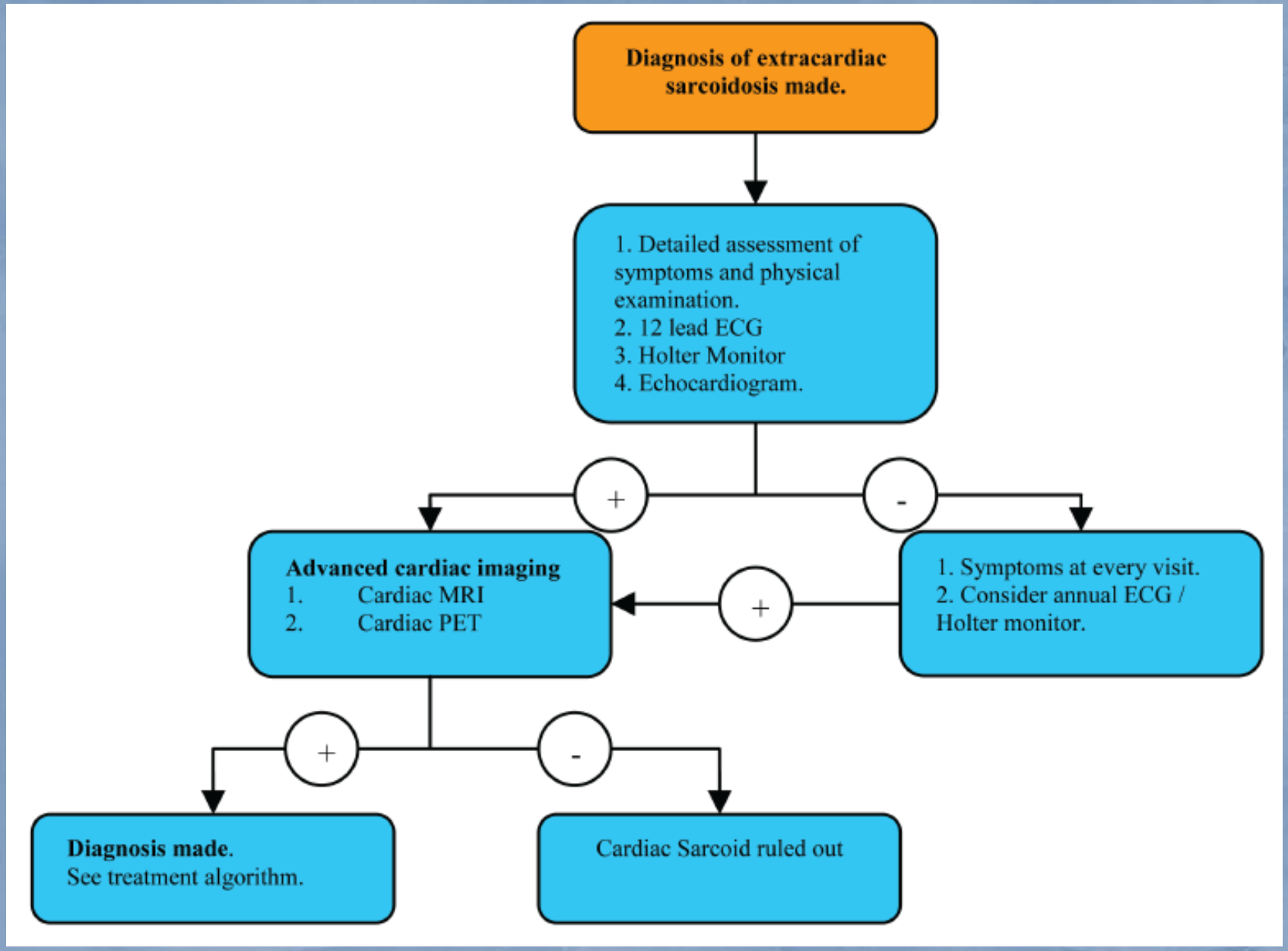
There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

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]

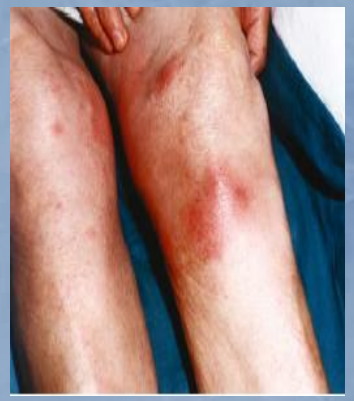
Birnie DH, *et al. Heart Rhythm 2014*



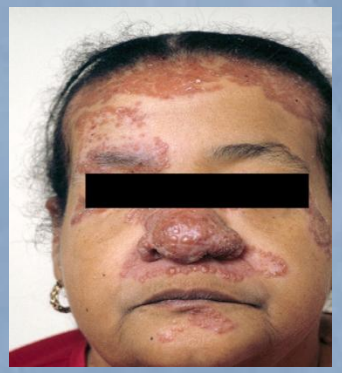
Evanchan P, *et al. JICRM 2013*

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, which **neither confirms nor negates the diagnosis of sarcoidosis**.

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

Ophthalmologic Complications

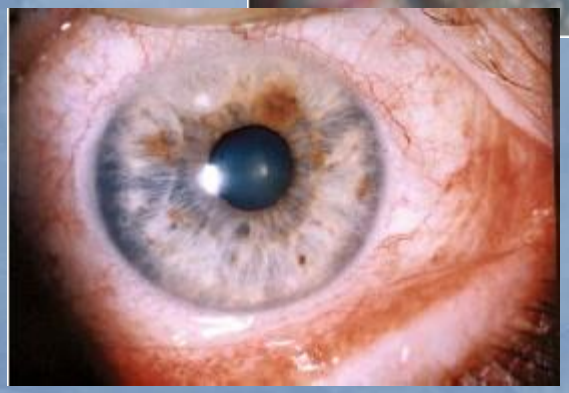
- The eye and adnexa are involved in 25 -80%
- Anterior or posterior granulomatous uveitis, Optic neuritis.
- Conjunctival lesions and scleral plaques may also be noted.
- Ocular involvement may lead to blindness if untreated.

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*

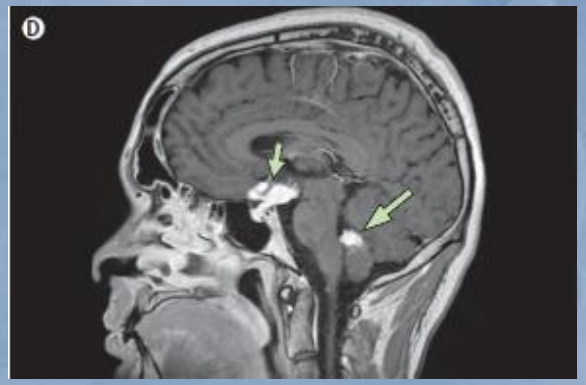
Neurologic Involvement

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.

