Sarcoidosis Update 2019

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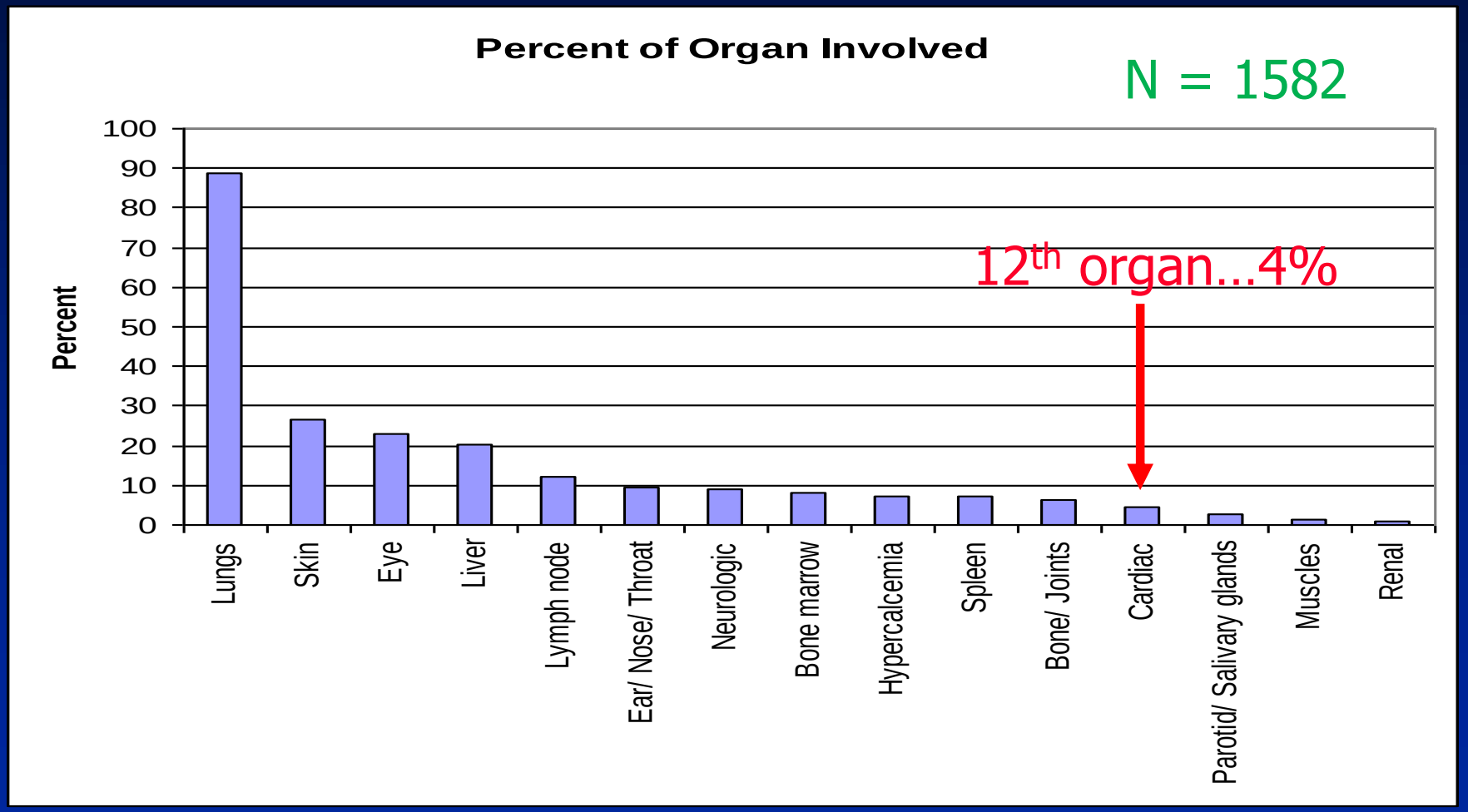
Disclosures

- Institutional grants
  - Mallinckrodt
  - Novartis
  - aTyr

Sarcoidosis Update - 2019
Learning objectives

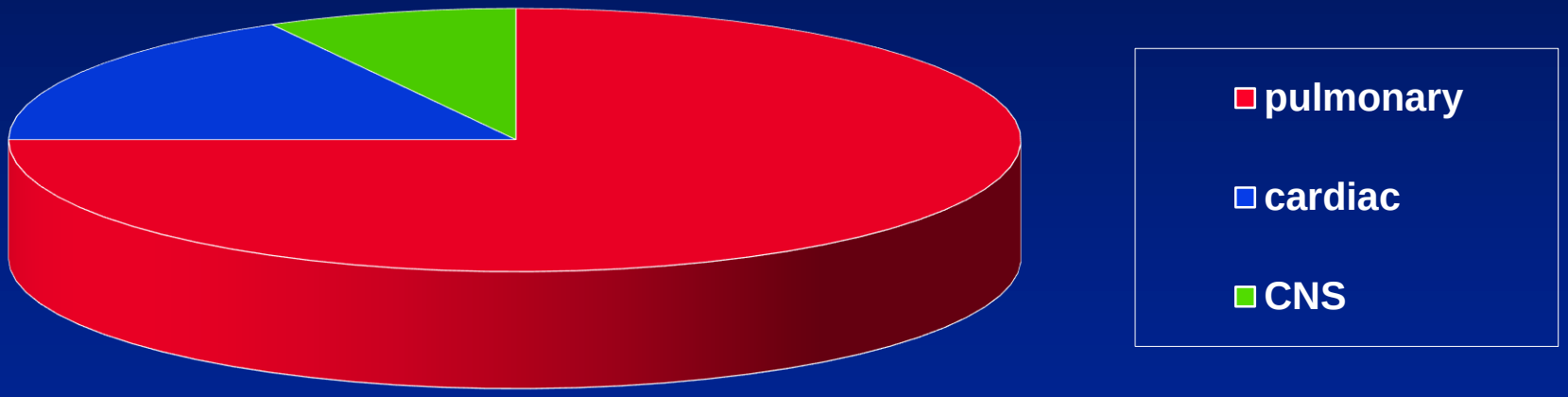
- Describe the major screening approaches to cardiac sarcoidosis
- List common drugs that may cause a drug-induced sarcoidosis-like reaction
- Discuss the approach to the treatment of symptomatic fibrotic pulmonary sarcoidosis

Organs are involved with sarcoidosis?



Judson MA. Sarcoidosis Vasc Diff Lung Dis. 2012; 29:119

Death from sarcoidosis



Eur J Respir Dis 1981: 94:169

Causes of Death in Chronic Sarcoidosis Patients[1]

- **Non-sarcoidosis related: 66%**
  - **Cardiac 31%**
  - **Pneumonia 17%**
- **Sarcoidosis related: 34%**
  - **Cardiac sarcoidosis 47%**
  - **Pulmonary sarcoidosis 27%**

1. Hu X. SVDLD 2016; 33:275-280

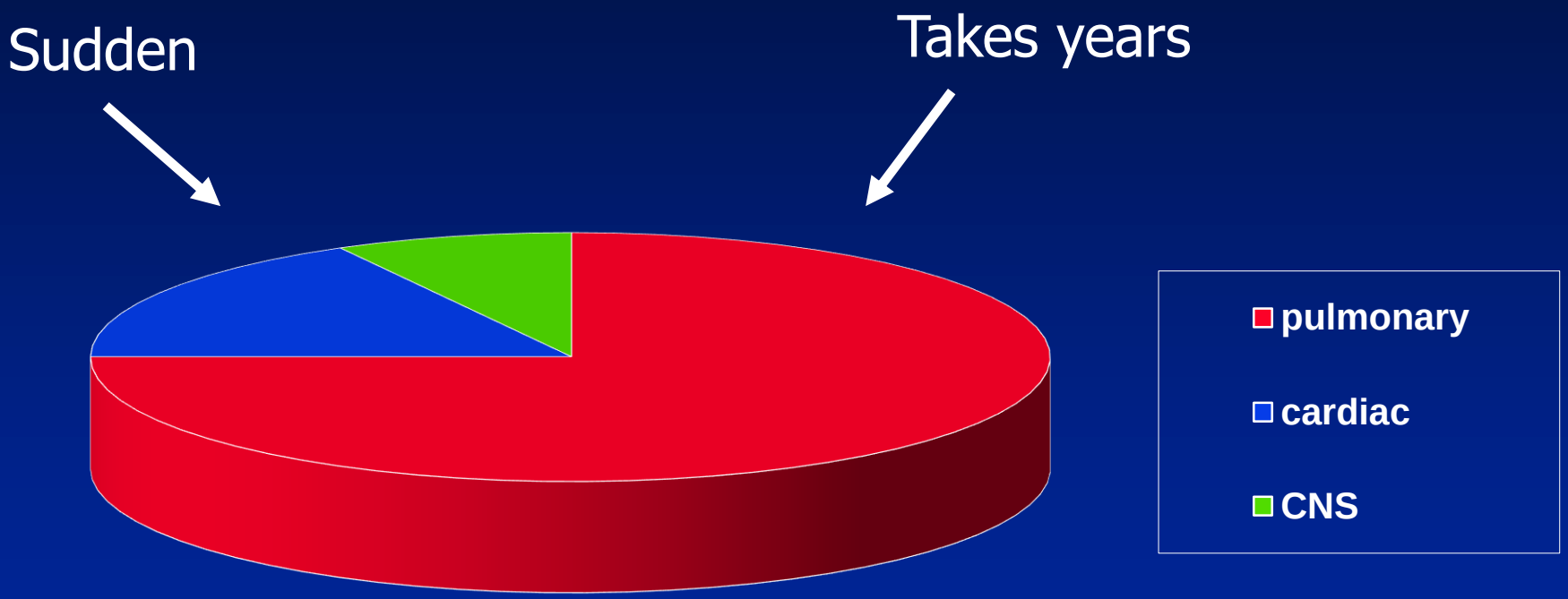
Sarcoid granulomas usually cause organ damage slowly

- **It often takes weeks/months for granulomas to reach macroscopic size and cause significant symptoms[1]**
- **Most morbidity/mortality in sarcoidosis relates to fibrosis that takes months/years**

- **EXCEPTIONS**
  - **Heart**
    - **arrhythmia / sudden death[2]**
  - **CNS**

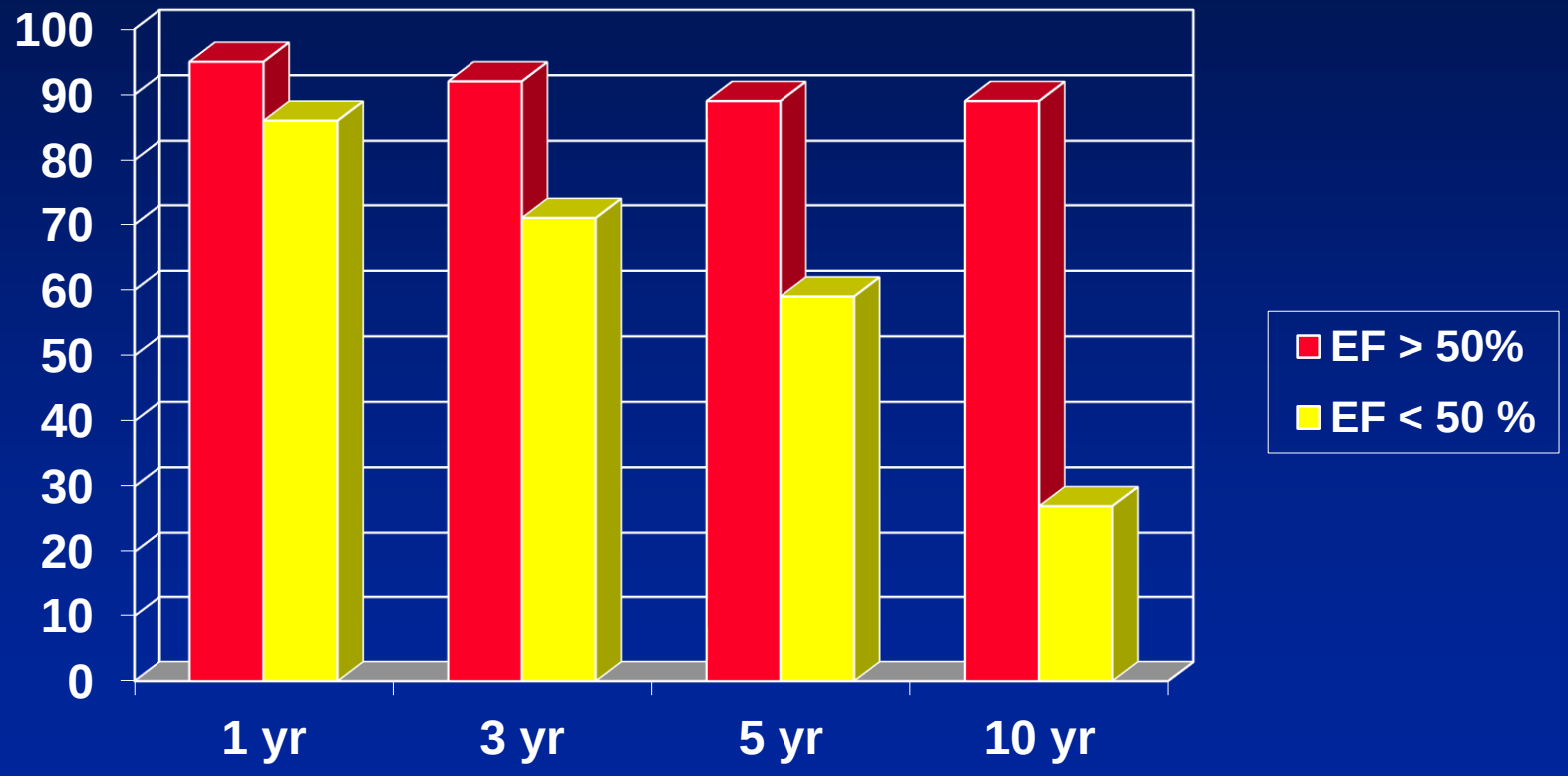
1. Moller DR. Eur Respir J. 2014; 44:1123
2. Koplan BA. Heart Rhythm 2006; 3:924

