THE OHIO STATE UNIVERSITY

Sarcoidosis: Pathogenesis, Diagnosis, and Treatments

Van Le, MD

Pulmonary and Critical Care Fellowship

Disclosures

- No conflicts
- Project grant support
  - T32-HL007946 (Van Le)
  - Foundation for Sarcoidosis Model Grant
  - L-Grant Phase 1 and 2 (OSU CTSA/UL1-TR001070)

Objectives

- Identify etiologies and pathogenesis of sarcoidosis
- Emphasize on pulmonary, cardiac, and neuro sarcoidosis
- Recognize complications and treatment strategies

Background

- Described 1800s
- Multisystem granuloma formation
- Rare: 1-64/100,000
- More common African American/Northern European

Question 1

Which of the following have been implicated as potential etiology for sarcoidosis?

A. M. TB

B. P. acnes

C. CMV

D. Beryllium

E. All above

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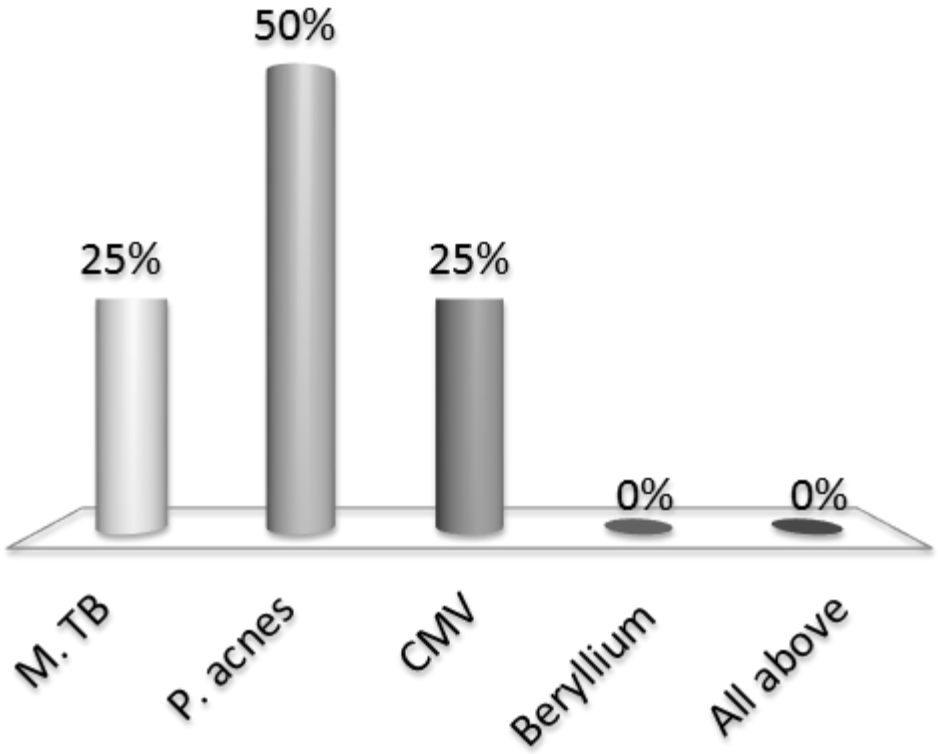


Infectious Hypothesis

- Bacterial
  - Mycobacterium tuberculosis[1]
  - Propionibacterium acnes[2]
- Viral
  - Epstein–Barr virus[3]
  - Cytomegalovirus[3]
  - Human herpes virus[3]

[1] *J Exper Med* 2005; 5: 755-67.
[2] *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 371-4.
[3] *Semin Respir Crit Care Med* 2014;35:285–95.

Environmental Hypothesis

- Berylliosis
  - Pathologically and clinically indistinguishable[1]
- Post 9/11 crisis
  - EMS and firefighter had excessive rate[2]
- Geography
  - Varies greatly by region[3]

[1]*Semin Respir Crit Care Med* 2014; 35: 316-29.
[2]*Resp Med* 2017; 132: 232-7.
[3]*Am J Epidemiol* 1999, 150: 271-8.

Genetic Hypothesis

- Familial risk
  - Monozygotic twin (~ 80x OR)[1]
  - Siblings and parents (~ 3-6x OR)[2]
- Races
  - African American, Northern Europe, Japanese
- Specific genes
  - HLA (DRBQ) polymorphisms (Lofgren Syndrome)[3]
  - BTNL2 splice site mutation[4]

[1]*Thorax* 2008;63:894-6.
[2]*Genet Epidemiol* 1996; 13: 23-33.
[3]*Am J Respir Crit Care Med* 1997;156:1601-5.
[4]*Nat Genet* 2005;37:357-64.