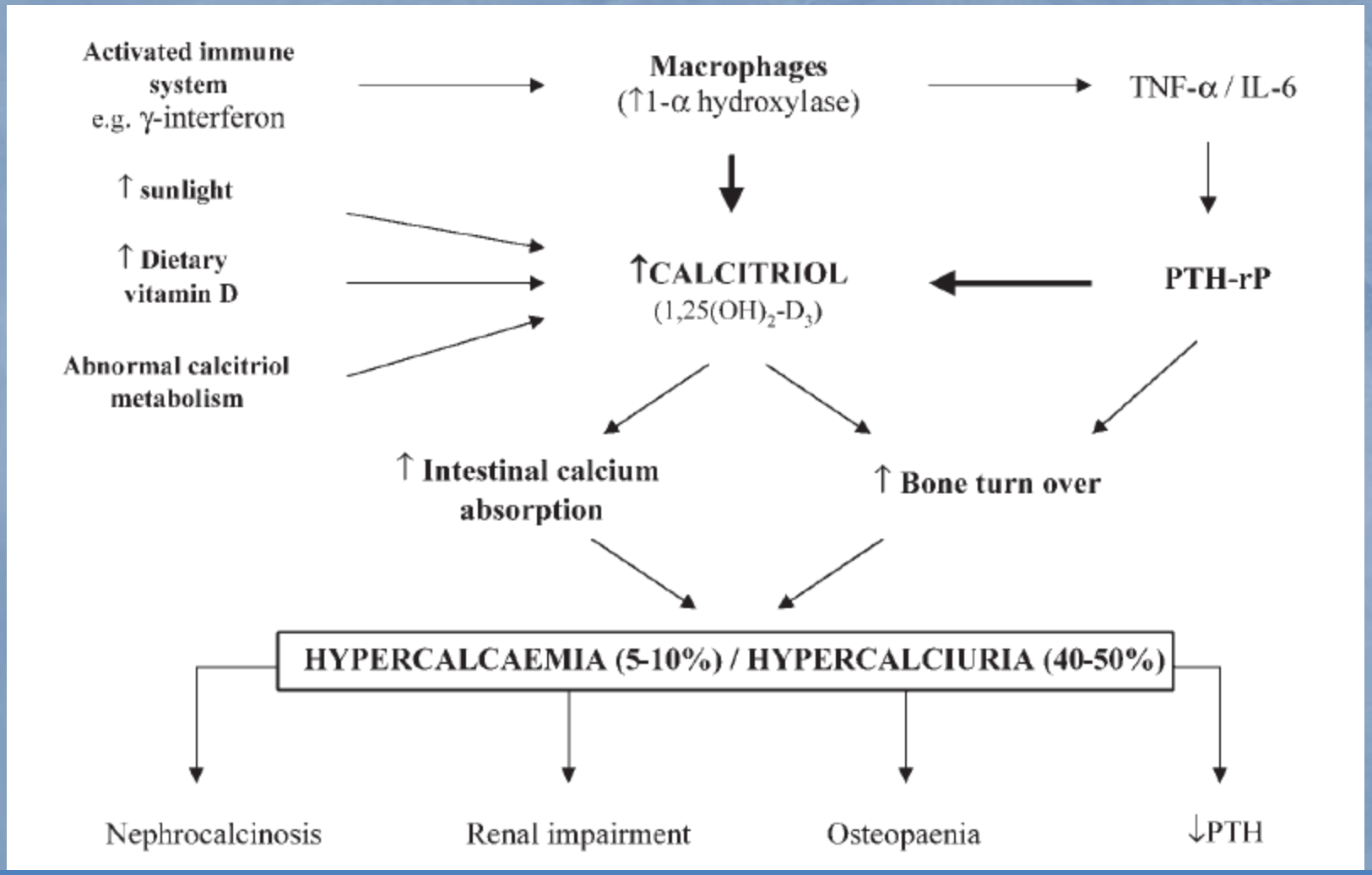


Depending on the location of the granulomas in the neuroaxis, the symptomatology reflects the neuroanatomical structures compromised. This means that potentially any neurological symptom and sign can be seen in patients with neurosarcoidosis.

- Magnetic resonance imaging (MRI), FDG-PET
- CSF analysis important in excluding TB/fungal infections – CSFace ↑ 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



Isolated hypercalciuria alone is not an indication for prednisone therapy

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

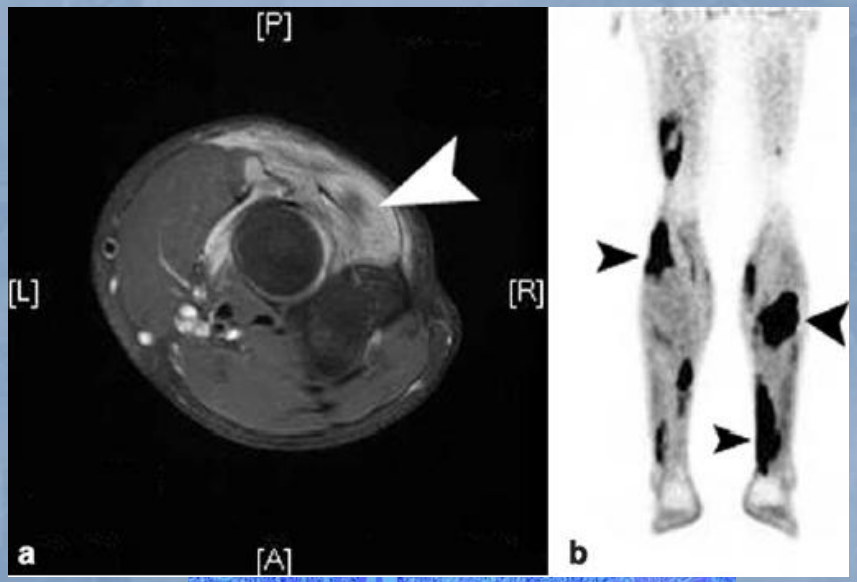
Rheumatol Int
DOI 10.1007/s00296-009-0989-1

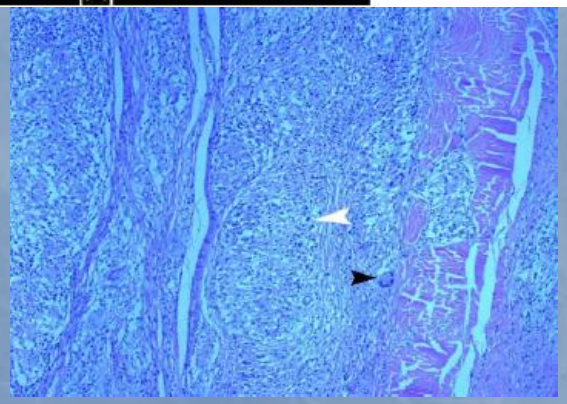
SHORT COMMUNICATION

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.