Death from sarcoidosis



Eur J Respir Dis 1981: 94:169

Cardiac sarcoidosis: survival



Am J Cardiol 2001; 88:1006

Multivariate analysis: mortality with cardiac sarcoidosis

variable	Hazard ratio	p value
sustained VT	(1.24 – 41.77)	0.03
LV wall thickening	(0.37 – 5.00)	0.64
LV wall thinning	(0.16 – 1.76)	0.30
LV end-dias diam	(1.15 – 5.84)	0.02
LV EF	(0.56 – 1.56)	0.80

Am J Cardiol 2001; 88:1006

Cardiac Sarcoidosis: Granuloma location[1]

Autopsy series. N= 40

- **Left ventricular free wall: 98%**
- **Intraventricular septum: 60%**
- **Right ventricle: 55%**
- **Papillary muscle: 45%**
- **Atria: 8%**

1. Roberts WC. Am J Med 1977; 63:86-108

Spectrum of Cardiac Sarcoidosis

- conduction disturbances/heart block
- ventricular arrhythmia/sudden death
- congestive heart failure
- supraventricular arrhythmias
- valvular dysfunction
- pericarditis
- ventricular aneurysm

Chest 1993; 103:253

Myocardial sarcoidosis: diagnosis

- Thallium scan
  - reverse distribution[1]
- Gallium scan[2]
- Gadolinium MRI[3,4]
- PET scan[5]
- Endomyocardial bx: < 25%% yield[6]

1 J Natl Med Assoc 1983; 63:478 2 Int Med 2000; 39:245

3 Ordovas KG. Radiology 2011;261:358-74

4 Crouser ED, Am J Respir Crit Care Medicine 2014;189:109

5 J Nucl Med 2004; 45:1989 6 Chest 1986 90:528

Criteria for the Diagnosis of Cardiac Sarcoidosis: Heart Rhythm Society[1]

- **Histologic dx (myocardium)**

  OR

- **Histologic dx of extra-cardiac sarc**

  AND

  - **Steroid-responsive CM**
  - **Unexplained EF < 40%**
  - **Unexplained sustained VT**
  - **Mobitz II or 3º heart block**
  - **Patchy uptake on cardiac PET**
  - **Late gadolinium enhancement on cardiac MRI**
  - **+ cardiac gallium scan**

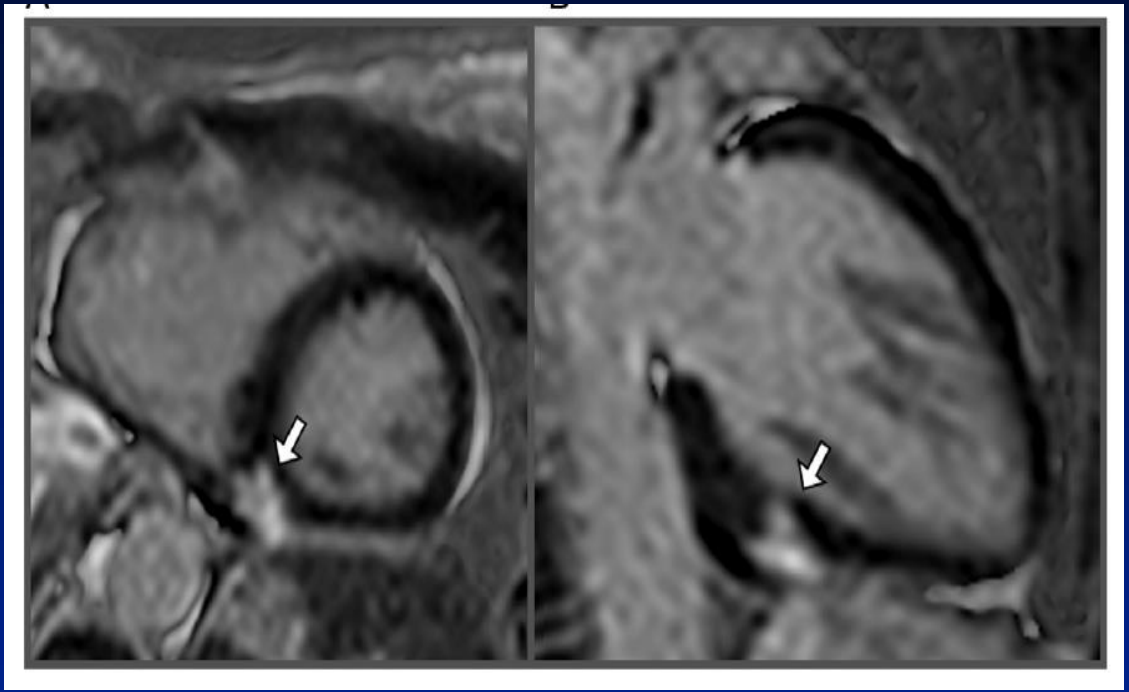
  AND

- **No other causes for these findings**

Birnie DH. Heart Rhythm 2014; 11:1304

Cardiac MRI findings with cardiac sarcoidosis

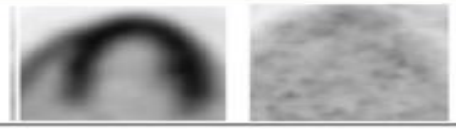
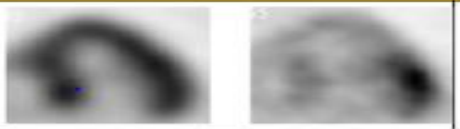
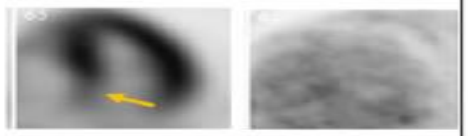
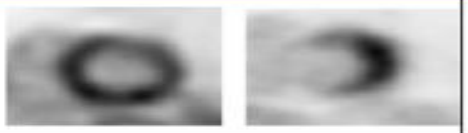
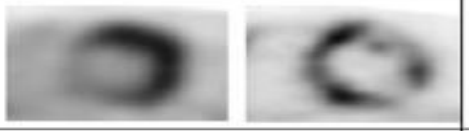
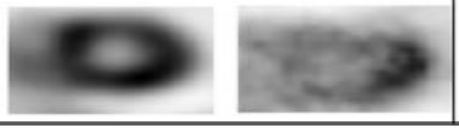
- No pathopneumonic pattern[1]
- delayed enhancement
  - scar from previously active cardiac sarcoidosis[2]
- patchy
- not in a coronary artery distribution
- NOT transmural, endocardial
- T2 hyperenhancement
  - suggests active cardiac sarcoidosis[3]



Delayed gadolinium enhancement

1. Birnie DH. Heart Rhythm 2014; 11:1304
2. Ordovas KG. Radiology 2011;261:358-74
3. Crouser ED, Am J Respir Crit Care Medicine 2014;189:109