Infectious

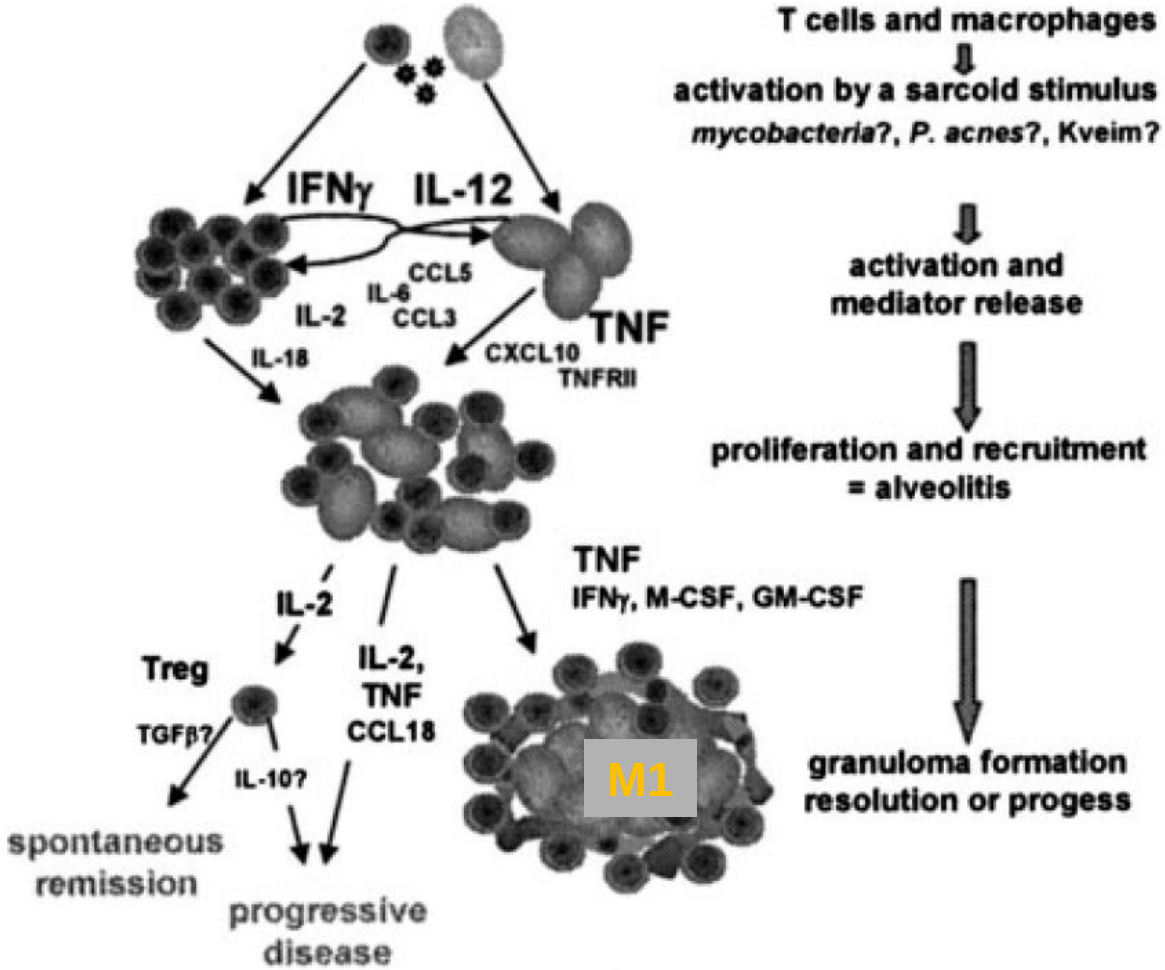
Environmental

Sarcoidosis = Exposure + Genetics + Others

Occupational

Dysregulated immune system

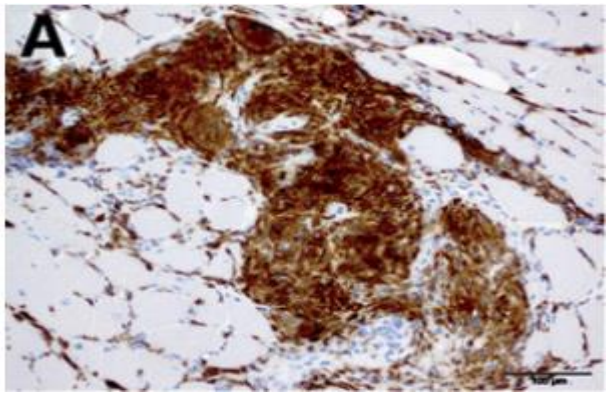
Mechanisms



Semin Respir Crit Care Med 2007; 28:3-14.

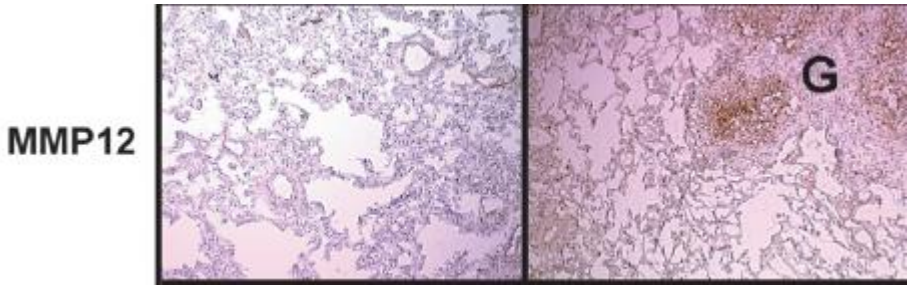
Mechanisms

- Pathology data showed strong CD206 expression.



Immunohistochemistry of CD206 in human sarcoidosis muscle granuloma.[1]

- BAL and tissue gene and protein expression indicated M2 polarization (e.g., high MMP12 gene and protein expression).



Immunohistochemistry of MMP12 in human sarcoidosis lung granuloma.[2]

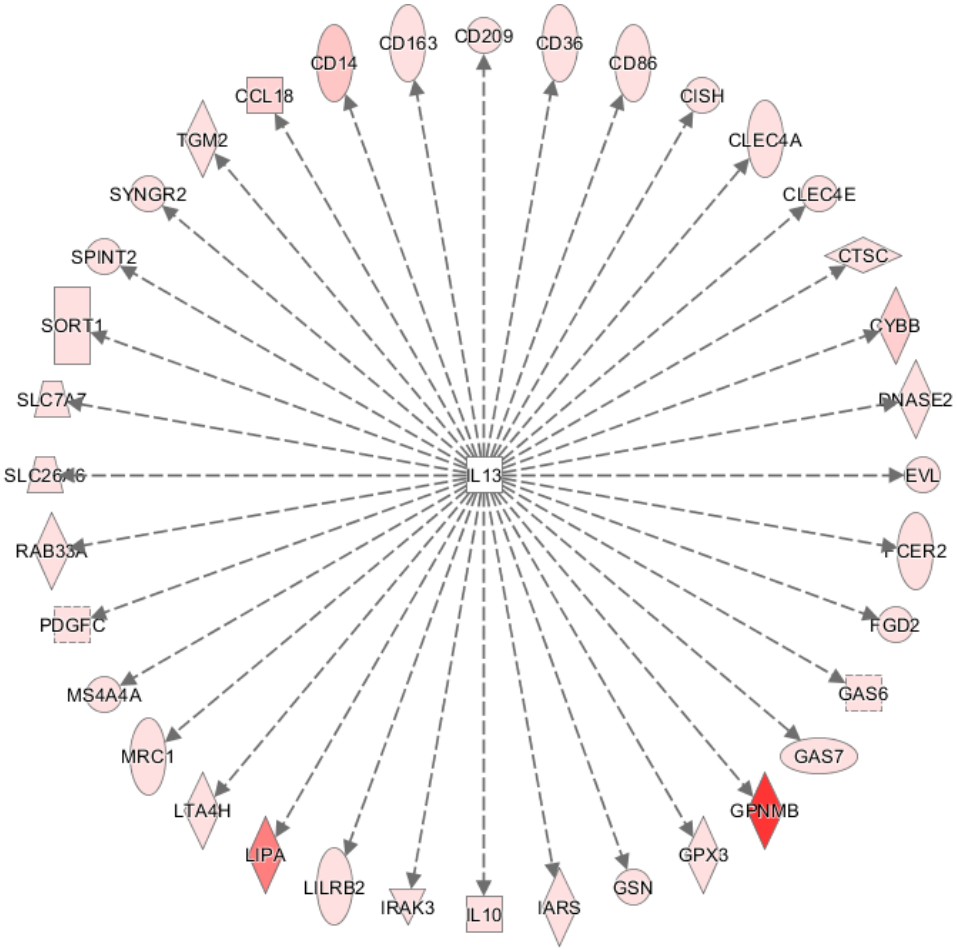
[1]*Am J Pathol* 2011; 178:1279-86.
[2]*AJRCCM* 2009; 179: 929-38.

Results: M1/M2 genes

M2 Macrophage Genes		M1 Macrophage Genes	
Genes	Fold Δ	*Genes*	Fold Δ
CD163	11.1	*CXCL9*	4.0
MMP2	10.0	*HLA-DMA*	4.0
HNMT	7.9	*CXCL10*	3.3
HS3ST2	7.2	*IL18*	3.2
STAB1	6.7	*CD68*	3.1
CHIT1	6.4		
MS4A4A	6.3		
CCL18	6.2		
MMP12	5.8		
MAF	5.1		
CCL13	4.7		
IL10	4.4		
CD163L	4.2		
MRC1	4.0		
LTA4H	3.4		

Gene expression reflecting M1/M2 polarization. Representative of a total of 30 M1/M2 genes included, using cut-off values of greater than a 2-fold change in expression ($p < 0.02$).

"Upstream analysis": *IL-13 is a primary molecular driver of Sarcoidosis Granuloma formation*.



All genes are differentially expressed and are regulated by IL-13/STAT6

Common Presentations

- Nonspecific/Constitutional
  - Fever, sweats
  - Weakness
  - Weight loss
  - Fatigue
- Psychological
  - Depression

Common Organ-Specific

- Lung: cough, short of breath, chest pain
- Eye: blurred vision, pain, redness
- Skin: rash, nodules, E. nodosum
- Heart: palpitations, presyncope, syncope
- Bones/Joints: arthritis, pain, joint swelling

Organ Involvement

Organ Involvement	Number	Percent
Lungs	699	95.0
Skin*	117	15.9
Lymph node	112	15.2
Eye	87	11.8
Liver	85	11.5
Erythema nodosum	61	8.3
Spleen	49	6.7
Neurologic	34	4.6
Parotid/salivary	29	3.9
Bone marrow	29	3.9
Calcium	27	3.7
ENT	22	3.0
Cardiac	17	2.3
Renal	5	0.7
Bone/joint	4	0.5
Muscle	3	0.4

AJRCCM 2001; 164: 1885-89.