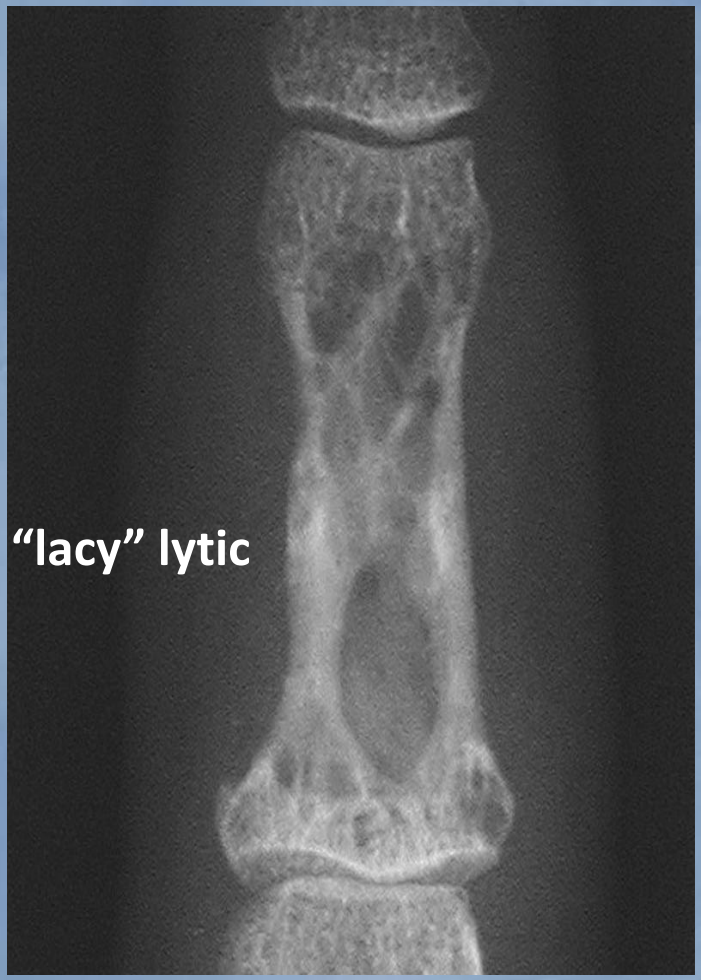


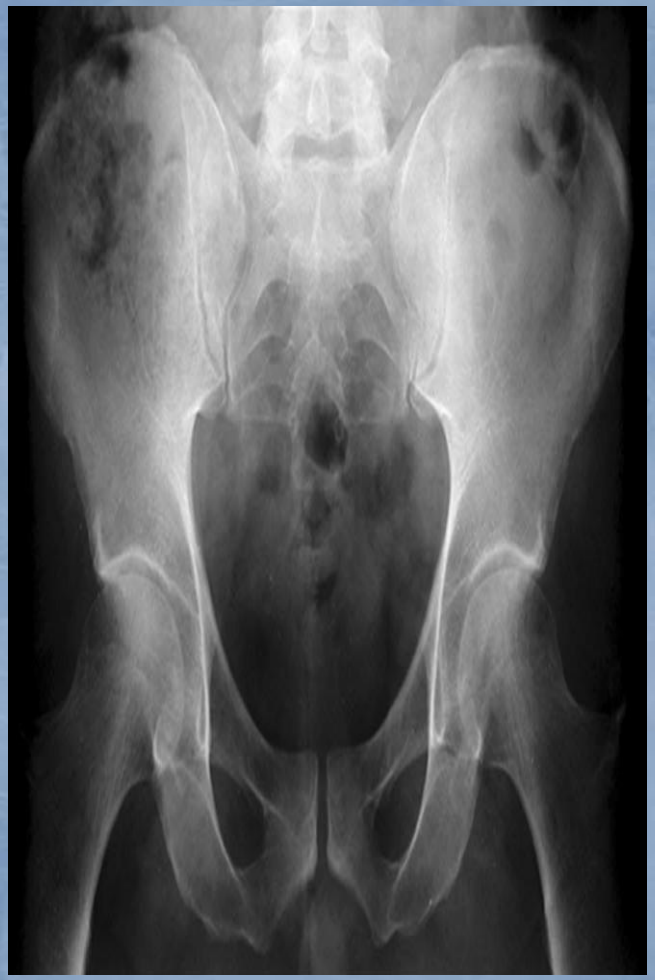


Three types of muscle sarcoidosis:

- chronic myopathy
- acute myositis
- nodular or tumorous type

Bone Involvement





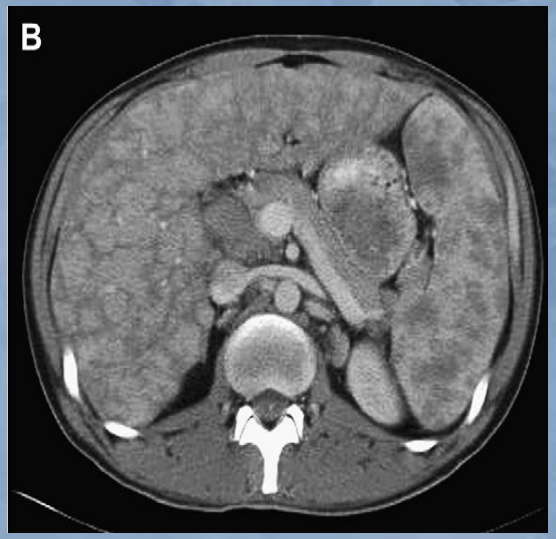
- Small and large bones, painfull or asymptomatic
- Cystic, lytic or sclerotic lesions (d.d.: Ca, TB, fungal infections)
- Sarcoid athropathy

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*

Respiratory Medicine (2012) 106, 1351–1361

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

The treatment of pulmonary sarcoidosis

Marc A. Judson [a]

Decisions regarding treatment of sarcoidosis rely on several factors:

Symptoms

Organ involvement

Signs of functional impairment

Who should be treated?

- Not all patients require therapy for sarcoidosis
  - About half never get treated
- Treatment strategies are different based on phase of disease
  - Acute
  - Chronic
  - Refractory

Acute vs Chronic Sarcoidosis

- **Acute, Self Limited Disease**
  - Disease for **less than two years**.
  - Any residual defects are due to fibrosis, not active inflammation.
- **Chronic**
  - Disease present **beyond two years.**
  - Some manifestations at presentation can predict chronic disease.
- **Refractory**
  - **Progressing despite therapy**

The decision to treat

- Progressive disease
- Functional impairment
- Respiratory failure
- Death

- Cough
- Dyspnea

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

Treatment: General considerations

- Treatment is not curative but only “suspensive” and a relapse of the disease can be observed in case of premature interruption
- Treatment suppresses the granuloma formation but it does not affect established fibrotic lesions
- The role of treatment in altering the natural history of sarcoidosis remains debated
- There is usually a threshold dose of treatment that controls granulomatous process

THORACIC INVOLVEMENT

No Treatment	Treatment recommended	Treatment controversial
Lofgren's syndrome	Stage II-III - with symptoms - and/or abnormal PFTs (FVC < 65 %, DLCO < 60 %) - and/or progressive	Asymptomatic Stage II-III with minimal PFTs impairment: observe 3-6 months and treat on deterioration
Asymptomatic Stage I	Extrinsic bronchial compression by enlarged lymph nodes §	Symptomatic Stage 0- I consider trial treatment
Asymptomatic patients with (sub) normal PFTs	Granulomatous bronchial involvement with airflow limitation or endo-bronchial stenosis §	
	Stage IV with symptoms and/or abnormal PFTs and residual granulomatous activity	

*** Rule out other causes of symptoms**

(PH, CHF, muscle disease, fatigue)

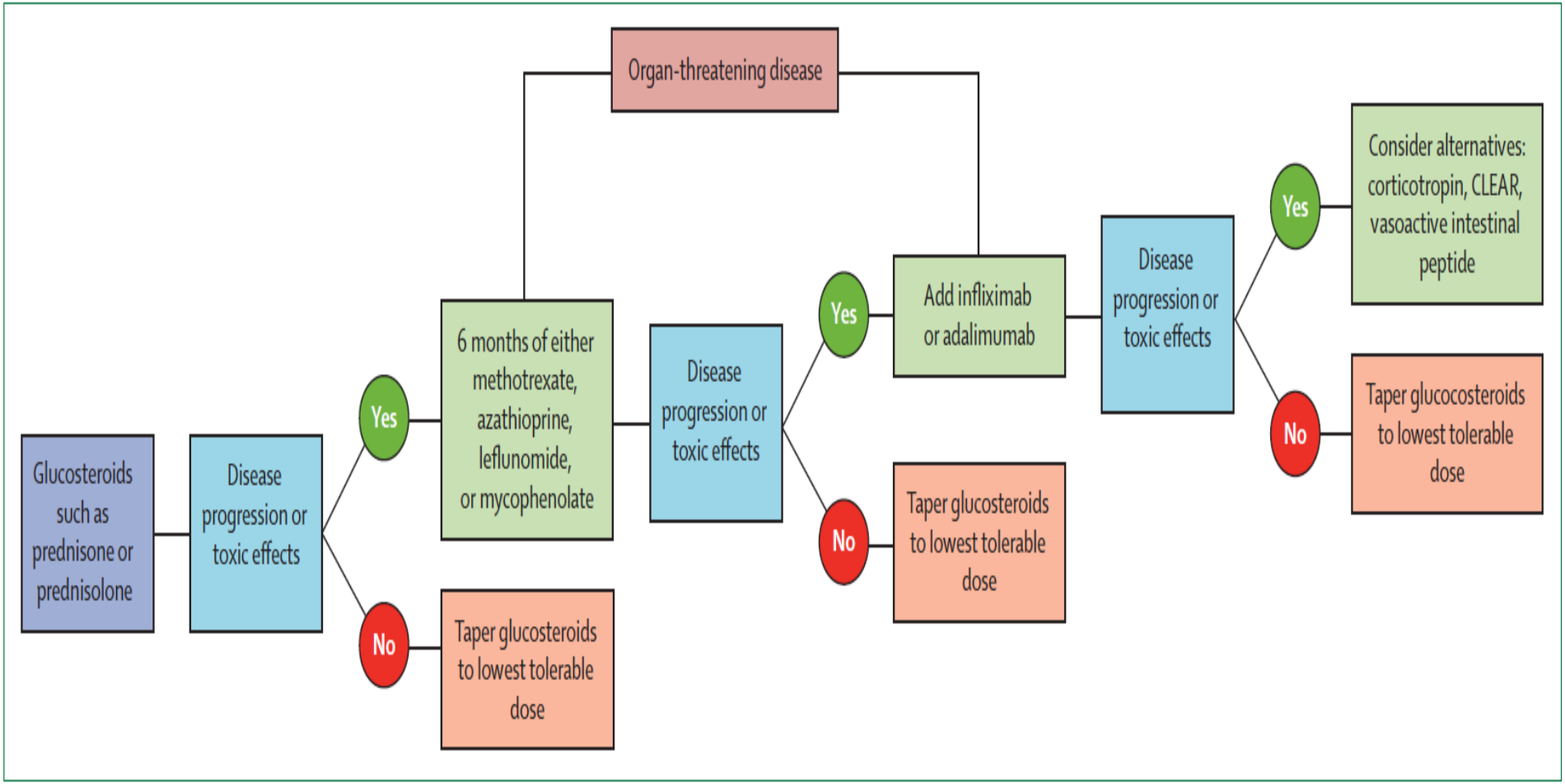
ATS/ERS/WASOG. *AJCCMM 1999*
Baughman et al. Expert Rev Clin Immunol. 2012
Valeyre et al. Lancet 2014
**Gibson et al. Thorax 1996,*Pietinalho et al. Chest 2002*
§ Naccache et al. J Comput Assist Tomogr 2008
§ Chambellan, Chest 2005