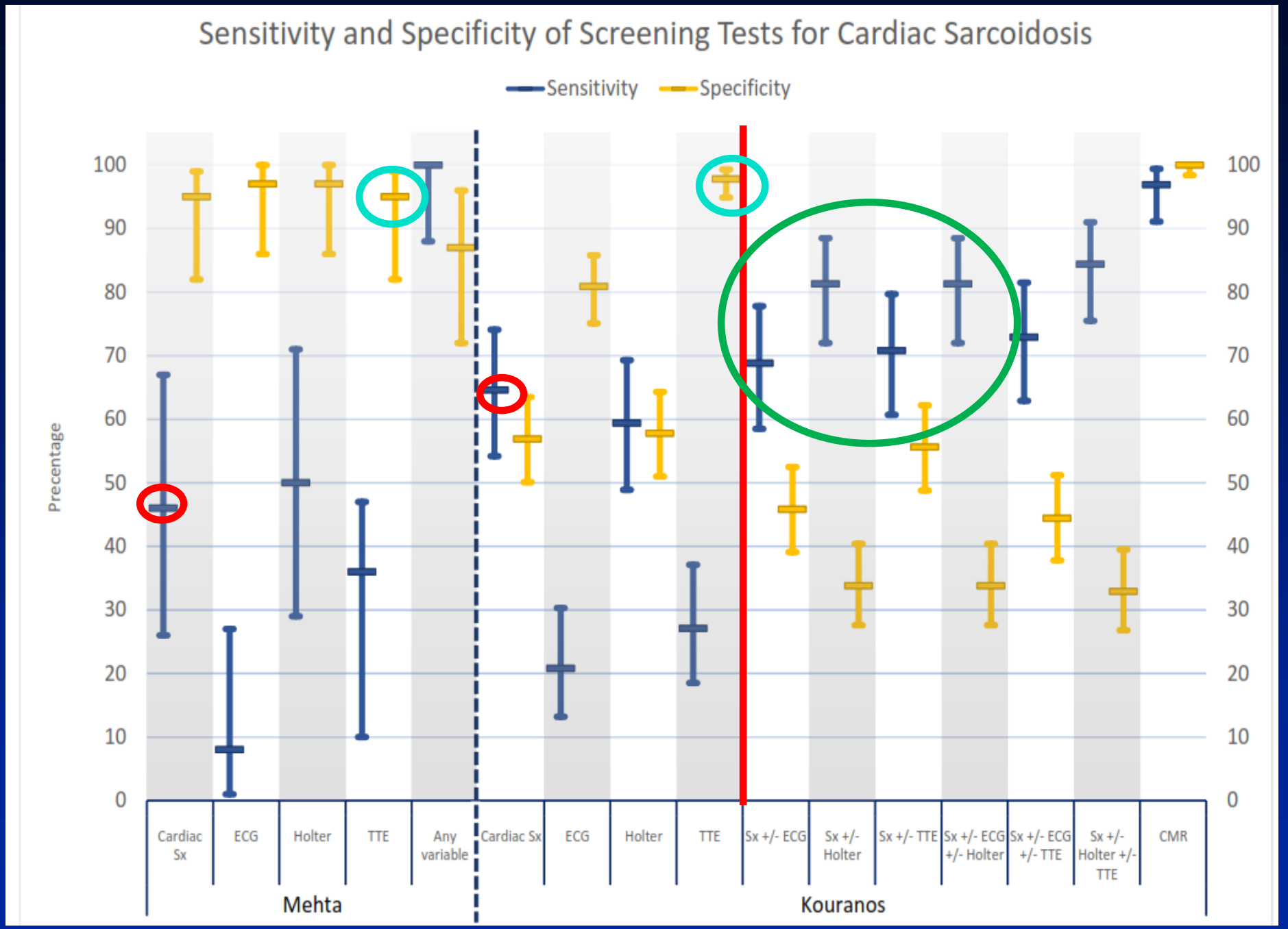
Cardiac PET Scan Classifications

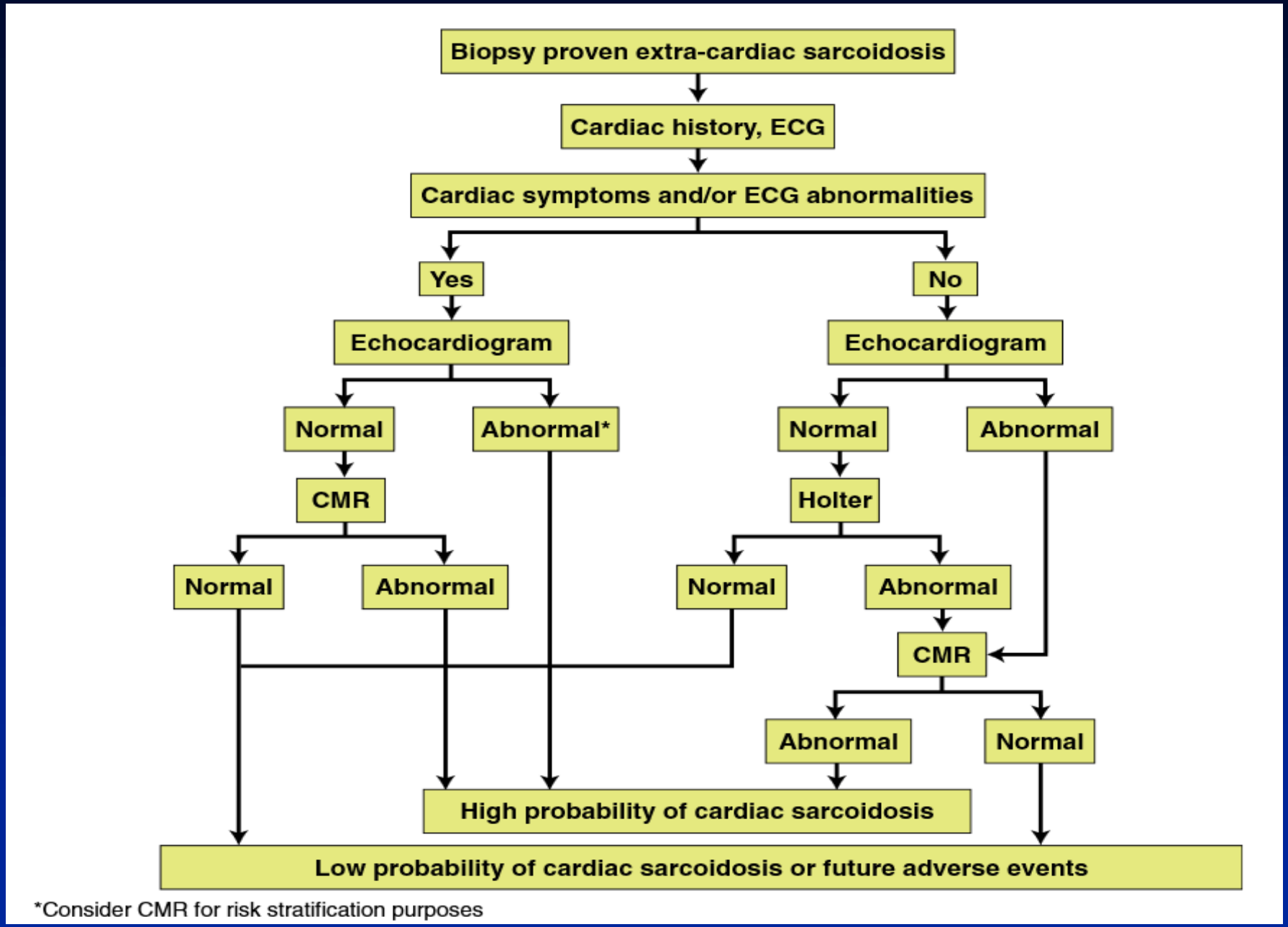
Rest Perfusion	FDG	Frequency	Example		Interpretation / Comment
			Perfusion	FDG	
Normal perfusion and metabolism					
Normal	Normal (negative)	32 (27%)			Normal
Normal	Diffuse (non-specific)	15 (12%)			Diffuse FDG most likely due to failure to suppress FDG from normal myocardium
Abnormal perfusion or metabolism					
Normal	Focal	20 (17%)			Nonspecific pattern; focal increase in FDG may represent early disease vs. normal variant
Positive	Negative	17 (14%)			Rest perfusion defect may represent scar from cardiac sarcoidosis or other etiologies
Abnormal perfusion and metabolism					
Positive	Focal increase ("mismatch pattern")	23 (19%)			Presence of active inflammation ± scar in the same location
Positive	Focal on diffuse	6 (5%)			Similar to above but also areas of inability to suppress FDG from normal myocardium vs. diffuse inflammation
Positive	Focal increase (different area)	5 (4%)			Presence of both scar and inflammation but in different segments

Screening tests for cardiac sarcoidosis

- **symptoms**
  - **palpitations (> 2 weeks)**
  - **syncope / presyncope**
  - **heart failure symptoms**
- **ECG**
  - **1º-3º AVB**
  - **BBB**
  - **supraventricular arrythmia**
- **echocardiogram**
  - **EF < 50%**
  - **wall motion abnormalities**
- **Holter**
  - **PVC's > 10/hr**
  - **NSVT**
  - **SVT**

1. Mehta D. CHEST 2008; 133:1426
2. Kouranos V. J Am Coll Cardiol Img 2017; 10:1437

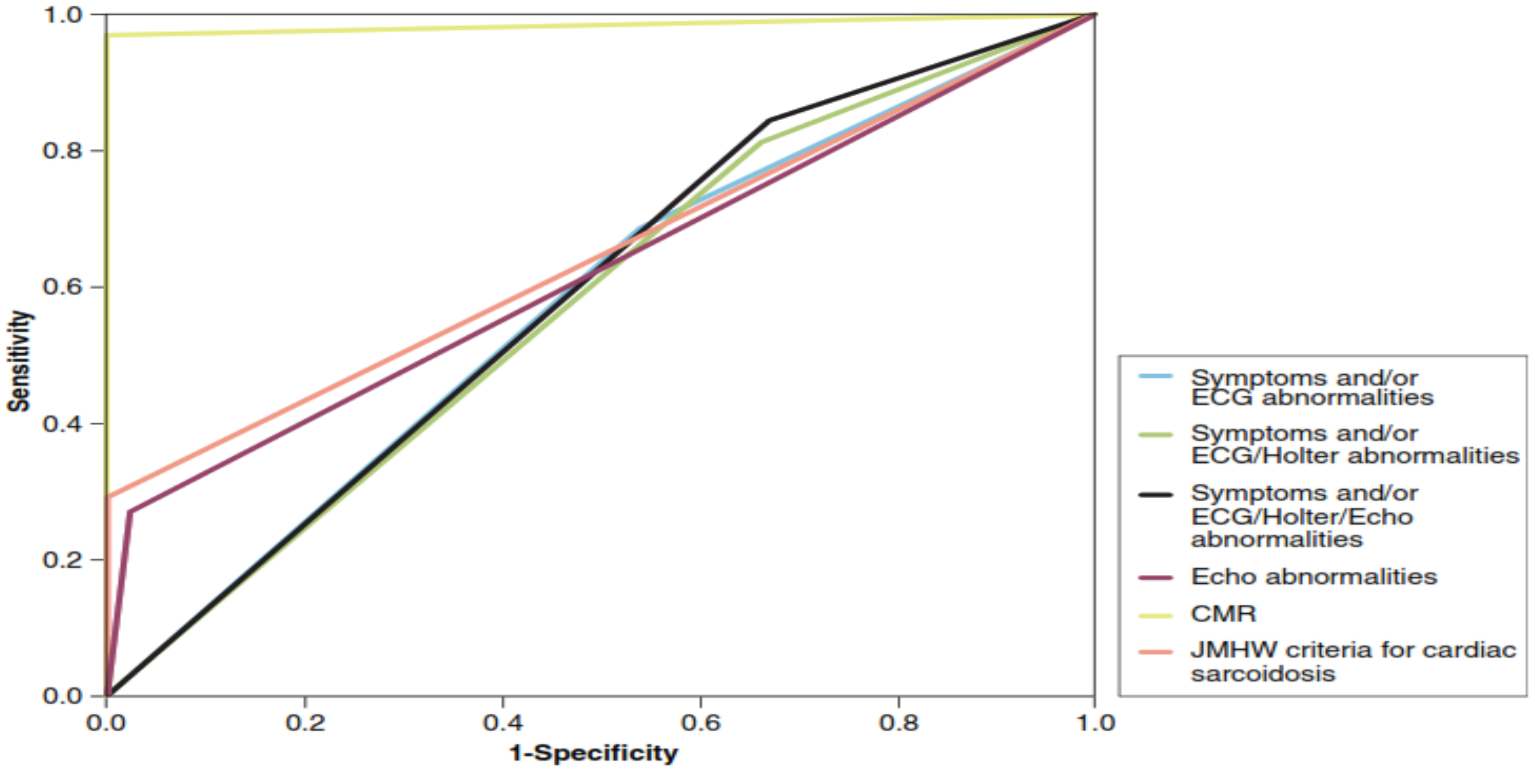

Sensitivity and Specificity of Screening Tests for Cardiac Sarcoidosis
Sensitivity
Specificity
Precentage
100
90
80
70
60
50
40
30
20
10
0
Cardiac Sx
ECG
Holter
TTE
Any variable
Cardiac Sx
ECG
Holter
TTE
Sx +/- ECG
Sx +/- Holter
Sx +/- TTE
Sx +/- ECG +/- Holter
Sx +/- ECG +/- TTE
Sx +/- Holter +/- TTE
CMR
Mehta
Kouranos



Kouranos V. J Am Coll Cardiol Img 2017; 10:1437

Screening for cardiac sarcoidosis with Cardiac PET or Cardiac MRI???

FIGURE 2 ROC Curves for the Clinical Diagnosis of Cardiac Sarcoidosis Based on HRS Criteria



Kouranos V. JACC Cardiovasc Imaging 2017; 10:1437

Other potential screening tests for Cardiac Sarcoidosis

- **Signal-averaged ECG[1]**
  - **> 7-fold increased risk of cardiac sarcoidosis**
  - **baseline QRS duration > 100 ms is 100% sensitive**
- **Cardiac biomarkers**
  - **BNP[2], high sensitivity troponin[3,4]**
- **Strain echocardiography[5]**

1. Schuller JL Cardiovasc. Electrophysiol 2011; 22, 1243
2. Date T. Cardiol 2007; 107: 277
3. Baba Y. Int Heart J 2012; 53:287
4. Kandolin R. Am J Cardiol 2015; 116:960
5. Sperry BW. Am J Cardiol 2017; 119:1663

Multi-logistic analysis of risk factors for cardiac sarcoidosis N = 201

Table 6

Cardiac sarcoidosis risk index.

Risk factor	Score
Any abnormalities in ECG	1
Any cardiac-related symptoms	1
Extrathoracic sarcoidosis	1
X-ray chest progression when CMR	1
NT-proBNP >125 pg/mL	2
Sex: male	2

CMR = cardiac magnetic resonance, ECG = electrocardiography, NT-proBNP = N-terminal of the prohormone brain natriuretic peptide level. For example: male patient seen when disease progressing in the lung with ECG abnormalities but without evidence of extrathoracic disease, without symptoms, with normal NT-proBNP level has the CSRI = 2 + 1 + 1 + 0 + 0 + 0 = 4.

Table 7

Numbers of CS positive (+) and negative (–) patients according to chosen CSRI intervals with likelihood ratio.

CSRI interval	No. of CS (+) patients	No. of CS (–) patients	Likelihood ratio (95% CI)
0–1	0	26	0 (0.000–0.874)
2–4	23	96	0.677 (0.498–0.920)
5–6	19	8	6.712 (3.2–14)
7–8	4	0	∞ (1.2–∞)
Total	46	130	

CI = confidence interval, CS = cardiac sarcoidosis, CSRI = cardiac sarcoidosis risk index.

Martusewicz-Boros MM. Medicine 2016; 95(32): e4518

Treatment of Heart Block from Cardiac Sarcoidosis[1]

- Pacemaker
- Consider AICD
- Immunosuppression
  - 6 studies
    - Received steroids: 47% nodal recovery
    - Did not receive steroids: 0% nodal recovery

1. Birnie DH. Heart Rhythm 2014; 11:1304

Cardiac sarcoidosis: specific immunosuppressive therapy

- corticosteroids are the drug of choice[1]
- 30 mg/day of prednisone is a good initial dose[1]
- all other anti-sarcoidosis drugs have been used including infliximab

1 Yazaki Y. Am J Cardiol 2001; 88:1006

Treatment of Ventricular Arrhythmias from Cardiac Sarcoidosis

- anti-arrhythmic therapy
  - amiodorone[1]
  - sotalol[1]
- immunosuppression
- ablation
  - 40+% recurrence[1,2]