Pulmonary Sarcoidosis

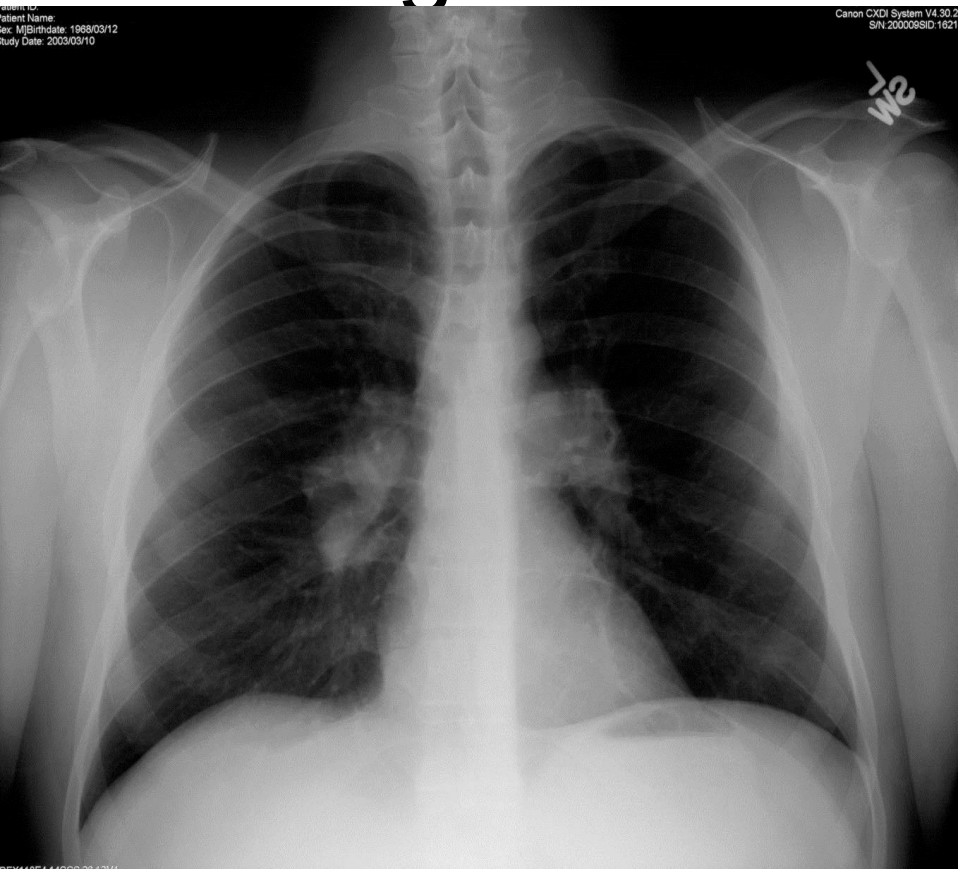
- >90% of the time
- Hilar adenopathy is most common
- PFT: restrictive w/ ↓DLCO; 50% obstruction
- 6-23% has pulmonary hypertension

Scadding System

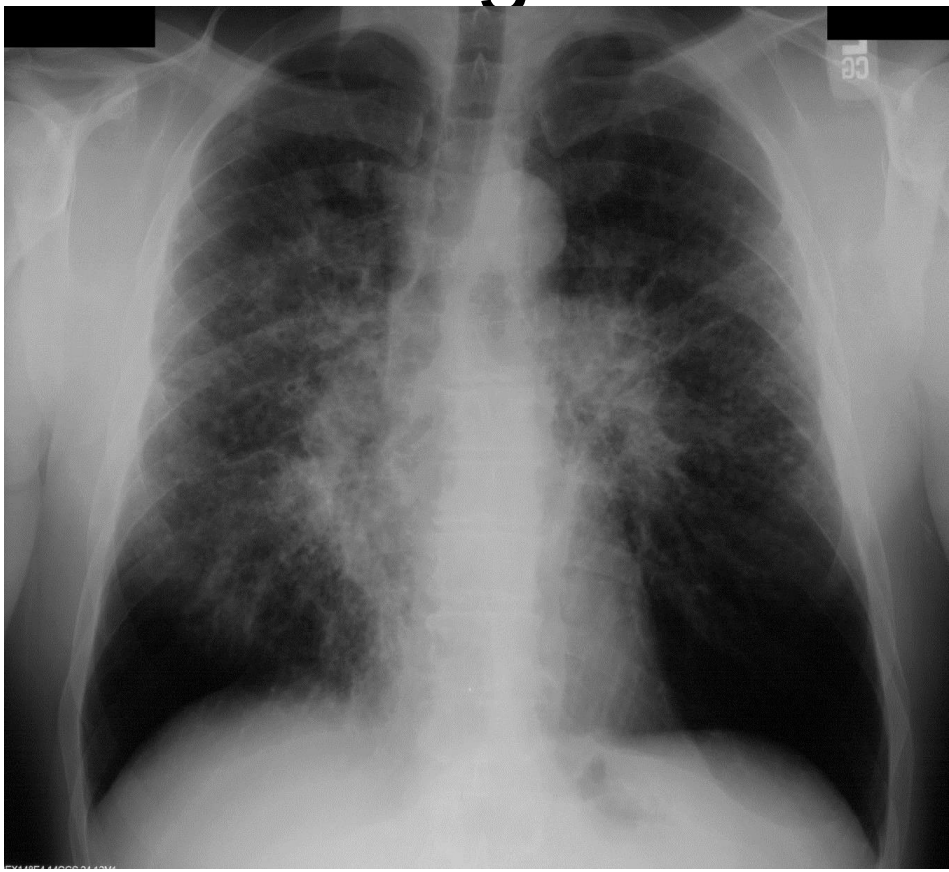
		Number	Percent
Roentgenographic stage*			
Stage 0	Normal	61	8.3
Stage 1	Large chest lymph nodes	292	39.7
Stage 2	Lung nodes and infiltrates	270	36.7
Stage 3	Lung infiltrates only	72	9.8
Stage 4	Fibrosis	40	5.4

AJRCCM 2001; 164: 1885-89.