Main anti-inflammatory drugs in sarcoidosis

Drugs	Line no.	Efficacy evidence	Main contraindications	Main adverse effects	Comments
Corticosteroids	1	+++++	Unstable psychiatric disorders	Weight gain, osteoporosis, diabetes, infections, etc.	Rapid efficacy Multiple adverse effects with prolonged treatment
Methotrexate	2	+++	(Project of) pregnancy Liver and severe renal failure, liver disease	Digestive tract disturbance, abnormal liver tests	Preferred 2nd-line treatment, need contraception
Azathioprine	2	+++	Use of allopurinol	Digestive disturbance, infections, skin carcinomas, liver, and blood cell toxicity	Good 2nd-line treatment, useful when contraception is dubious
Leflunomide	2	+ (few data)	(Project of) pregnancy Liver and renal failure	Digestive disturbance, diarrhea, hypertension, neutropenia	Well tolerated
Mycophenolate mofetil	2	+ (few data)	(Project of) pregnancy	Diarrhea, skin carcinoma	Few available data
Cyclophosphamide	2	++ (few data)	(Project of) pregnancy Renal or bone marrow failure, decreased fertility	Numerous severe adverse effects, cancer risk (bladder)	Reserved to very severe and refractory cardiac and central nervous system sarcoidosis, preserve gametes before
Aminoquinolines	2	+	Macula impairment	Rare retinal impairment, digestive disturbance	When a response is not urgent Well tolerated
Thalidomide	2	+/−	(Project of) pregnancy	Teratogenicity, peripheral neuropathy, deep vein thrombosis	Dubious efficacy, severe complications, not recommended
Infliximab	3	+++++	(Project of) pregnancy, severe CHF, TB	Infections +++, allergic reactions, increased risk of carcinoma	Very useful in severe refractory sarcoidosis, association of methotrexate if infliximab antibodies are suspected
Adalimumab	3	++	(Project of) pregnancy, TB, latex allergy, severe CHF	Infections, local allergy	Indicated in case of failure or intolerance with infliximab

Decision tree for symptomatic sarcoidosis

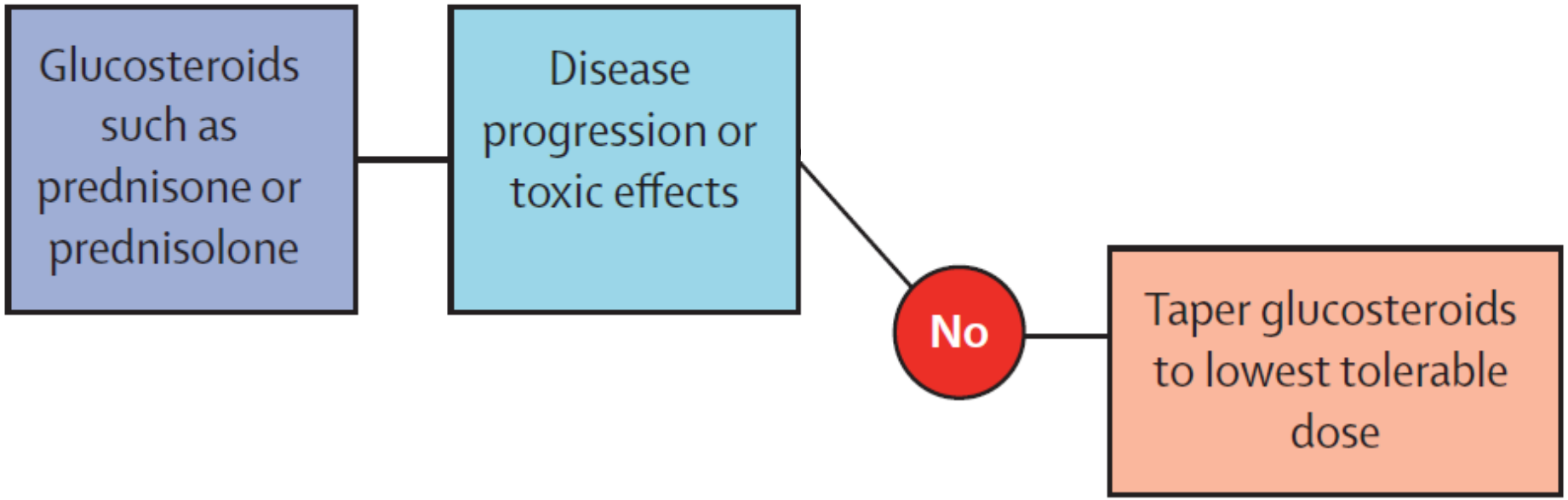
Three-step approach



Baughman RP et al. *Lancet Respir Med 2015*

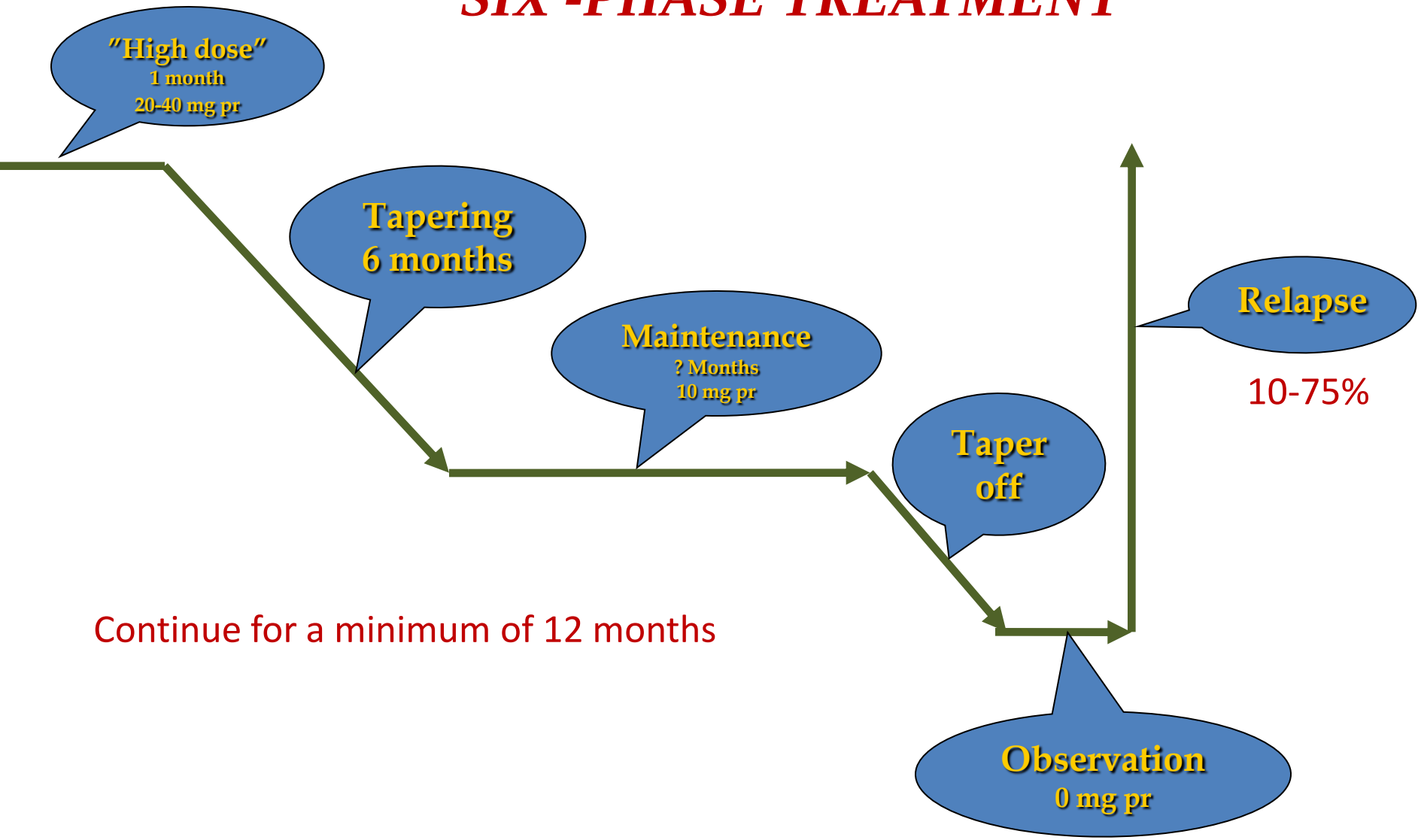
Decision tree for symptomatic sarcoidosis