1. Jefic D. Heart Rhythm 2009; 6:189
2. Koplan BA. Heart Rhythm 2006; 3:924

Treatment of Left Ventricular Dysfunction from Cardiac Sarcoidosis

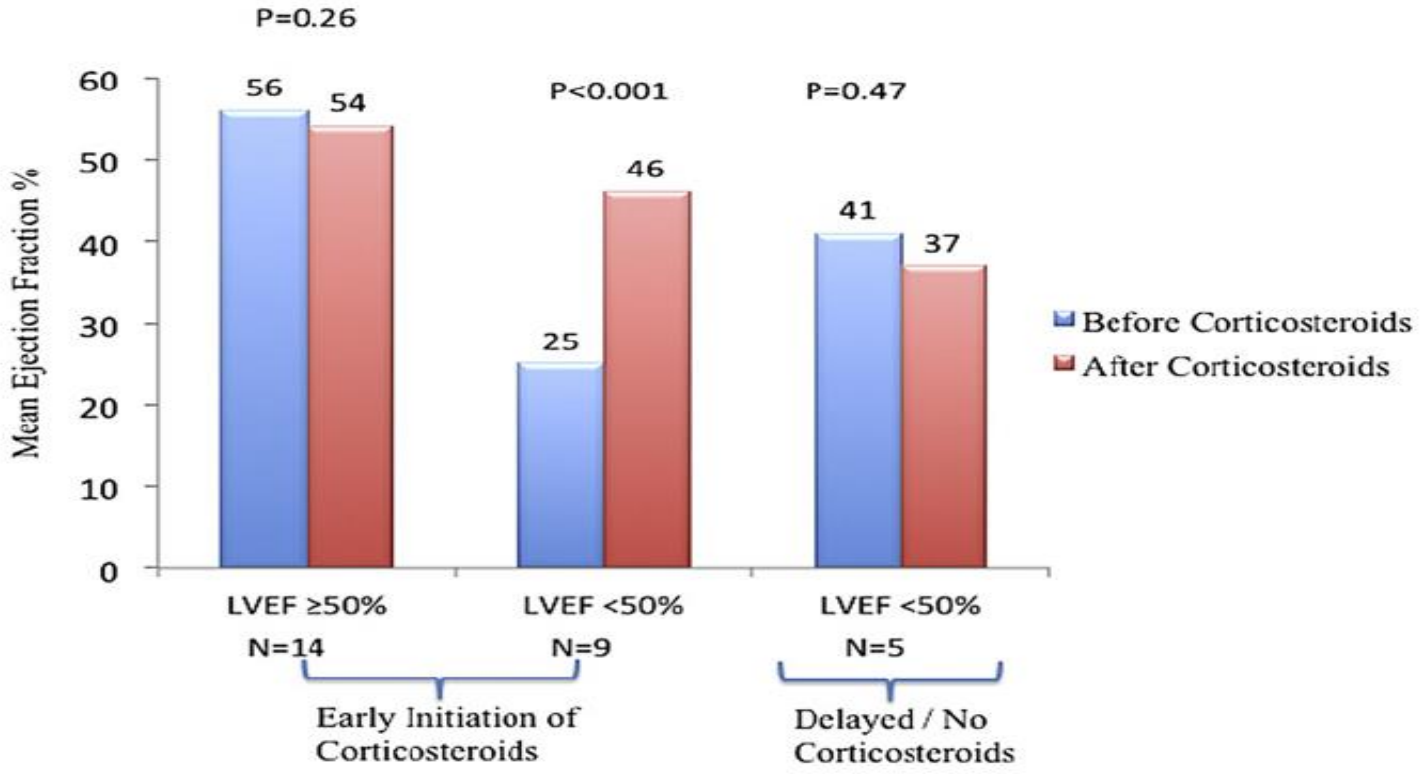
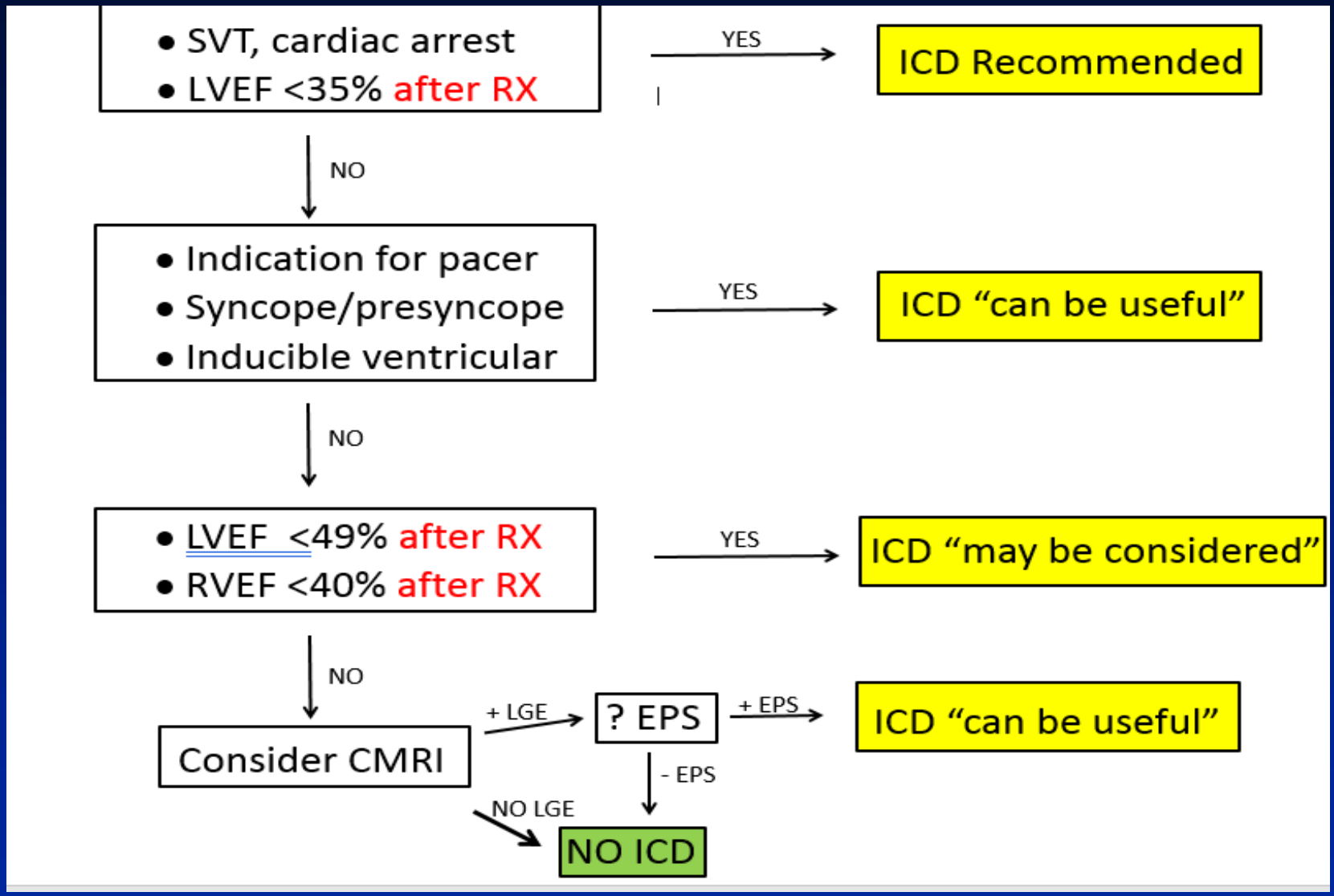


Fig. 1. Impact of corticosteroid therapy on left ventricular ejection fraction in patients with cardiac sarcoidosis.

Padala SK. Int J Cardiol 2017; 227:565

Cardiac Sarcoidosis: AICD Recommendations



1. Birnie DH. Heart Rhythm 2014; 11:1304

Cardiac Sarcoidosis: Take Home Points

- #1 or #2 cause of death from sarcoidosis
- #1 cause of early death from sarcoidosis
- Death associated with VT, poor LV function
- Must screen all sarcoidosis patients
  - Sx
  - EKG
  - Echo?, other testing?
- Dx made by PET + perfusion scans or MRI

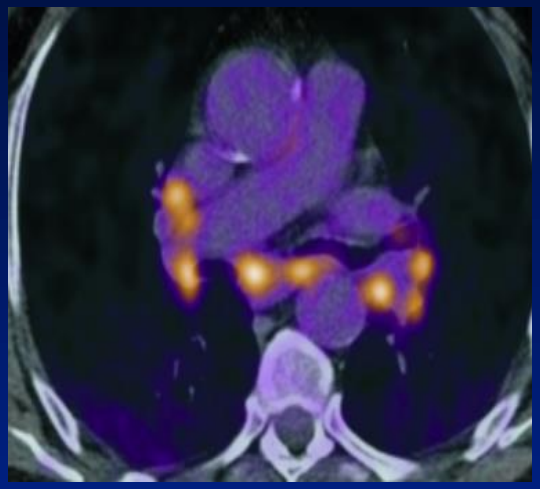
Cardiac Sarcoidosis: Take Home Points

- Corticosteroids are the initial drug of choice
  - VT; LV dysfunction
- Amiodorone, sotolol drugs of choice for vent. arrythmias
- AICD
  - Definite: EF < 35%; VT; cardiac arrest
  - Strongly consider: EF 36-49%; pacer indication
- ? Consider all with +LGE on CMRI for EPS

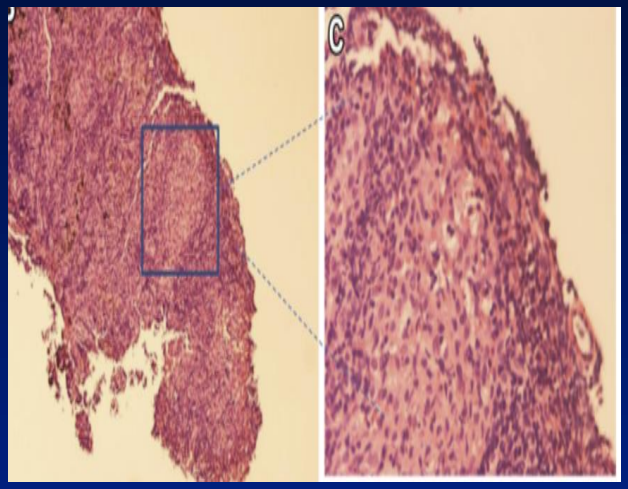
Case 1

- 55 yo man
- metastatic malignant melanoma
- pembrolizumab 200 Mg IV q 3 wks x 4
- near complete tumor response

Case 1



+ FDG PET uptake



EBUS Bx: NCG

- 4 months later
  - - FDG PET
  - Complete resolution of malignant melanoma

Drugs have been associated with sarcoidosis-like reactions (DISRs)

- the immunopathogenesis of sarcoidosis is unknown
- Are these drugs
  - causing sarcoidosis?
  - rendering the immune system more vulnerable to the development of sarcoidosis?
  - exacerbating sub-clinical cases of sarcoidosis?
  - causing conditions distinct from sarcoidosis?

Definition
Drug-Induced Sarcoidosis-Like Reaction

- systemic granulomatous reaction
- indistinguishable from sarcoidosis
- occurs in a temporal relationship to an offending drug

Chopra A. Chest 2018;154:664

DISRs are clinically indistinguishable from sarcoidosis

- bilateral hilar adenopathy[1]
- uveitis[2]
- granulomas in scars,[3] tattoos[4]
- hypercalcemia[3]
- elevated ACE[5]
- + FDG PET uptake[6]
- neurosarcoidosis[7]

1. Nakajima R. Clin Nucl Med 2015; 40:58
2. Doycheva D. Arch Clin Exp Ophthalmol 2009; 247:675
3. Menon Y. Am J Med Sci 2004; 328:173 4. Kim C. BMJ Case Reports 2016: Oct. 26, 2016
5. Gitlin N. Eur J Gastroenterol Hepatol 2002; 14:883 6. Reuss JE. J Immunother Cancer 2016; 4:94 7. Durel CA. BMC Neurol 213; 13:212

DISRs are histologically indistinguishable from sarcoidosis

- epitheliod granulomas
- giant cells
- lymphocytes in the periphery
- Schaumann bodies
- asteroid bodies
- birefringent foreign bodies

1. *Danlos FX. CHEST 2016; 149:e133*
2. *Lomax AJ. Int J Rheum Dis 2017; 20:1277*
3. *Diaen CI. Rheumatol 2009; 148:883*

Unlike sarcoidosis, DISRs…

- may resolve after discontinuation of the offending agent
- may recur with re-challenge

Diagnosis of DISR

- similar to sarcoidosis
- rarely
  - very specific clinical presentation (eg, Lofgren's syndrome)
- otherwise
  - granulomatous inflammation
  - exclude alternative causes
    - infections
    - malignancy
      - sarcoidosis-like reaction of malignancy
      - granulomas in cancerous organ, metastatic sites and draining lymph nodes