Stage I

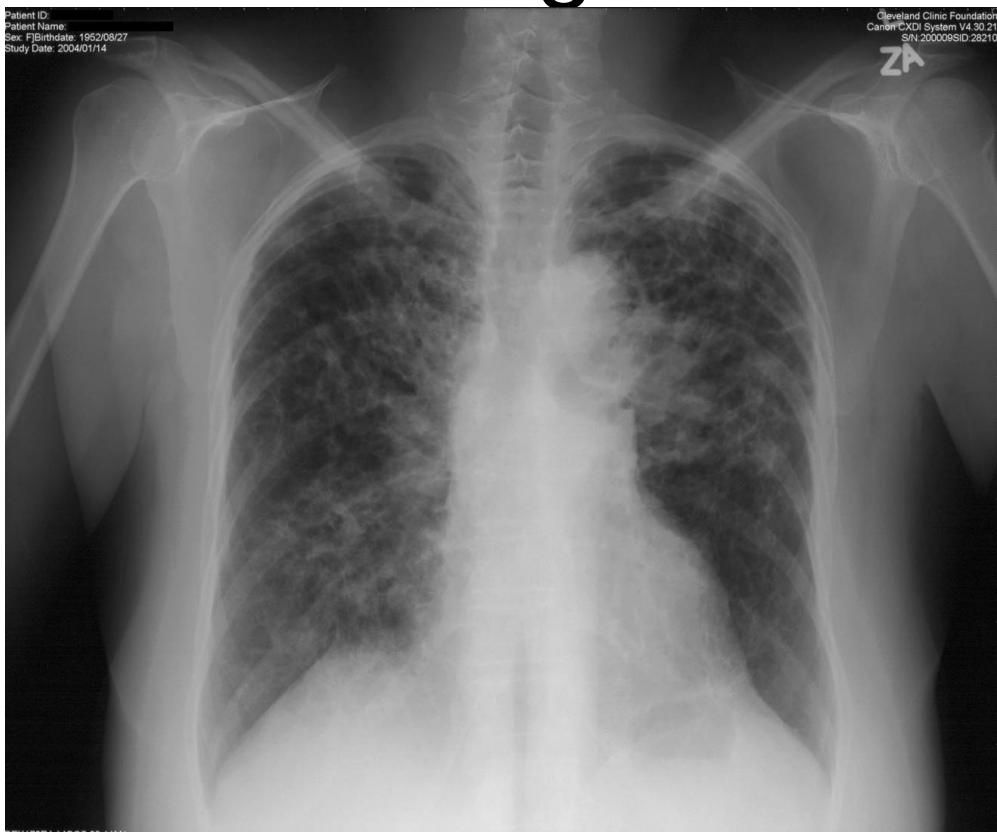


Stage II

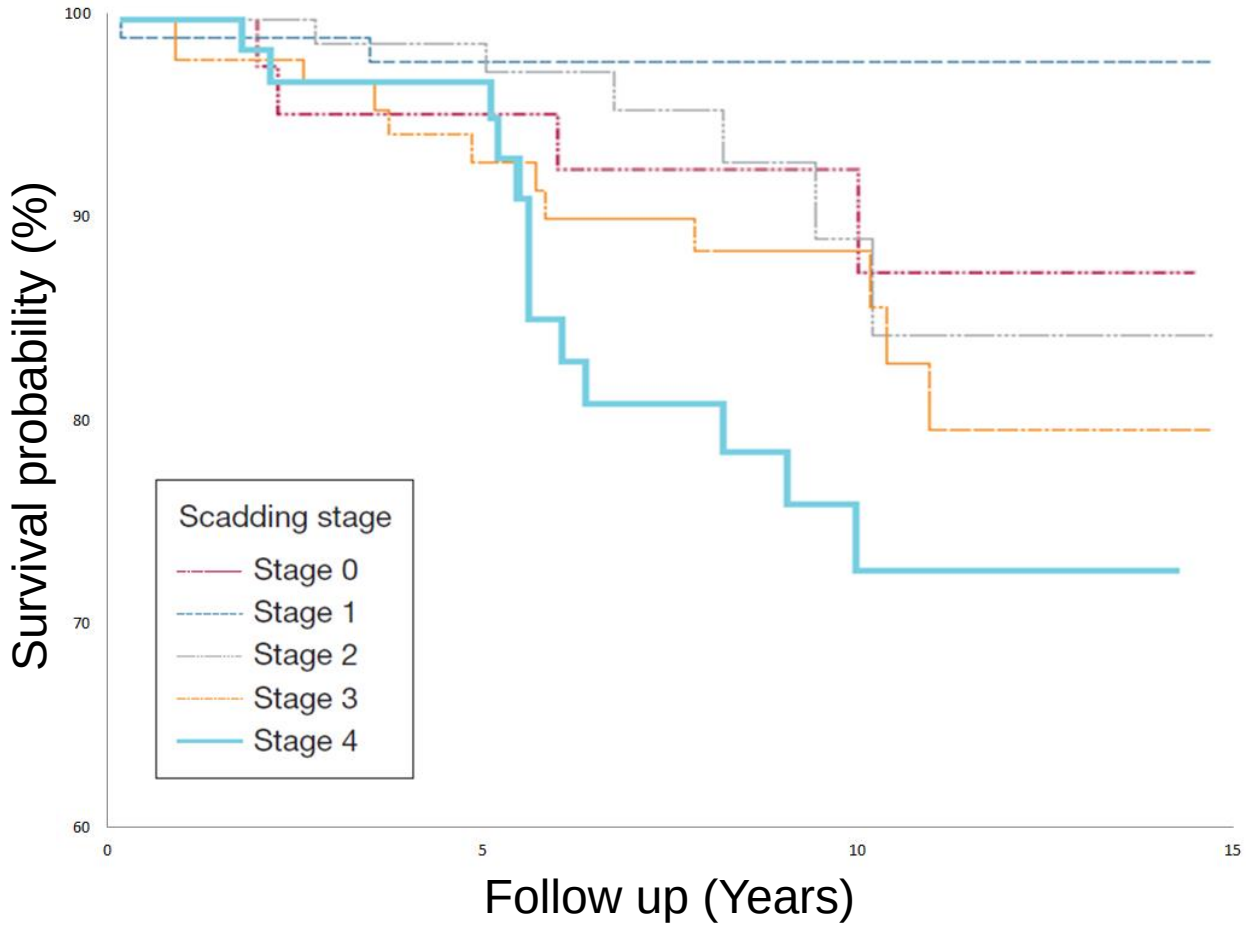


Stage III

Stage IV

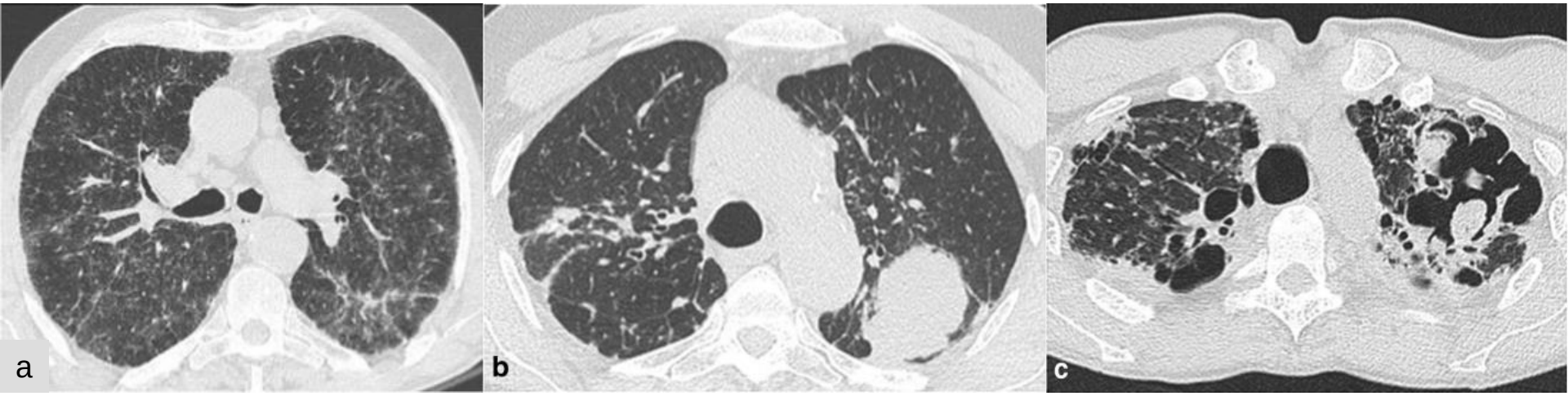


Prognosis



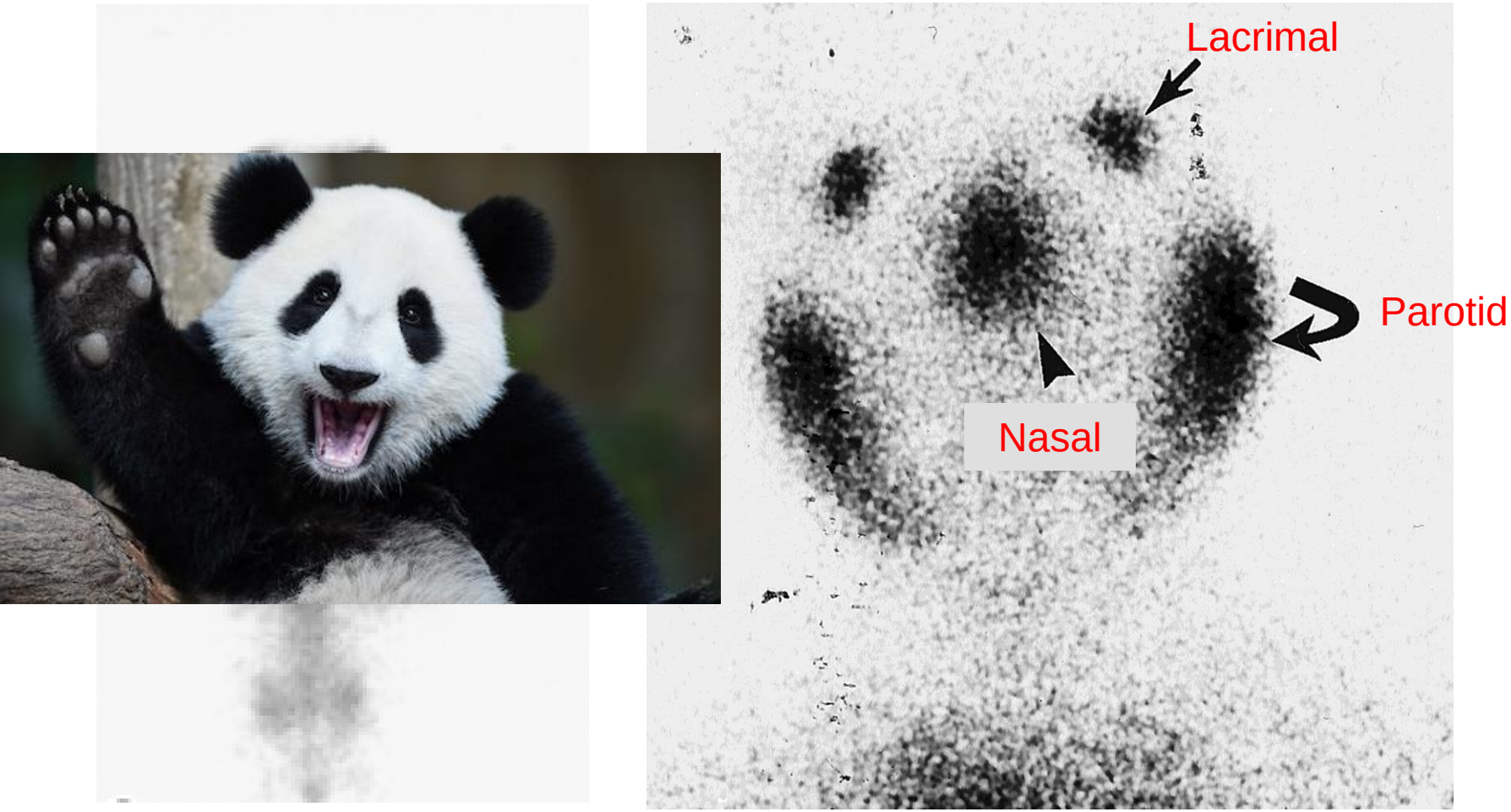
Chest 2018; 153: 105-113.

CT Chest



Clinic Re Allerg Immunol 2015, 49: 45-53.

Gallium scan



Radiology 2000;215:884-5.

Initial Evaluation

RECOMMENDED INITIAL EVALUATION
PATIENTS WITH SARCOIDOS

1. History (occupational and environm
2. Physical examination
3. Posteroanterior chest radio
4. Pulmonary function te
5. Peripheral blood ed blood cells, platelets