First line



Baughman RP et al. *Lancet Respir Med 2015*

SIX -PHASE TREATMENT

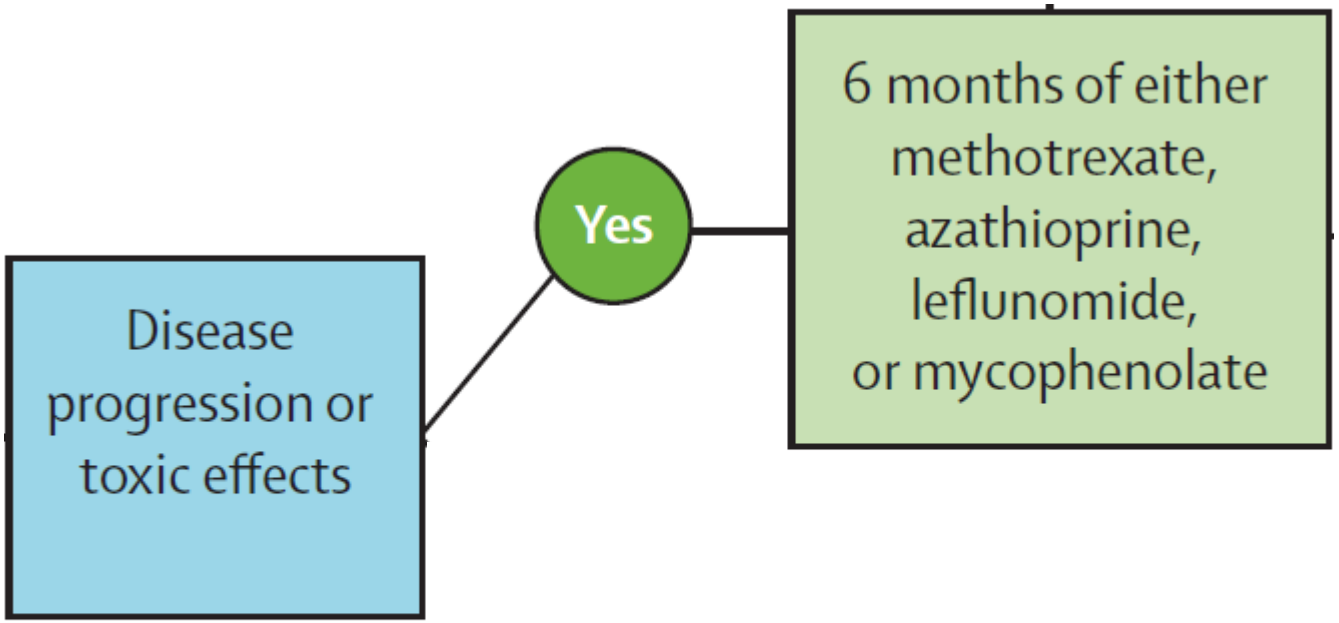


Continue for a minimum of 12 months

Judson MA. *Respir Med 2012*

Decision tree for symptomatic sarcoidosis

Second line

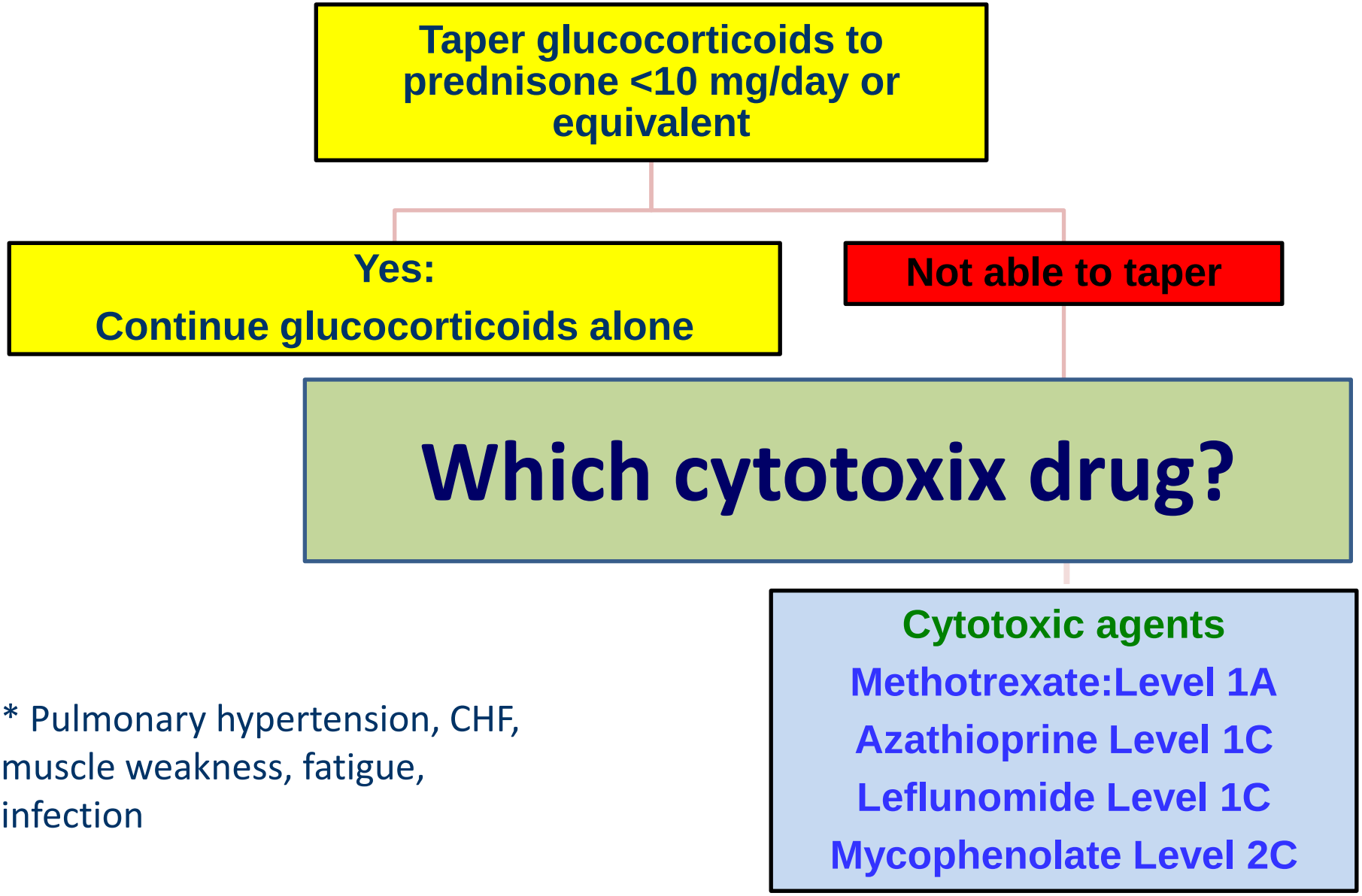


Baughman RP et al. *Lancet Respir Med 2015*

Avoid Prednisone Side Effects

Consider a switch

Cytotoxic Drugs



* Pulmonary hypertension, CHF, muscle weakness, fatigue, infection

Cytotoxic Drugs

	Level of evidence in sarcoidosis	Most common toxic effects (>1%)	Rare but important toxic effects
Methotrexate	Double-blind placebo-controlled trials, prospective case series, case reports	Nausea, mouth ulcers, leucopenia, hepatotoxicity, nausea, infections	Pneumonitis, teratogenic
Azathioprine	Prospective case series, case reports	Leucopenia, nausea, infections	Severe leucopenia, heptatoxic effects, pancreatitis, skin cancer
Leflunomide	Double-blind placebo-controlled trials, prospective case series, case reports	Leucopenia, hepatotoxic effects, infections, alopecia	Pneumonitis, teratogenic, peripheral neuropathy, hypertension
Mycophenolate mofetil	Case series	Nausea, diarrhoea, infections	Skin cancer