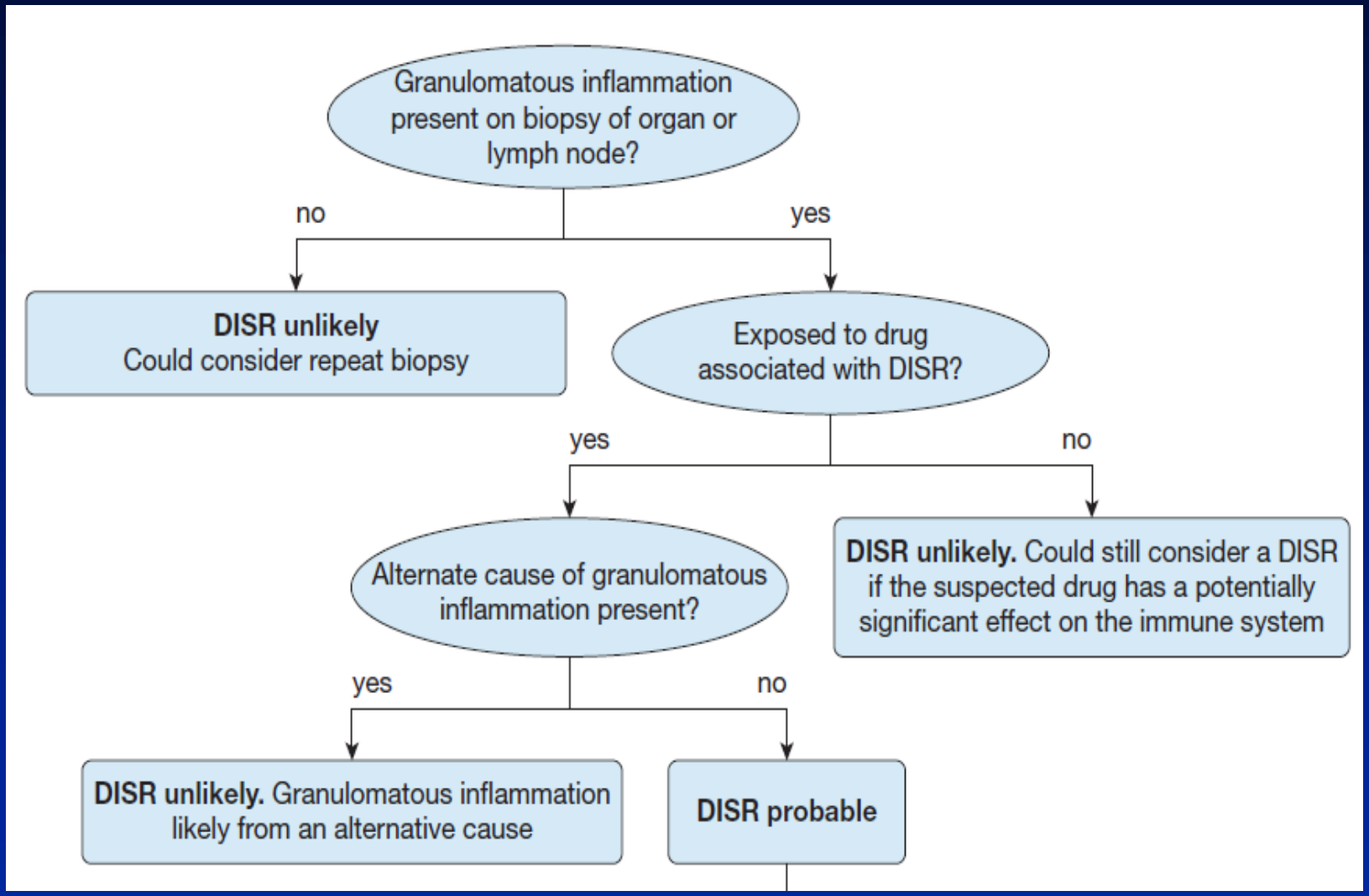
The mis-diagnosis of a DISR may lead to unnecessary or inappropriate treatment.

differential diagnosis without a biopsy (e.g., imaging)

- infections
- malignancy
- drug induced ILD
- immune-related adverse events (irAEs)

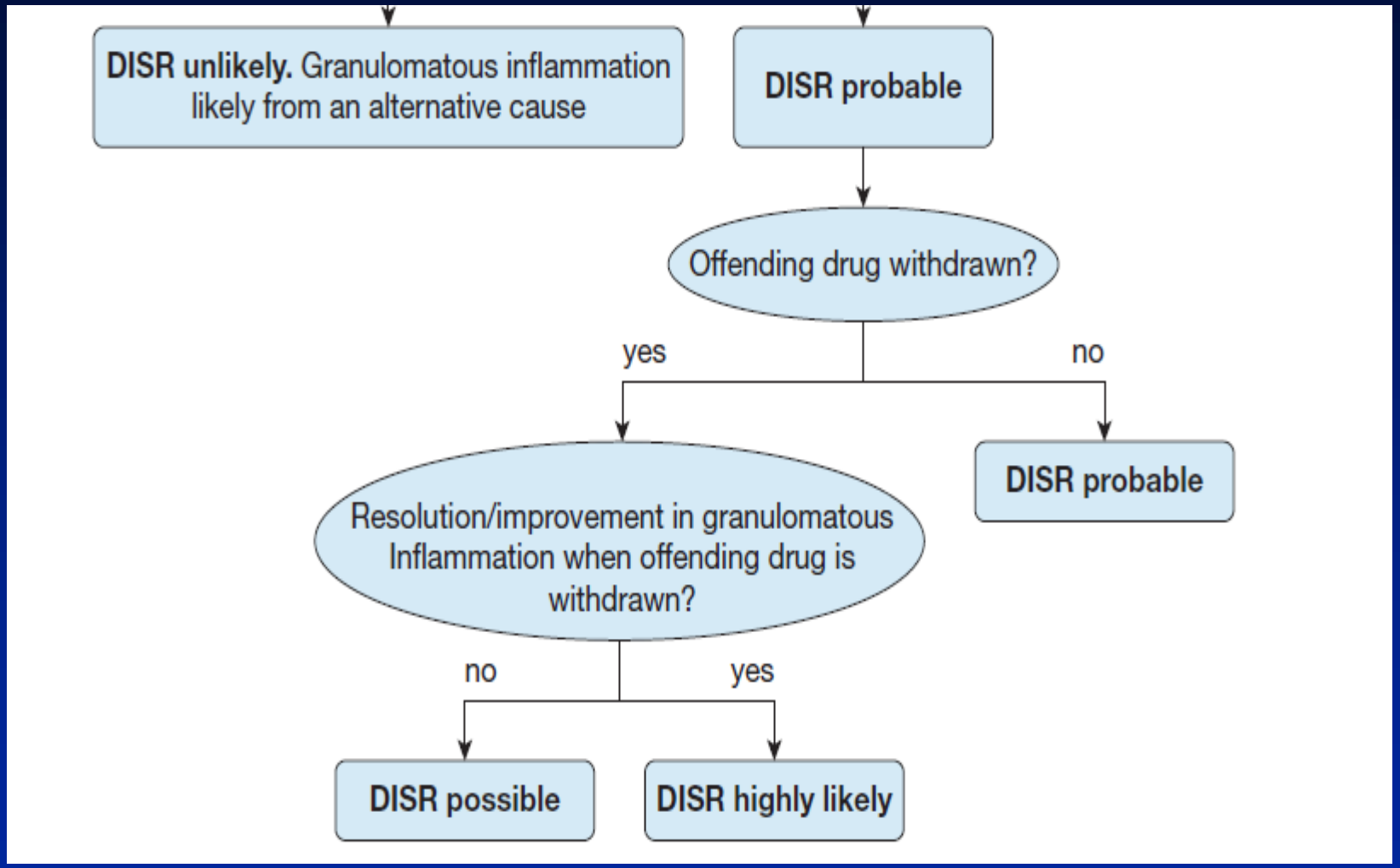
The mis-diagnosis of a DISR may lead to unnecessary or inappropriate treatment.

Proposed DISR Diagnostic Algorithm



Chopra A. Chest 2018;154:664

Proposed DISR Diagnostic Algorithm



Chopra A. Chest 2018;154:664

Major drugs causing DISRs

Drug Class	Drugs	No. of Patients
Immune checkpoint inhibitors	Ipilimumab	14
	Nivolumab	4
	Pembrolizumab	4
Highly active antiretroviral therapy	...	23
Interferons	Interferon-alpha	99
	Interferon-beta	9
Tumor necrosis factor-α antagonist	Etanercept	47
	Adalimumab	18
	Infliximab	17
Miscellaneous drug class	*BRAF* inhibitors	8

Chopra A. Chest 2018; 154:664

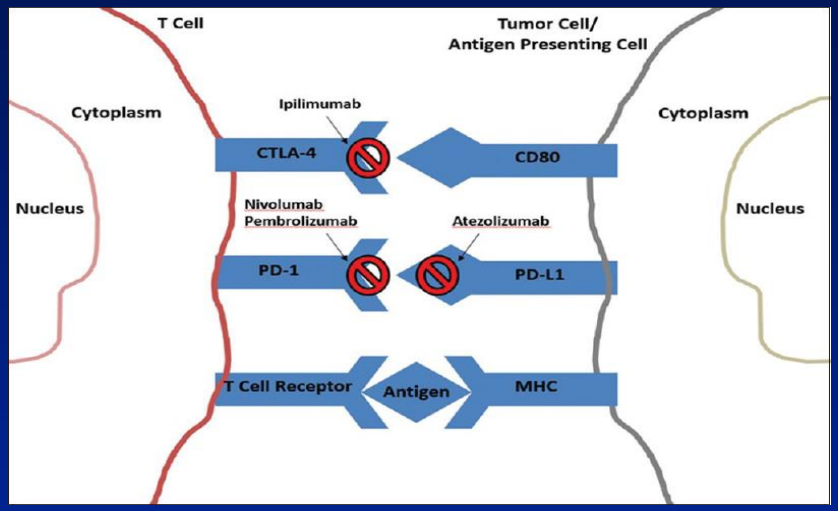
Time course of DISR development with common inducing drugs

Drug Class	Time From Drug Initiation to the Diagnosis of DISR (mo)		Requiring Antisarcoidosis Prescription (%)		Outcome Resolution (%)[a]	
	No. of Patients	Mean (range)	%	No. of Patients	%	No. of Patients
ICIs	23	4.6 (0.7-21.2)	57.2	21	62	21
HAART	22	19.8 (3-48)	41.1	17	64.2	9
IFN	99	9.6 (1.5-120)	42.9	98	75.5	94
TNF-α antagonist	82	24.2 (1-84)	59.5	79	84.3	77

Chopra A. Chest 2018; 154:664

Immune Checkpoint Inhibitors (ICIs)

- alleviate tumor-induced suppression of T-lymphocytes
- enhance tumor immunity
- used for melanoma, NSSC lung cancer, renal cell carcinoma



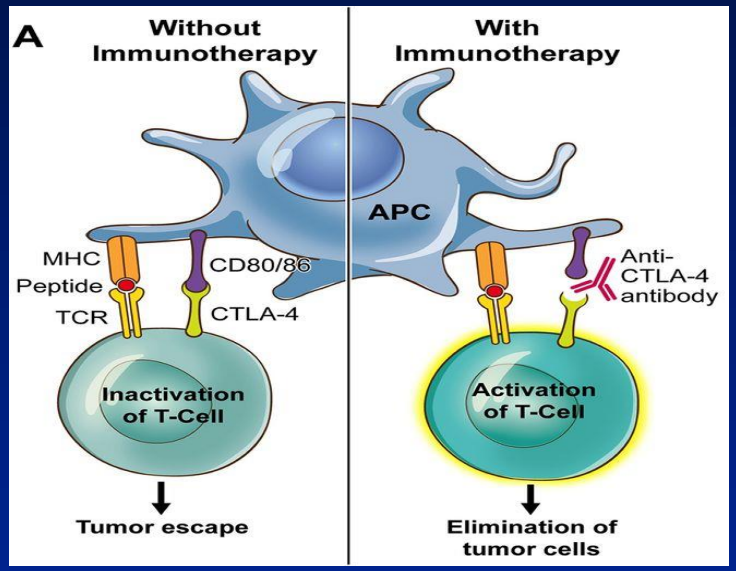
Immune Checkpoint Inhibitors (ICIs)

- enhance anti-tumor activity
- stimulate the immune system
- immune related adverse events (IrAE's)[1]
  - immune thrombocytopenia
  - RA
  - psoriatic arthritis
  - DISR
    - 908 patients received ICI's[2]
    - 21 (2%): IrAE's
    - 2 DISRs (2 mediastinal adenopathy, 1 uveitis)

1. *Chen TW. Ann Oncol 2015; 26:1824*
2. *Cousin S. Ann Oncol 2016; 27:1178*

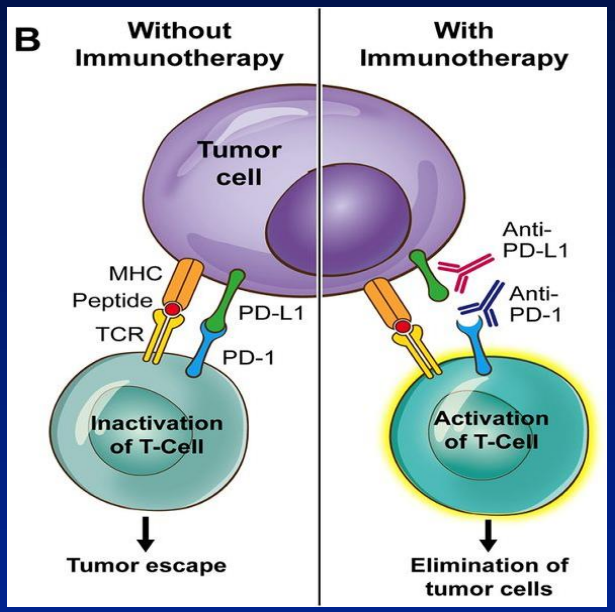
Potential Mechanisms of ICI DISRs

anti-CTLA-4



- block CD80 and CD 86
- block T-cell signaling, prolong T-cell activation
- restore T-cell proliferation increases T17 cells

anti-PD-1



- PD-1 upregulated in sarcoidosis (??!!??)[1]
- increases T17 cells[2]