6. Serum chem es (alanine aminotransferase, aspart ne phosphatase), creatinine, BUN
7. Uri
8.
9. gic examination
10. test

Defin ations: BUN = blood urea nitrogen; D_{LCO} = diffusing capacity of the lung ECG = electrocardiogram.

Biopsy required

Granuloma

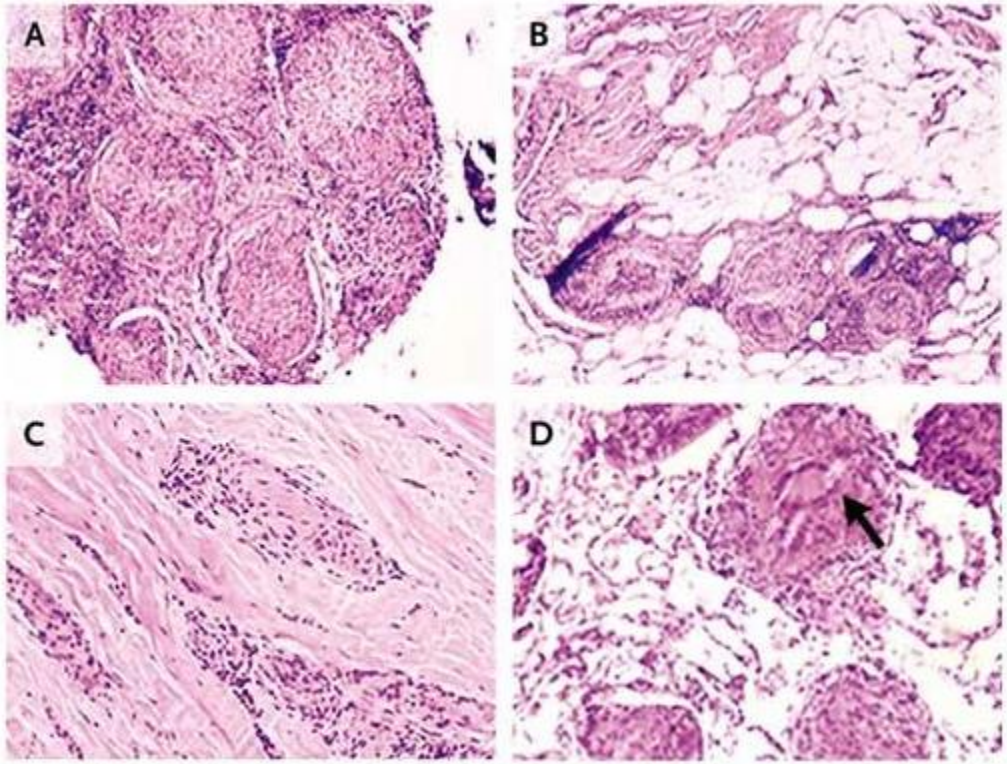
Tuberculosis

Histoplasmosis

Berylliosis

HP

Malignancy



N Engl J Med 2007; 357:2153-2165

Question 2

Mr. MC 40M African American w/ 20-pack-years p/w SOB and wheezing. Multiple admissions at OSH; better with prednisone and antibiotics but relapsed when off steroid.

Question 2

What would you do next?