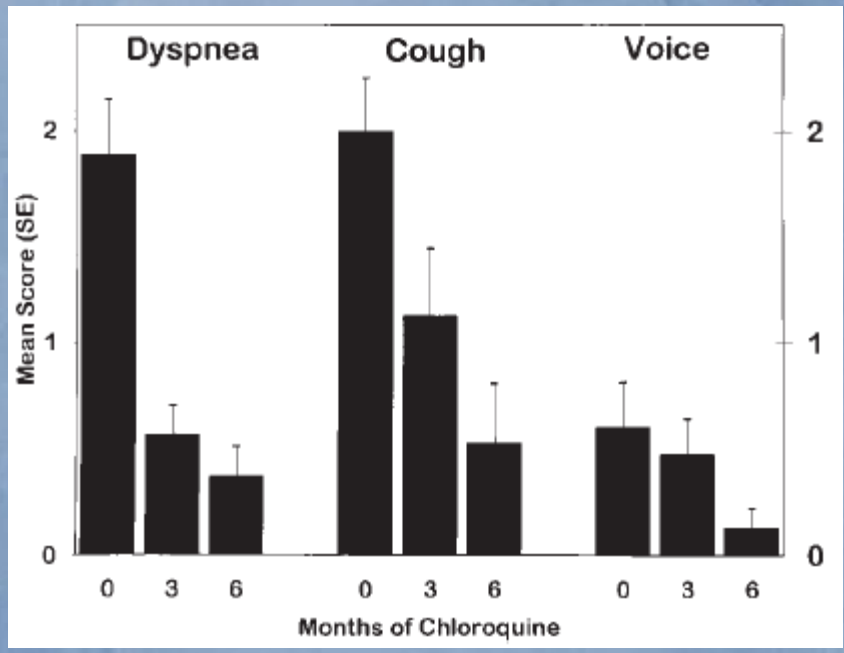
Baughman RP et al. *Lancet Respir Med 2015*

Randomized Trial of Prolonged Chloroquine Therapy in Advanced Pulmonary Sarcoidosis

MARCEL BALTZAN, SANJAY MEHTA, TREVOR H. KIRKHAM, and MANUEL G. COSIO

Respiratory Division and the Division of Neuro-Ophthalmology, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada

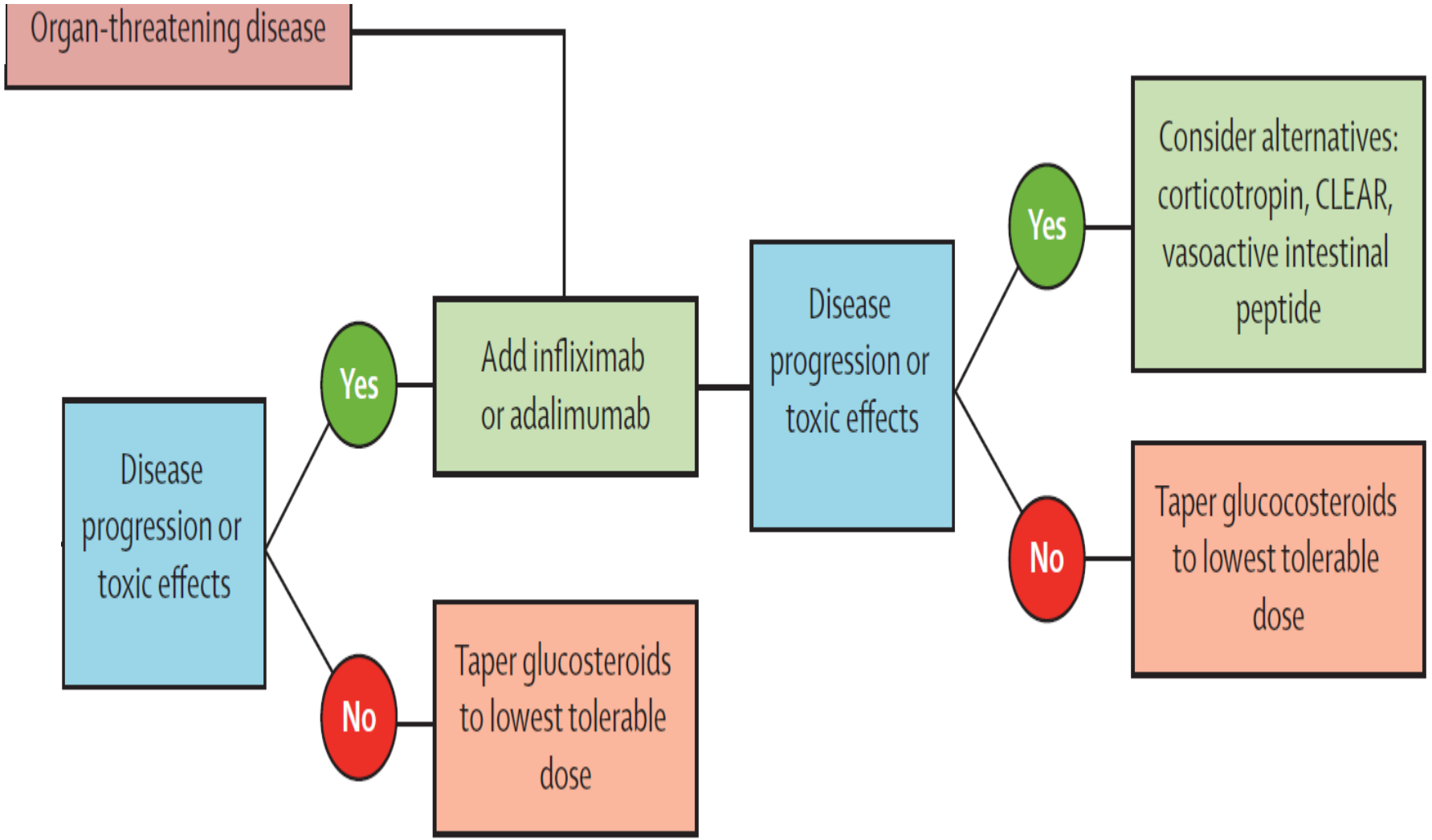
Parameter	Baseline (*mean ± SD*)	Month 6 (*mean ± SD*)	p Value
FEV_1, L	2.01 (0.58)	2.36 (0.64)	0.001
Percent predicted	66 (15)	74 (16)	0.002
FVC, L	2.97 (0.78)	3.36 (0.90)	0.003
Percent predicted	71 (13)	80 (13)	0.005
TLC, L	5.07 (1.31)	5.36 (1.18)	0.07
Percent predicted	85 (13)	92 (13)	0.08
D_{LCO}-SB, mm Hg/min	18.8 (5.2)	20.2 (5.6)	0.02
Percent predicted	68 (13)	73 (13)	0.02
ACE, nmol/L	1,750 (1,336)	977 (886)	0.01
Calcium, mmol/L	2.42 (0.15)	2.32 (0.12)	0.01
Gallium, score 0 to 4	1.9 (1.3)	0.8 (0.8)	0.004



Chloroquine should be a consideration as a first-line drug for the treatment and maintenance therapy of pulmonary sarcoidosis. Effective steroid-sparing agent in 40% of chronic pulmonary sarcoidosis