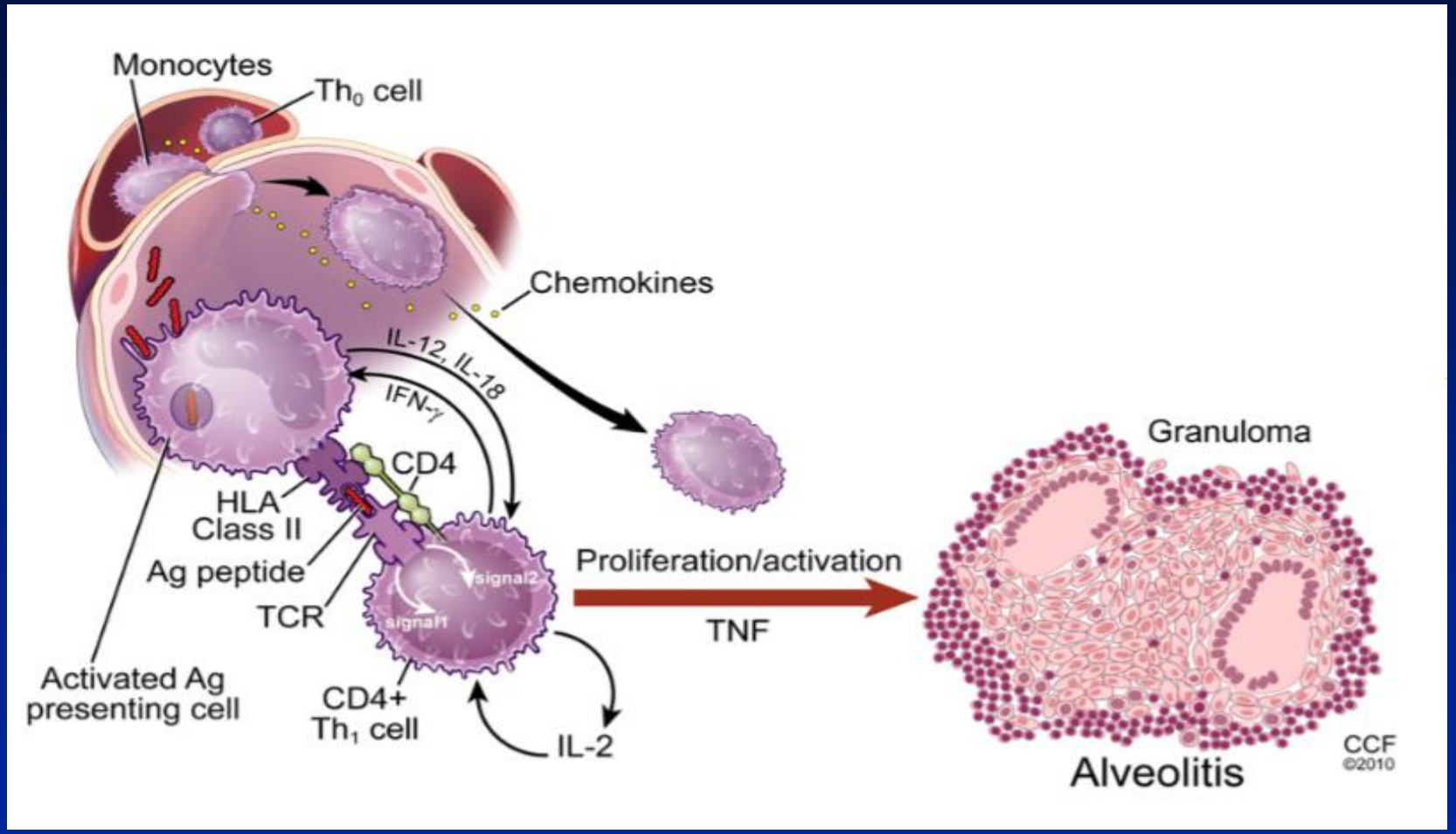
1. *Braun NA. AJRCCM 2014; 190:560*
2. *Brahmer NEJM 2012; 366:2455*

ICI DISRs

- **IrAE's suggest a good anti-tumor response[2]**

1. *Delaunay M. Eur Respir J. 2017; 50*
2. *Ricciuti B. J Cancer Res Clin Oncol 2019; 145:479*

TNF-α Antagonist DISR



Baughman RP. AJRCCM 2011; 183:573

Potential Mechanisms of TNF-α Antagonist DISR

- antibodies to TNF-α soluble receptor: activation of autoreactive T-cells[1]
- unopposed interferon production: shift toward a Th1/Th2 profile[2]

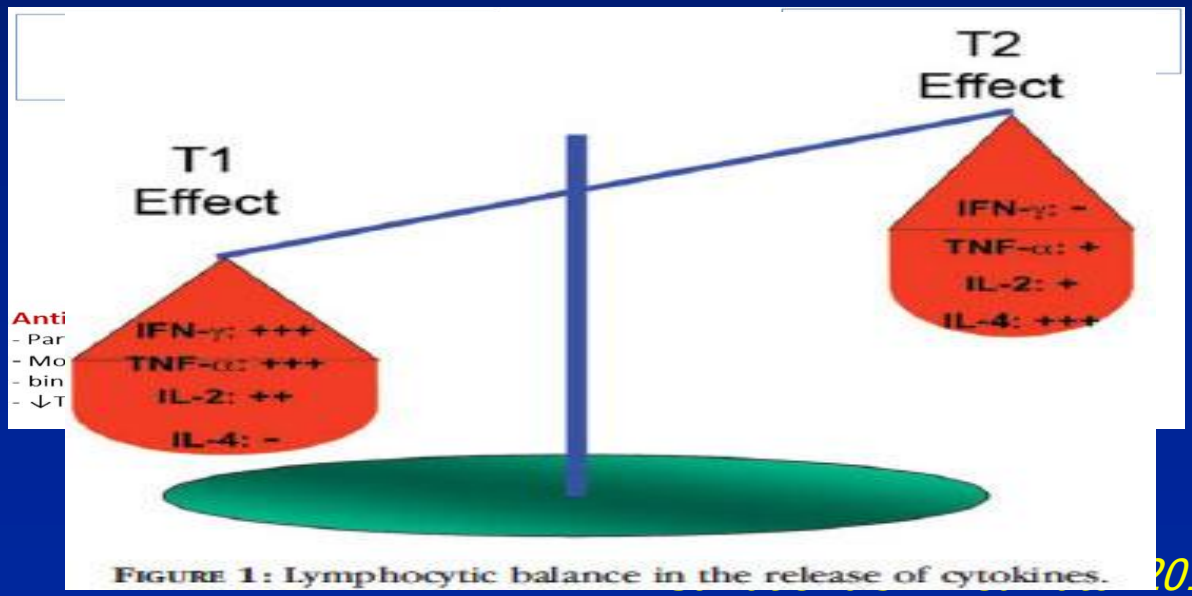


FIGURE 1: Lymphocytic balance in the release of cytokines.

2011; 50:1346
2. Garrido MC. Am J Dermopathol 2015; 37:795
3. Toussirot E. RMD Open 2016; 2:e000239

TNF-α Antagonist DISR

- only 1 of 4 patients with a TNF-α antagonist DISR had a recurrence on an alternative TNF-α antagonist

Chopra A. Chest 2018; 154:664

Interferon (IFN) DISR

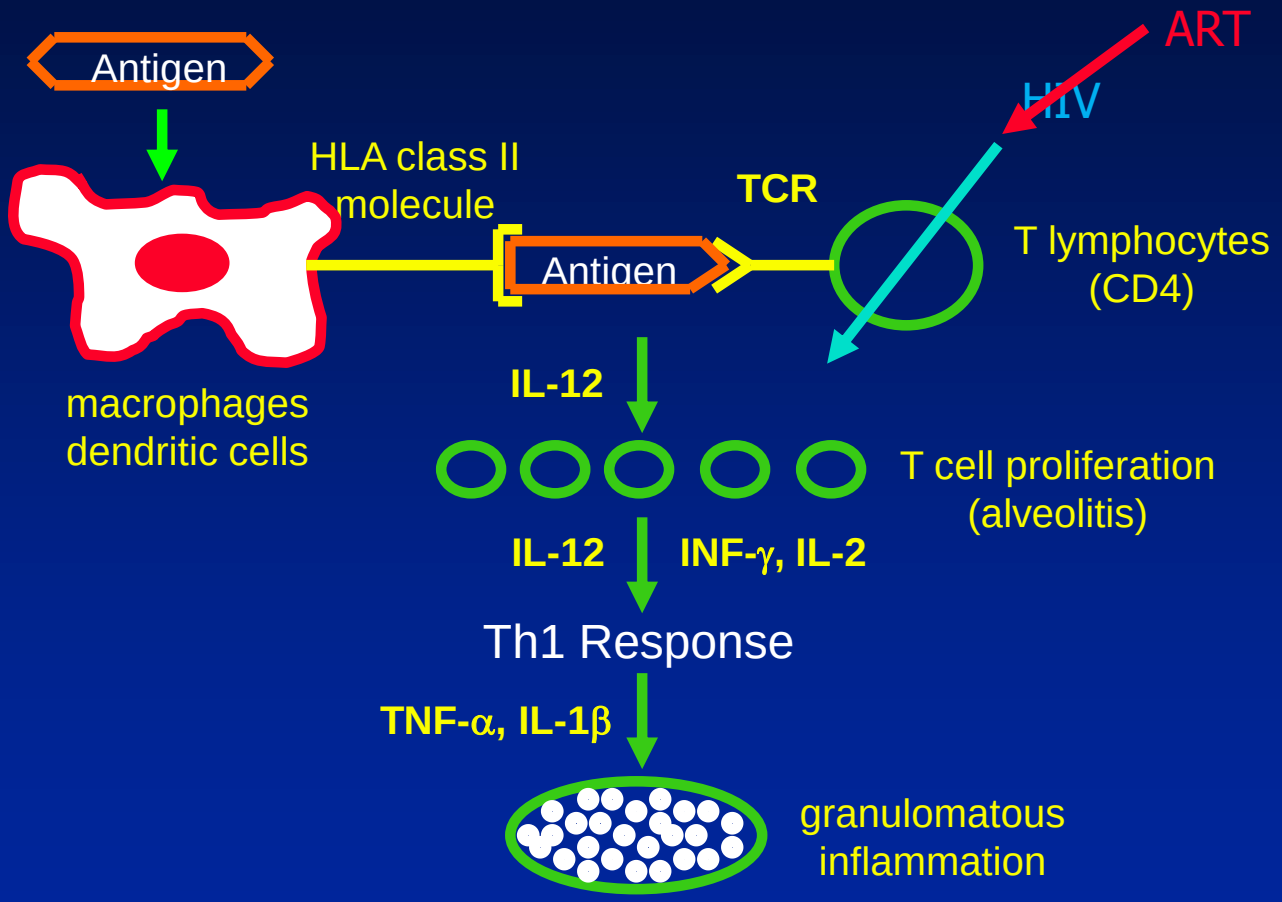
- IFN-α
  - macrophages and dendritic cells
  - RX: Hep B, C, leukemia, melanoma, renal cell ca
- IFN-β
  - fibroblasts
  - RX: multiple sclerosis
- IFN-γ
  - T-lymphocytes
  - RX: limited
- IFN-DISRs most common with IFN-α