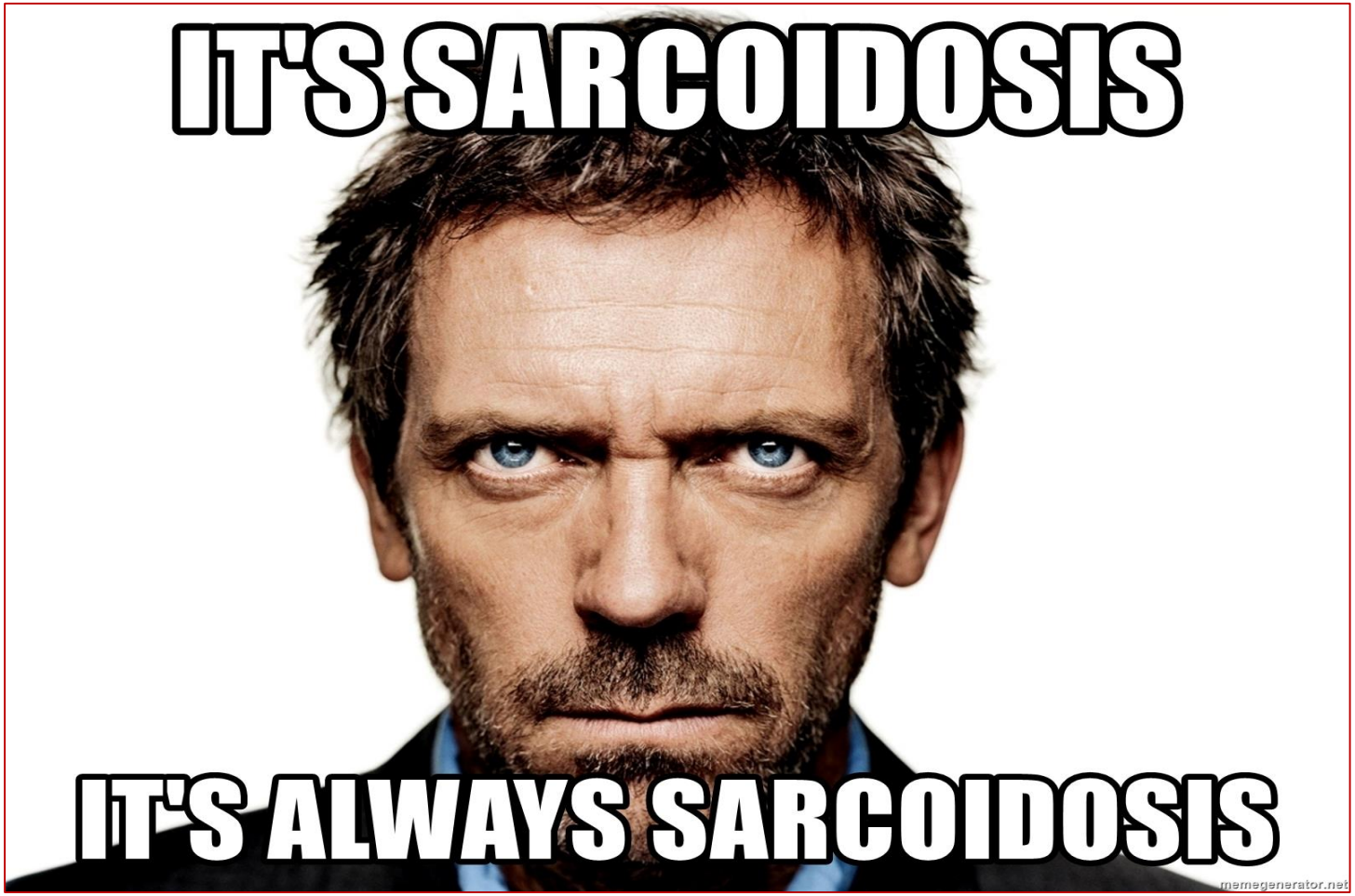
A. Prednisone and antibiotics

B. Inhaler ICS/LABA/LAMA

C. Alpha-1 level

D. Biopsy

Diagnosis Delay



Chest 2003; 123: 406-12.

Mr. MC

- Prednisone → Methotrexate
- Reduced 6MW; SpO2 86%
- Lung transplantation evaluation

Biopsy Modality

- Stage I and II
  - EBUS-TBNA Sensitivity 93%; specificity 100%[1]

Outcome	Conventional TBNA Group (n = 62)	EBUS-TBNA Group (n = 55)	*P* Value
Primary outcome			
TBNA plus TBLB and EBB[a]	53 of 62 (85.5)	51 of 55 (92.7)	.34
Secondary outcomes			
TBNA	30 of 62 (48.4)	41 of 55 (74.5)	.004
EBB	26 of 58 (44.8)	14 of 53 (26.4)	.04
TBLB	40 of 60 (66.7)	38 of 52 (73.1)	.46
TBNA plus EBB[a]	45 of 62 (72.6)	45 of 55 (81.8)	.24
TBNA plus TBLB[a]	49 of 62 (79.0)	50 of 55 (90.9)	.16

[1]*Rev Port Pneumol* 2014; 20: 237-41.
[2]*Chest* 2014; 146: 547-56.

Biopsy Modality

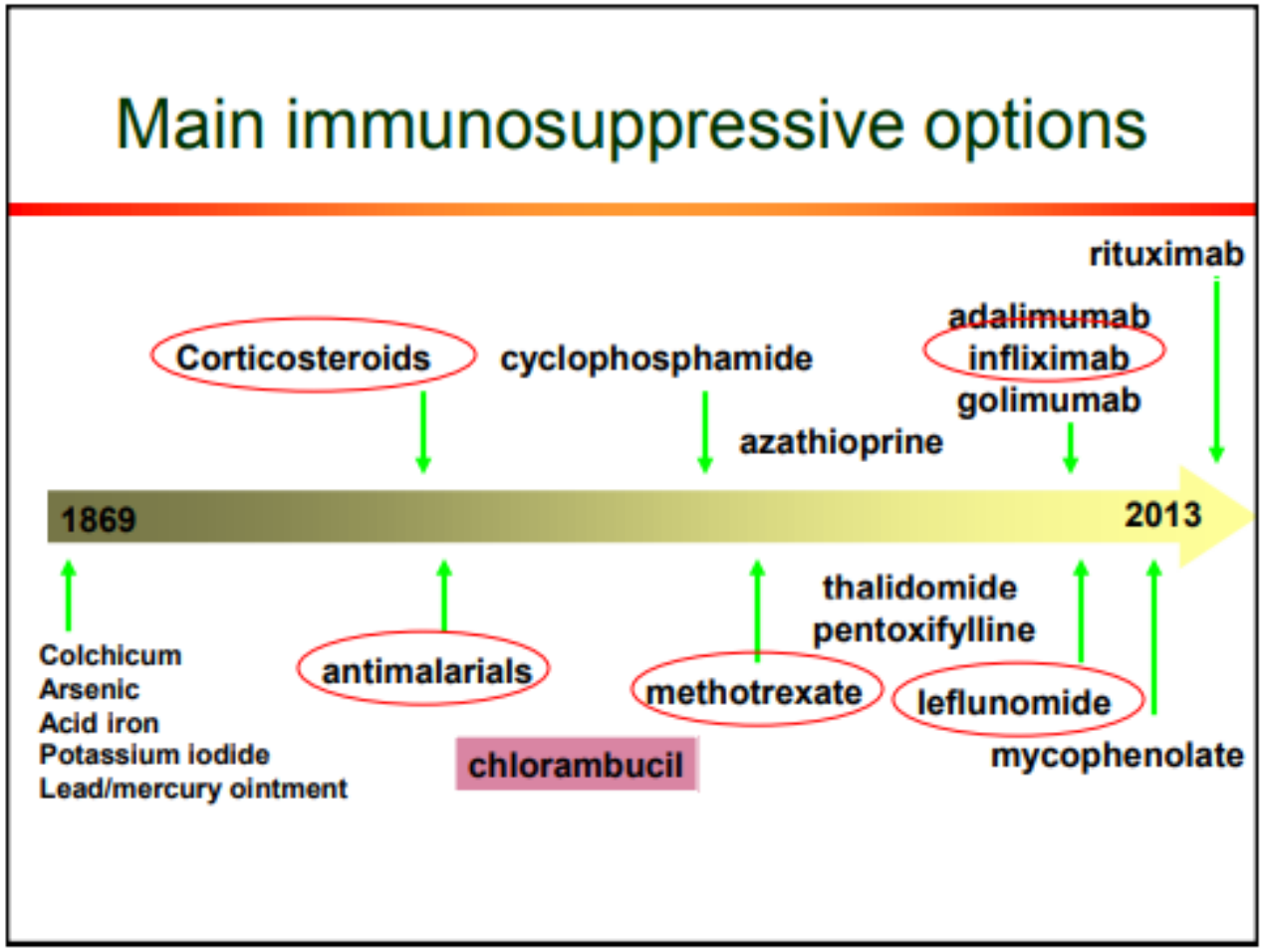
Biopsy technique	Sensitivity, %	Specificity, %	Accuracy, %
TBNA	62.5 (44–79)	100 (16–100)	64.7 (48–79)
EBUS-TBNA	79.3 (60–92)	100 (25–100)	80 (62–91)
EUS-FNA	88.6 (73–97)	100 (25–100)	88.9 (74–96)

Pol Arch Med Wewn 2015; 125: 321-6.