Refractory - Complicated sarcoidosis

Third line



Baughman RP et al. *Lancet Respir Med 2015*

Who to treat with anti-TNF therapy

- Improved response to drug
  - **Unsuccessful treatment with CS and antimetabolites (such as MTX)**
  - **FVC<70%**
  - **Dyspnea ≥ 2**
  - **Disease > 2 years**
  - Significant extrapulmonary disease
    - Lupus pernio
    - CNS

- Possible predictors of response
  - Elevated CRP
  - TNF –α 308 polymorphism

Baughman RP et al. *Sarcoidosis Vasc Diffuse Lung Dis 2008*

Limitations of Infliximab therapy

- **Cost**
- **Allergic reactions to medication**
  - 10% of UC patients withdrawn from infliximab because of reactions
- **Increased rate of infections**
  - TB, fungus
- **Can not use in advanced CHF**
- **Possible increased rate of malignancy**

EXPERT OPINION ON ORPHAN DRUGS, 2018
VOL. 6, NO. 1, 17–33
https://doi.org/10.1080/21678707.2018.1411260

Taylor & Francis
Taylor & Francis Group

REVIEW

Emerging and potential treatment options for sarcoidosis

Debabrata Bandyopadhyay[a] and Marc A. Judson[b]

[a]Division of Pulmonary and Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA; [b]Division of Pulmonary and Critical Care Medicine, MC-91, Albany Medical College, Albany, NY, USA

Agents	Dosage used	Mechanism of action	Common toxicities	Target organs	Evidence in sarcoidosis Study	N	Ref
Apremilast	20 mg twice daily	PDE-4 inhibitor	GI intolerance, Headache	Cutaneous	PC	17	[57]
Pentoxifylline	2 mg/kg/day	PDE-4 inhibitor	GI intolerance	Pulmonary	RCT	27	[58]
					PC	18	[59]
Roflumilast	500 mg/day	PDE-4 inhibitor, reduces IL-17 level	GI intolerance, weight loss	Pulmonary	RCT	38	[60]
Rituximab	375 mg/m^2 IV every 2 weeks	Monoclonal antibody against CD20 surface antigen of B-lymphocytes	Transfusion reaction, pancytopenia, opportunistic infection, fatigue, headache, neuropathy,	Ocular, pulmonary, neurosarcoidosis, bone	OL	10	[61]
					CS	3	[62]
					CR		[63]
							[64]
Tetracycline	200 mg/day	Tetracycline antibiotics-inhibits T-cell proliferation	GI intolerance	Cutaneous	OL	12	[65]
Thalidomide	50–400 mg/day	TNF-α antagonist; possibly reduce IL-18 levels.	Edema, thrombosis, CNS toxicities, skin reaction, hypocalcemia, fatigue, weight loss, hypotension	Cutaneous, Pulmonary	RCT	39	[66]
					OL	15	[67]
					RR	19	[68]
Cyclosporine	500 mg/m^2 IV every 3–4 weeks	Calcineurin inhibitor	Hypertension, edema, hirsutism, GI intolerance	Pulmonary, neurosarcoidosis	CS	2	[69]
					CS	6	[70]
ACTHAR gel	40–80 IU IM/SC twice weekly	Synthetic ACTH hormone	Seizure, hypertension, cushingoid state, infection	Pulmonary, Eye	CR		[71]
Cyclophosphamide	500–1000 mg IV every 2–4 weeks	Alkylating agent	Pancytopenia, opportunistic infections, Malignancy, hemorrhagic cystitis	Neurosarcoidosis, Renal, cardiac	RR	13	[72]
					CS	7	[73]
					CR		[74]
							[75]
Repository Corticotropin (RCI)	40–80 unit SC twice weekly	Stimulates ACTH secretion	Mood change, elevated HBA1c, bruising	Pulmonary	PC	16	[76]

EXPERT OPINION ON ORPHAN DRUGS, 2018
VOL. 6, NO. 1, 17–33
https://doi.org/10.1080/21678707.2018.1411260

Taylor & Francis
Taylor & Francis Group

REVIEW

Emerging and potential treatment options for sarcoidosis

Debabrata Bandyopadhyay[a] and Marc A. Judson[b]

[a]Division of Pulmonary and Critical Care Medicine, Geisinger Medical Center, Danville, PA, USA; [b]Division of Pulmonary and Critical Care Medicine, MC-91, Albany Medical College, Albany, NY, USA

Table 5. Prospective potential therapeutic targets for sarcoidosis treatment.

Drugs	Proposed mechanism of action	Evidence in sarcoidosis
Inhaled VIP	Inhibits TNF-α production	Open label phase II trial
Ustekinumab	Inhibits IL12/IL-23 complex	Negative phase II RCT
hIL-18	Inhibits expression and neutralizes of IL-18	Preclinical study
CLEAR	Inhibits expression of ESAT-6 antigen	Phase II RCT in progress
Nicotine	Immunomodulator by altering TLR2, TLR9 response	Phase II RCT in progress
PDA-001	Inhibits T lymphocyte proliferation and differentiation	Small phase I trial
Pirfenidone	TGF-β and PDGF inhibitor	No current trials
Nintedanib	Tyrosine kinase inhibitor	Phase II RCT in progress
Rilonocept, canakinumab,	NLRP3 inflammasome inhibitors	Phase II double-blind trial in progress
Atorvastatin	Suppresses Th-1 immune response	Phase II RCT in progress
BIRB 796, semapimod	P38 MAP kinase inhibitor	No current trials
Bortezomib, carfilzomib	Ubiquitin protease inhibitor	No current trials
Abatacept	CTLA receptor antagonists	No current trials
Tocilizumab, Olokizuma	Anti-IL-6 antibody	No current trials

VIP: vasoactive intestinal peptide; TNF-α: Tumor necrosis factor alpha; IL-12: interleukin 12; IL-23: interleukin 23; RCT: randomized controlled trial; hIL-18: human interleukin 18; CLEAR: trial of antimycobacterial therapy in sarcoidosis; ESAT 6: early secreted antigenic target 6; TLR2: Toll-like receptor 2; TLR 9: Toll-like receptor 9; PDA: human placenta-derived antigen; TGF-β: Transforming growth factor beta; PDGF: platelet-derived growth factor; NLRP3: nucleotide-binding domain, leucine-rich repeat family, pyrin domain containing 3; MAP: mitogen-activated protein kinase; CTLA: cytotoxic T-lymphocyte-associated protein; IL-6: interleukin 6.