Potential Mechanisms of IFN DISR

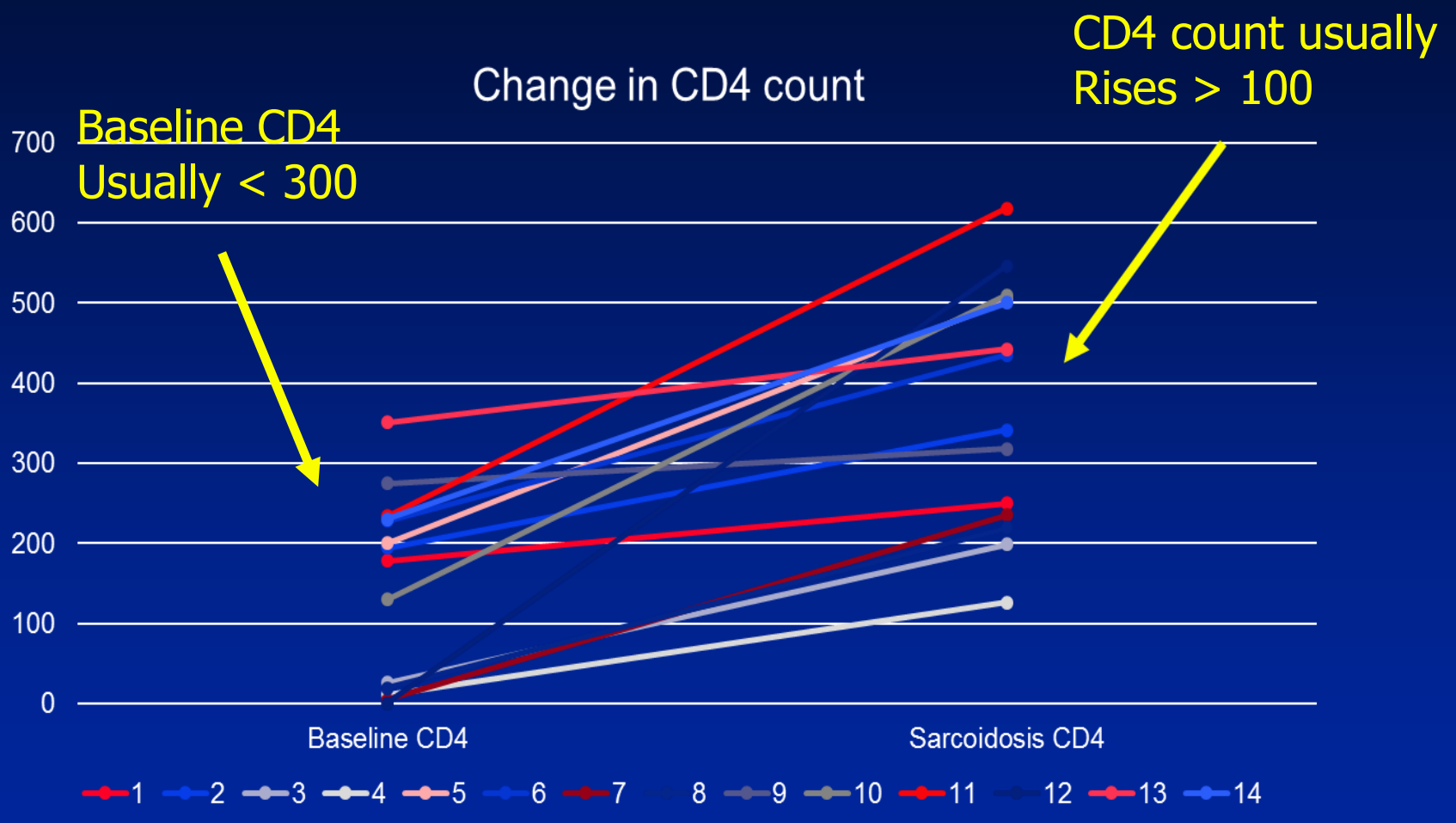
- **IFN-α**
  - **Th1 polarization**
  - **Th2 inactivation**
  - **increase in granuloma promoting cytokines[1,2,3]**
    - **IL-2, IL-8, IL-12, IL-18, IFN-γ**
  - **allele 2 polymorphism in the IFN-α gene (IFN-α17)**
    - **associated with sarcoidosis[4]**

1. *Marzouk K. Curr Opin Pulm Med 2004; 10:435*
2. *Greene CM. J Immunol 2000; 165:4718*
3. *Moller DR. J Immunol 1996; 156:4952*
4. *Akahoshi M. Hum Genet 2004; 114:503*

ART-induced DISR



ART-induced DISR



Church LWP. Microbiol Spectr 2017; Mar;(5)2

DISR Treatment Recommendations - I

- DISRs commonly resolve with or without drug withdrawal
- DISRs may cause minimal to no symptoms
- clinician must weight the benefit of the drug with the harm of the DISR
- drug may be continued
- consider anti-sarcoidosis therapy

  - standard anti-sarcoidosis drugs/doses appear effective

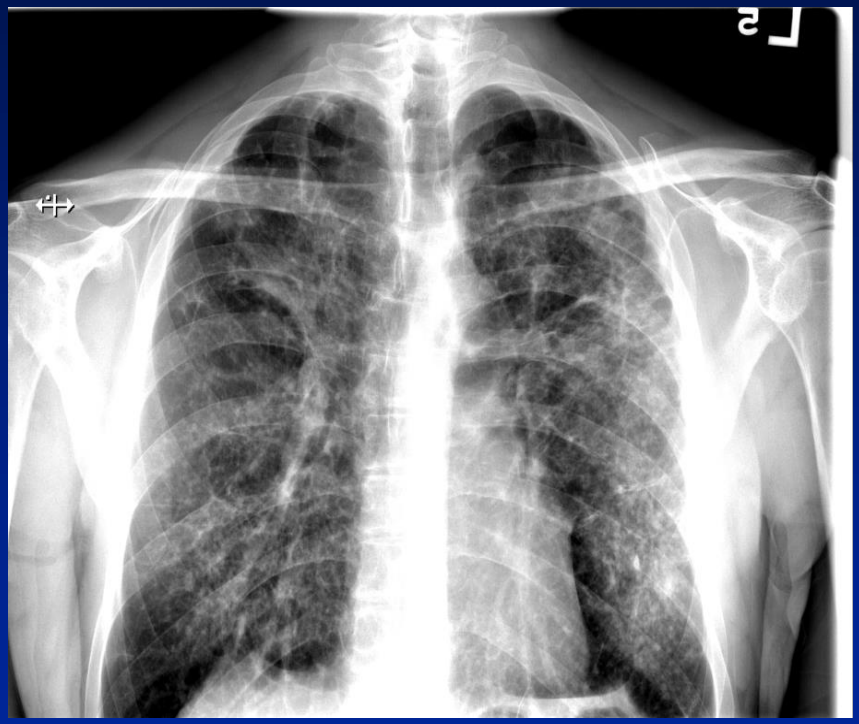
Chopra A. Chest 2018; 154:664

DISR Treatment Recommendations - II

- ICI-induced DISR suggests positive anti-tumor effect and suggests the drug should be continued
- switching to another drug of the same class may be effective
  - ?not so for ART?

Chopra A. Chest 2018; 154:664

Most serious and permanent damage from sarcoidosis is related to fibrosis

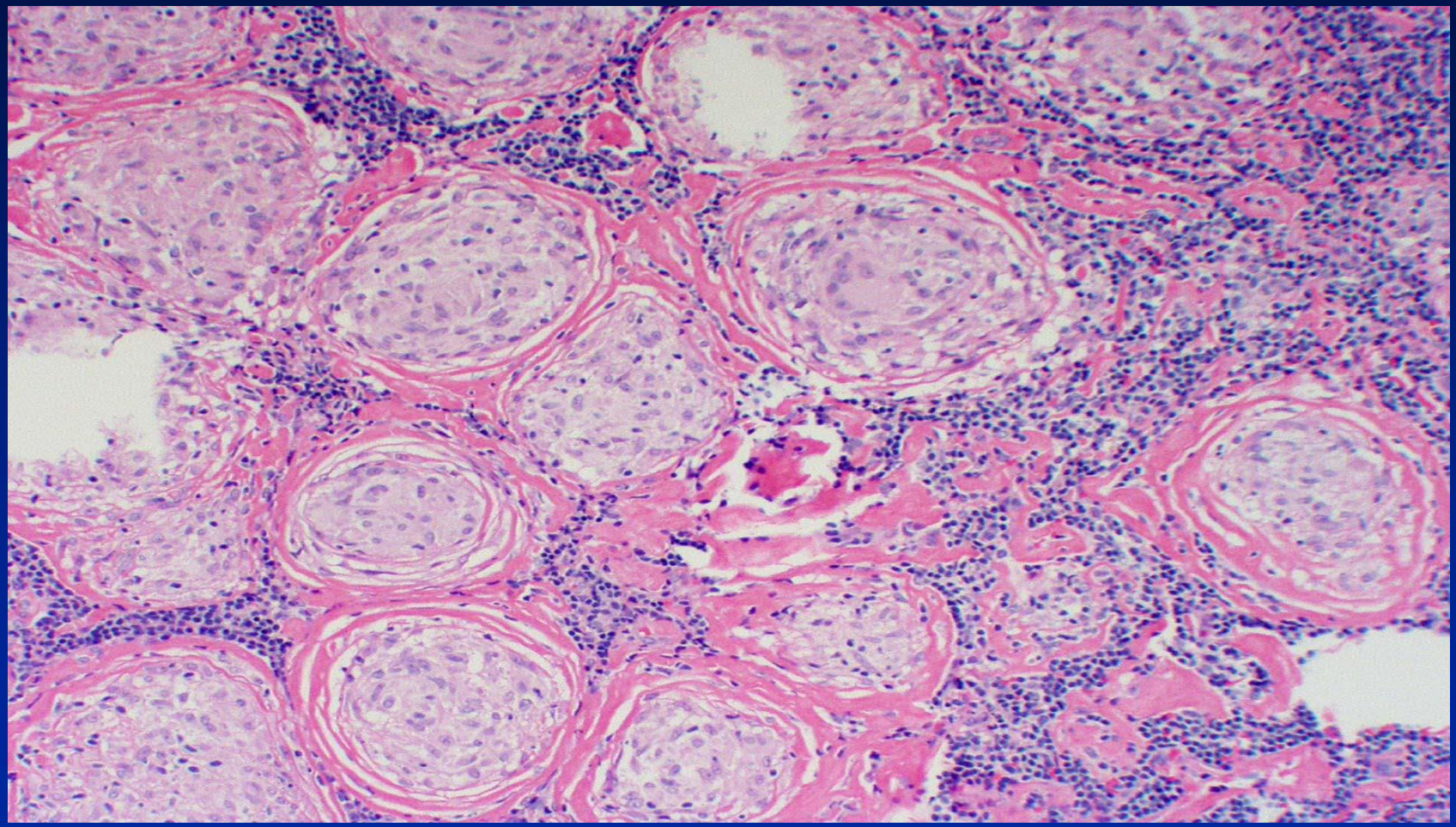


Stage 4 fibrocystic sarcoidosis

- most severe pulmonary dysfunction[1]
- most/all pulmonary deaths[1,2]

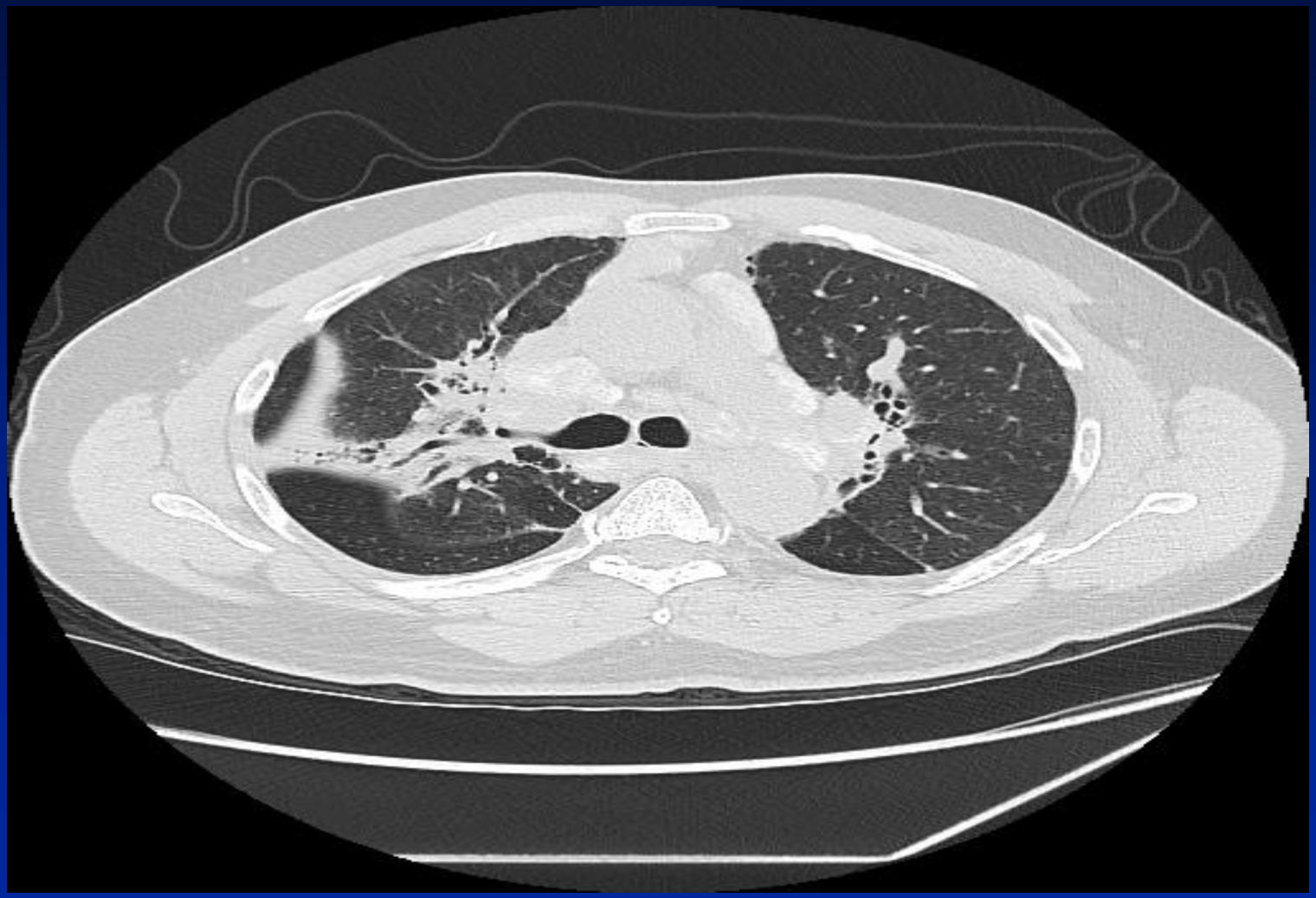
1. Viskum K. Eur Respir J 1993; 6:349 2. Reich JM Chest 2002; 121:32