	Treatment		
	Not Generally	Sometimes	Generally
Clinically active disease			
Neurological	No	No	Yes
Ocular	No	No	Yes
Cardiac	No	No	Yes
Renal	No	No	Yes
Hepatic	No	Yes	No
Splenic	No	Yes	No
Pulmonary			
Stage 0	Yes	No	No
Stage I	Yes	No	No
Stage II	No	Yes	No
Stage III	No	Yes	No
Stage IV	No	Yes	No
Cutaneous	No	Yes	No
Musculoskeletal	No	Yes	No
Comorbid conditions			
Depression	No	No	Yes
Fatigue	No	Yes	No
Pulmonary hypertension	No	No	Yes

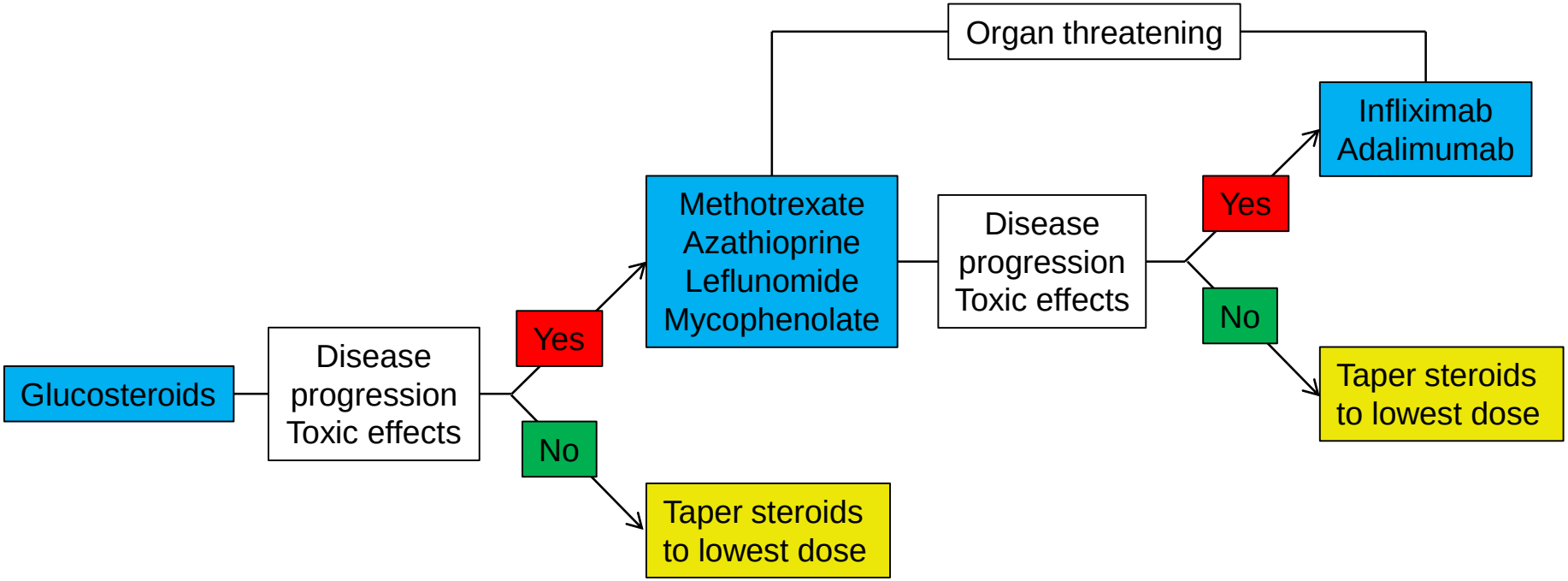
JAMA 2011; 305: 391-9.

Treatment History



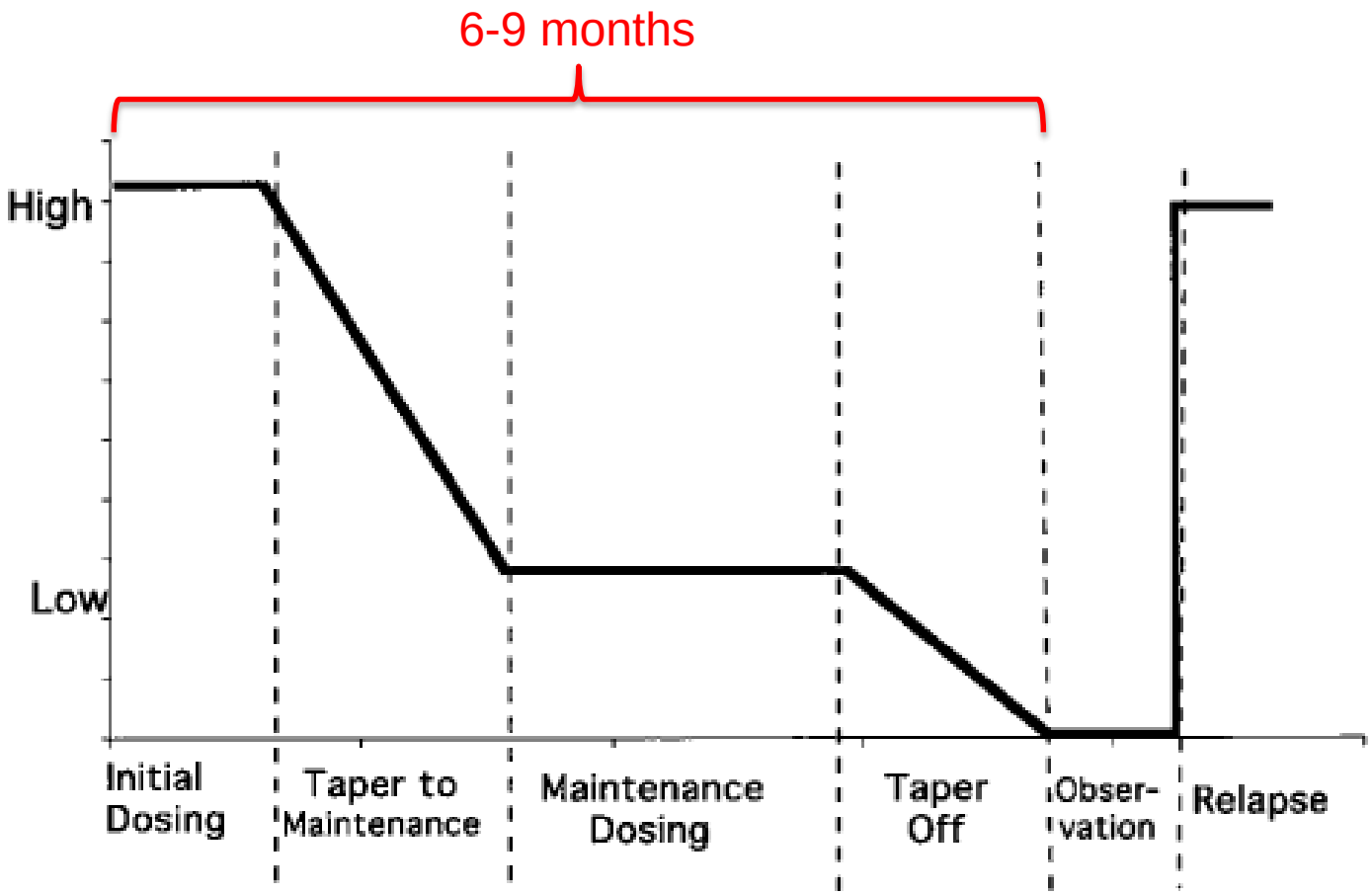
Culver. Cleveland Clinic.

Decision Tree



Adapted from *Lancet Respir Med* 2015; 3: 813-22.

Steroid Course



Chest 1999; 115: 1158-65.