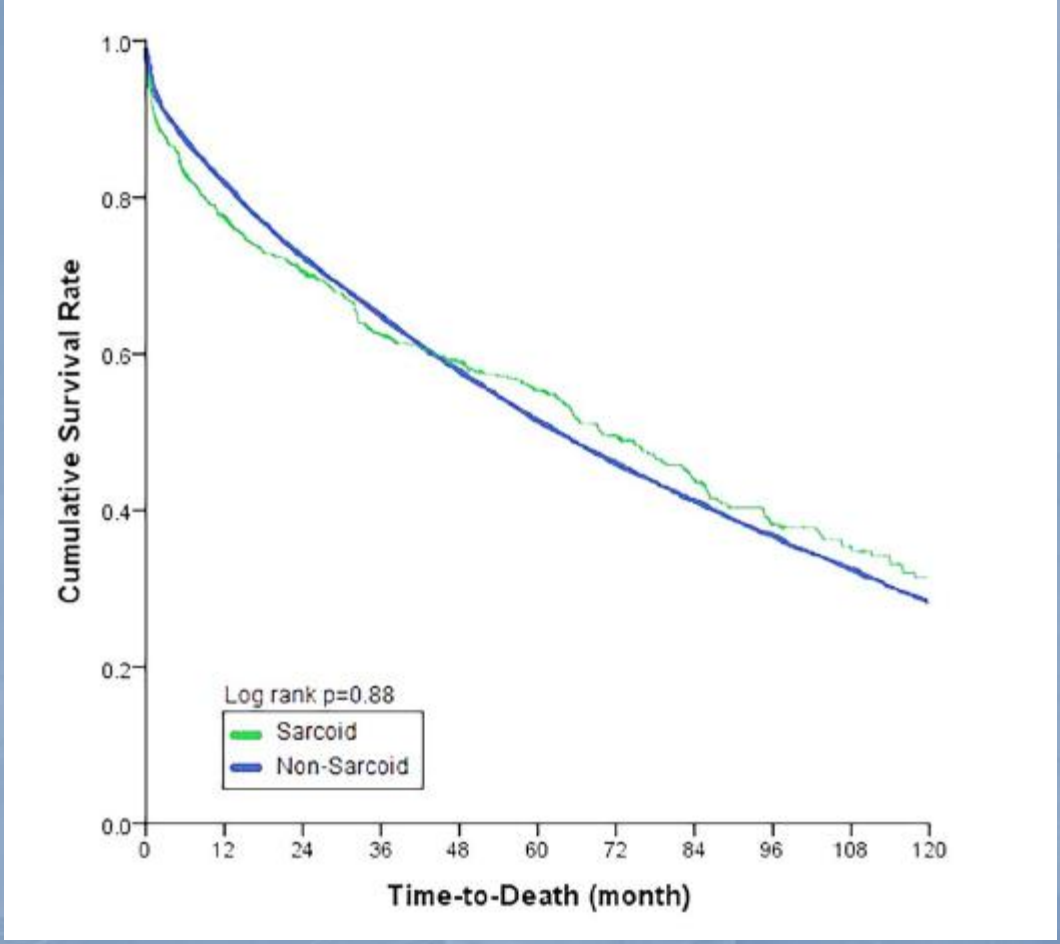
Therapy: Other general principles

- Inhaled steroids for cough, obstruction
- Pneumocystis prophylaxis
- Prophylactic vaccinations
- Age appropriate cancer screening
- TB screening
- Osteoporosis prophylaxis
- Counselling regarding effect on pregnancy
- Thiopurine methyl transferase (TPMT) level

Lung transplantation in sarcoidosis

20 896 lung transplants performed in the USA in 25 years
695 were transplanted for pulmonary sarcoidosis

Similar long-term outcomes compared with non sarcoid lung recipients



Taimeh Z, et al. *Thorax* 2016

FOLLOW-UP SARCOIDOSIS

- Detection of progression
- Detection and treatment of complications (e.g. PH, infections/aspergilloma)
- Need for oxygen therapy
- Optimal timing of referral for transplantation

There is not a best 'single test' to detect change

Hetereogeneity in patterns of functional impairment (PFTs)
Follow up functional deterioration (FVC, FEV1, DLCO) in time, from baseline
A cardinal parameter should sought in every patient

Integrate with CxR, symptoms, eventually HRCT, PET

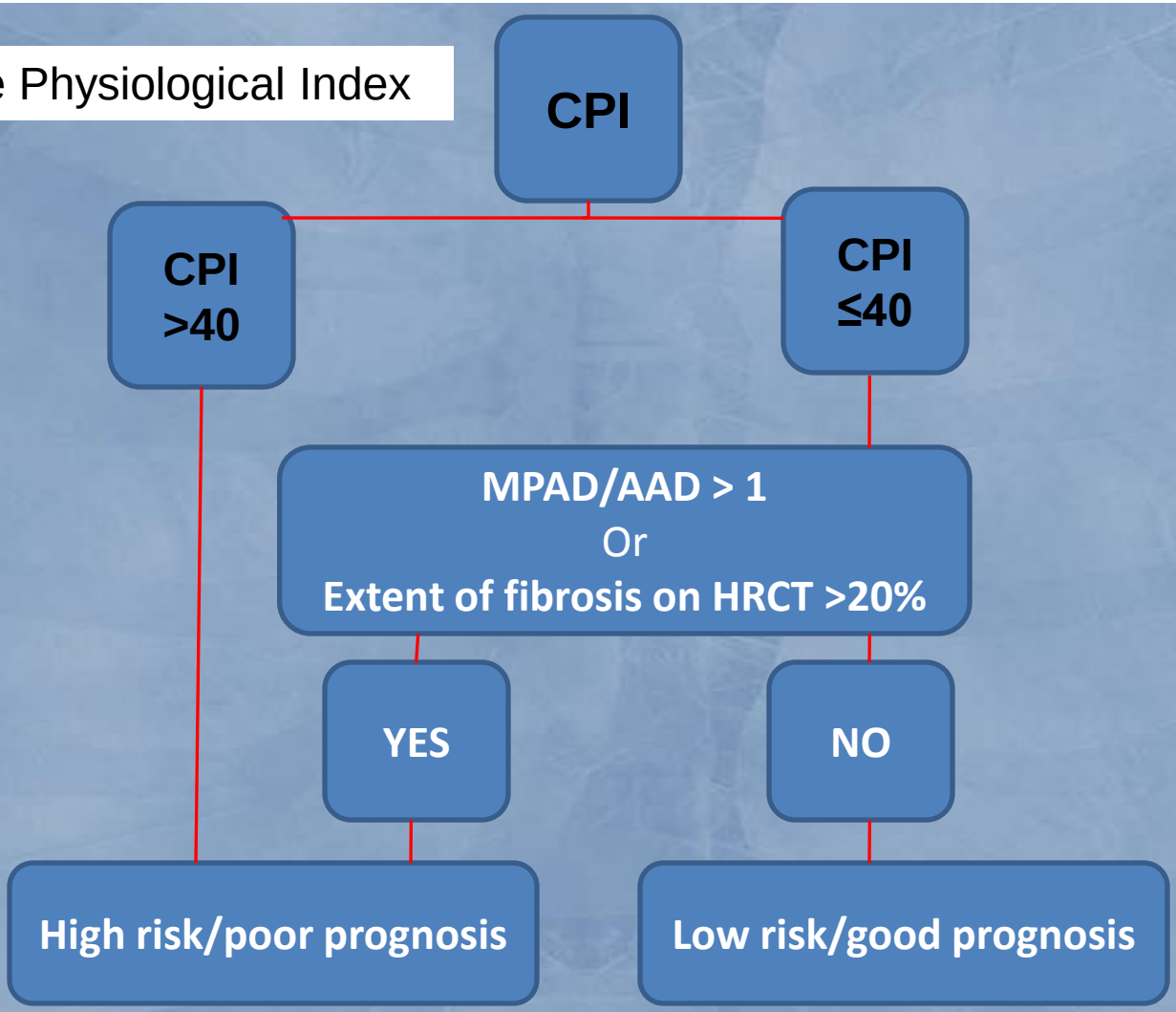
ATS/WASOG Statement on Sarcoidosis. *AJRCCM 1999*
Keijers R *et al. ERJ 2012*

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

CPI Composite Physiological Index



CPI=91.0-(0.65*percent predicted DLCO)-(0.53*percent predicted FVC)+(0.34*percent predicted FEV-1)

Risk factors for progression

Table 1. Risk factors for progression of pulmonary sarcoidosis

Risk factors	Strength of association
Black race vs. white race [6,16]	+++
Longer disease duration (median = 33 months vs. median = 12 months) [17]	+++
Female vs. male sex [6]	+
Older age [7]	+
Musculoskeletal sarcoidosis at presentation [6]	+
Calcium disorder, cardiac disease or neurologic disease secondary to sarcoidosis [17]	+
Extrapulmonary sarcoidosis [8]	+
Fibrocystic pulmonary sarcoidosis [7,18]	++
The presence or worsening of pulmonary symptoms [6,17]	++
Treatment with corticosteroids [6,17,19]	+++
Treatment with antisarcoidosis medications other than corticosteroids [17]	+
Treatment with higher doses of corticosteroids (mean = 17 mg vs. mean 11 mg of daily prednisolone) [8]	+
Interferon-α therapy [20–22]	++
ART [23–25]	++
Postlung transplant [26–29]	+
Treatment with tumor necrosis factor alpha antagonists (usually etanercept) [30–32]	+

FOLLOW-UP SARCOIDOSIS

- 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*

Treatment

- **Decision to treat sarcoidosis is a critical decision**, given its natural history and potential side effects of therapy
- **Not all patients with sarcoidosis require therapy**
- **At least half of patients treated will require two years or less of therapy**
- Steroid sparing agents may reduce toxicity from therapy and the place of infliximab needs to be better delineated
- Failure to respond to therapy can be due to secondary complications, e.g. pulmonary hypertension
- Role of pharmacogenetics to predict response to treatment (treatment “à la carte”)

Ευχαριστώ