Sarcoidosis: Granulomas Cause Fibrosis Histologic evidence[1]



1. Zhang C. Chest 2016; 149:499

Sarcoidosis: Granulomas Cause Fibrosis Anatomic evidence[1]



1. Xu L. Am J Pathol 2013; 37:593

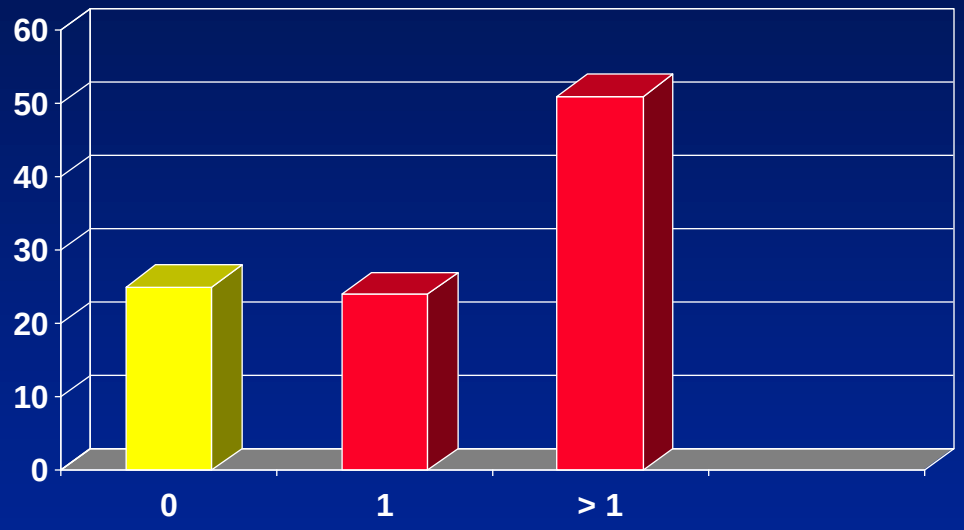
Sarcoidosis: Granulomas Cause Fibrosis Inflammatory evidence[1]

- 22/26 (85%) of fibrotic pulmonary sarcoidosis patients had + lung PET uptake[1]

1. Mostard RL. Respir Med. 2013; 107:439

Fibrotic Sarcoidosis is not necessarily "burnt out" sarcoidosis

Stage 4: Weaned off corticosteroids



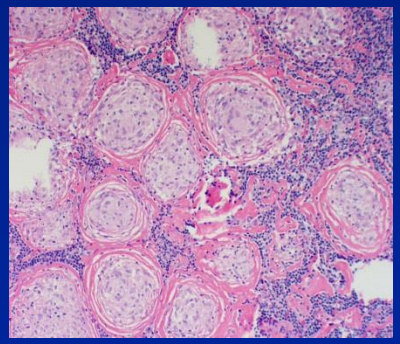
 # relapses

Johns CJ Ann NY Acad Sci 1986: 465:702

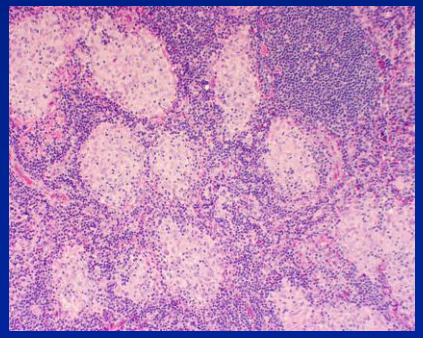
Outcomes of sarcoidosis

10% - 20%

FIBROSIS



GRANULOMA



80%

+/- therapy

RESOLUTION

relapse

Outcomes of sarcoidosis: why we need a fibrotic biomarker.

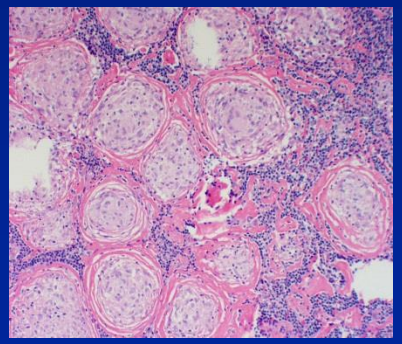
Treat all

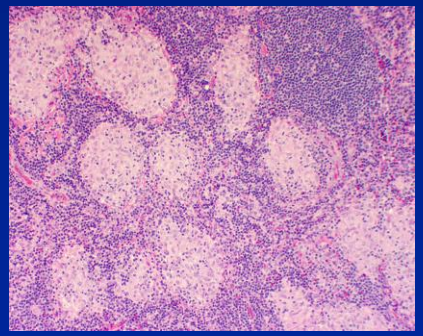
10% - 20%

80%

FIBROSIS

GRANULOMA





+/- therapy

RESOLUTION

relapse

Outcomes of sarcoidosis why we need a fibrotic biomarker

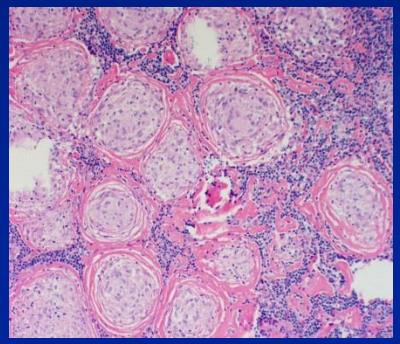
Treat none

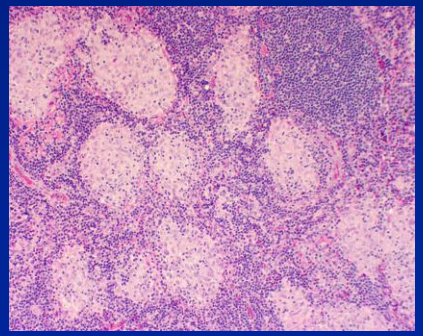
10% - 20%

80%

FIBROSIS

GRANULOMA





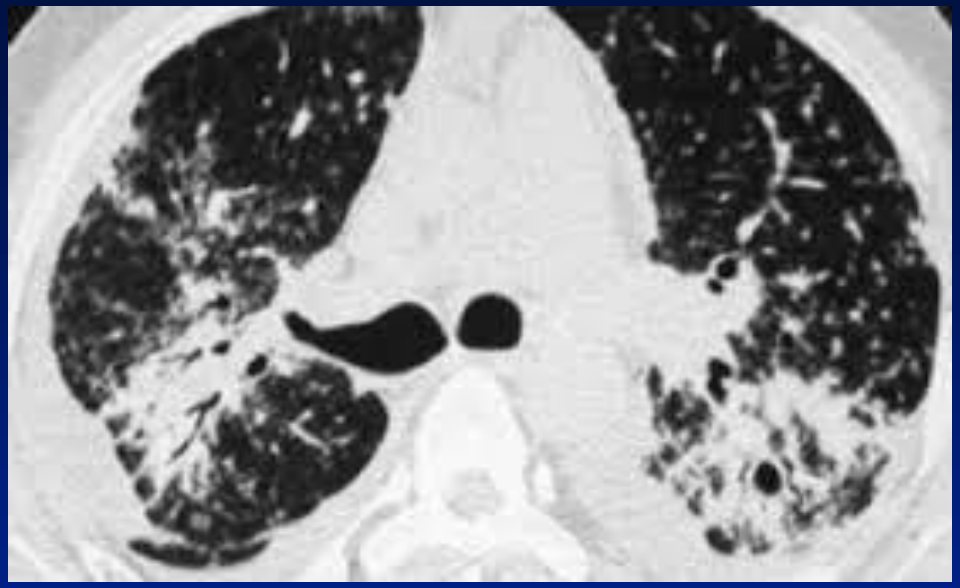
+/- therapy

RESOLUTION

relapse

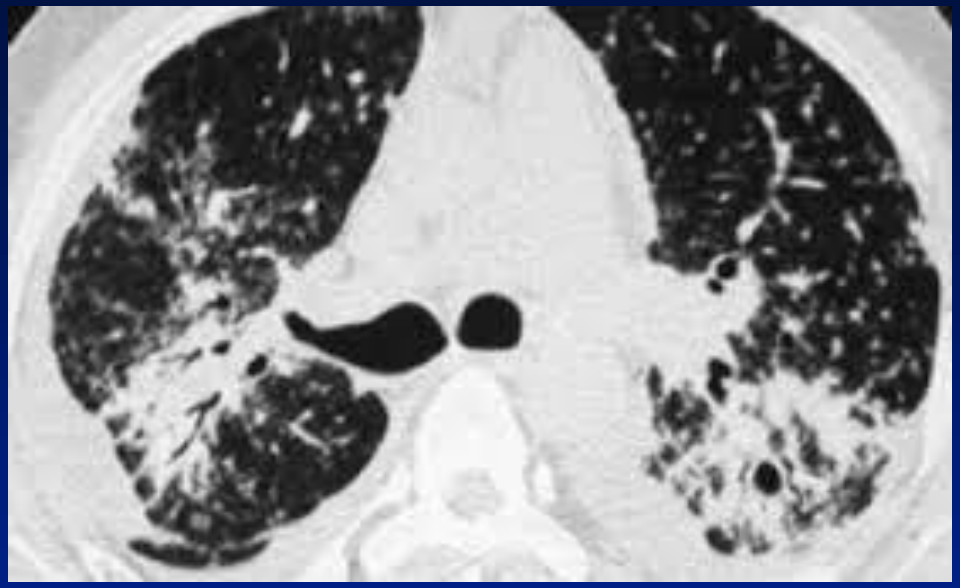
Fibrotic sarcoidosis: Should you treat?

- FVC 45% pred
- dyspnea
- cough
- no rx



Fibrotic sarcoidosis: Should you treat?

- **FVC 45% pred**
- **dyspnea**
- **cough**
- **no rx**



Is there granulomatous inflammation?

- Serum biomarkers positive?[1]
- PET scan positive[1]
- BAL: lymphocytosis
- Do they respond to 20 mg pred/d for 2-4 weeks?

1. Vorselaars AD Eur Respir J 2015; 46:175

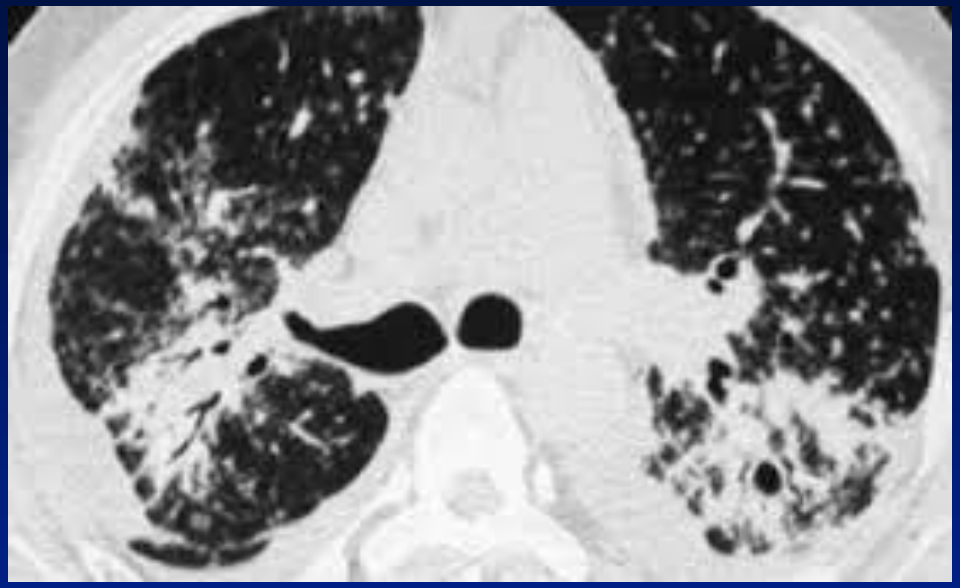
Fibrotic Sarcoidosis: Causes of pulmonary symptoms/dysfunction

- progressive fibrosis
- pulmonary hypertension[1]
- bronchiectasis / infection
  - especially with infliximab[2]
- pulmonary mycetoma[3]

1. Handa T. Chest 2006; 129:1246
2. Baughman RP. Respir Med 2013; 107:2009
3. Kravitz JN Chest 2013; 143:1414

Fibrotic sarcoidosis: Should you treat?

- **FVC 45% pred**
- **dyspnea**
- **cough**
- **no rx**



- Is there granulomatous inflammation?
- Is there pulmonary hypertension?
- Is there bronchiectasis/infection?
- Is there a mycetoma?

1. Vorselaars AD Eur Respir J 2015; 46:175

Fibrotic Sarcoidosis: Summary

- major cause of death from sarcoidosis
- most likely active pulmonary sarcoidosis
- pulmonary hypertension is common
- infection/bronchiectasis commonly occur
- pulmonary mycetoma can be life-threatening