Exploratory: CLEAR

- Levofloxacin, Ethambutol, Azithromycin, and Rifampin
- Beneficial in cutaneous and pulmonary sarcoidosis[1,2]
- Multi-center trial NCT02024555

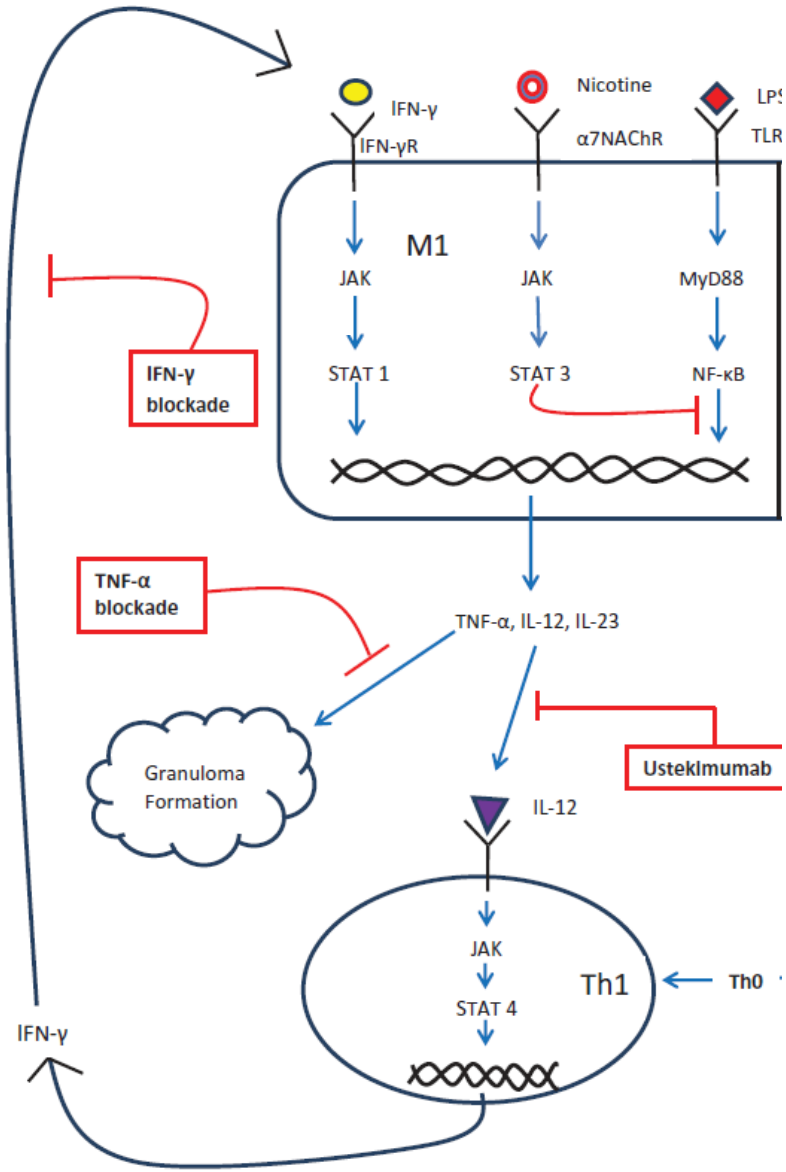
[1] *JAMA Dermatol* 2013; 149: 1040-49.
[2] *Sarc Vasc Diffuse Lung Dis* 2014; 30: 201-11.

Exploratory: Nicotine

- Reduces pro-inflammatory via α7nAChR
- Fatigue, cognitive slowing, depression, and anxiety
- Nicotine side effect helpful (NCT02265874)

Exploratory: Clinical Trials

- Roflumilast and Pirfenidone fibrosis
  - NCT01830959/NCT03260556
- Low versus medium dose prednisolone
  - NCT03265405
- ACTHAR Gel for chronic Pulmonary
  - NCT02188017



Expert Opin Biol Ther 2018;18:399-407

Question 3

Which of the following has the best survival with lung transplant?

A. Alpha-1

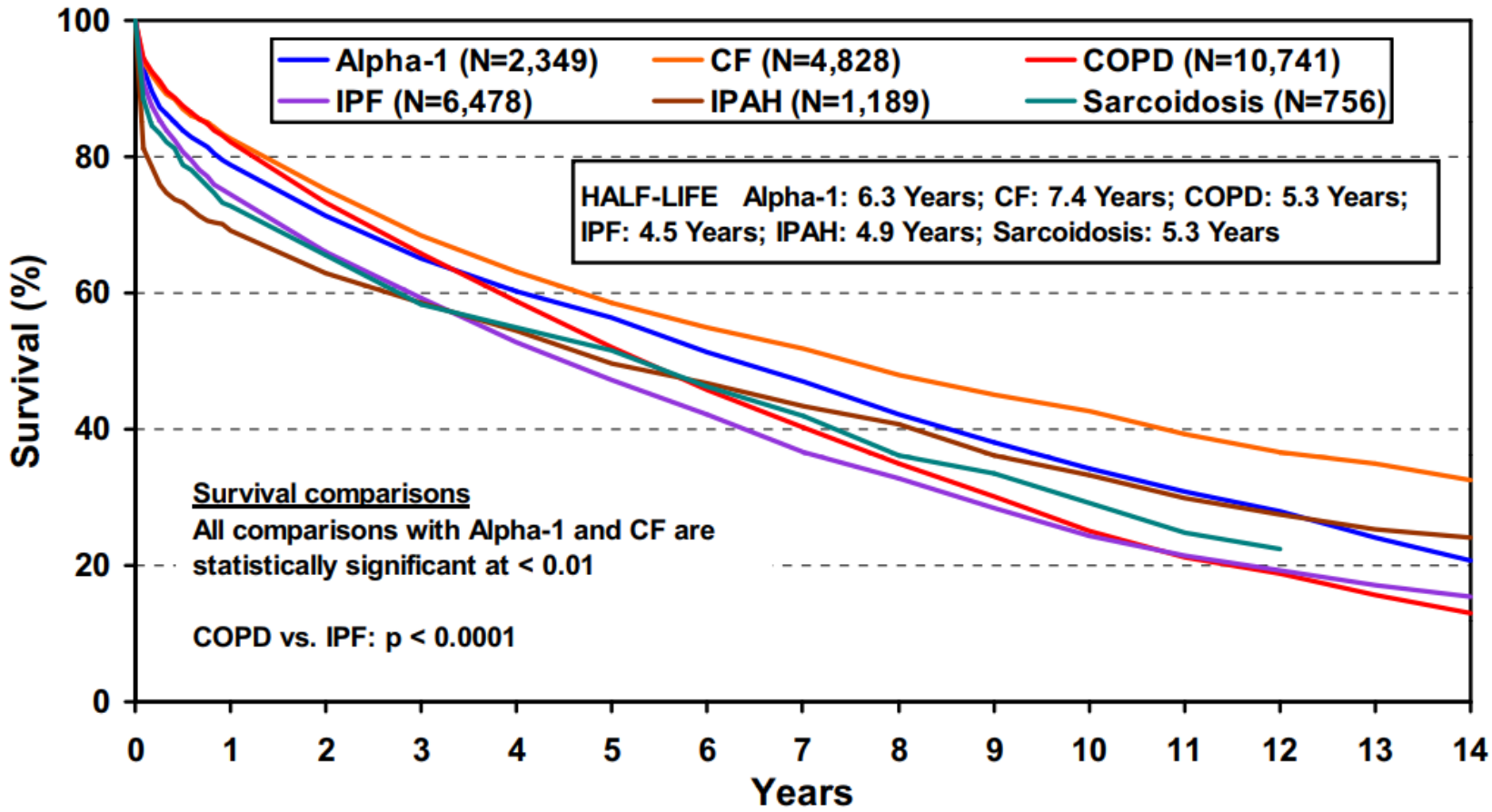
B. CF

C. COPD

D. IPF

E. Sarcoidosis

Sarcoidosis Lung Transplant



J Heart Lung Transplant 2011; 30: 1104-22.

Questions

1. Does treatment alter disease course?
2. Does treatment improve mortality?
3. Which are the best agents?
4. What dose and how long to treat patients with sarcoidosis?

Question 4

How well do you think we diagnose cardiac sarcoidosis?

A. Under diagnosed

B. Over diagnosed

C. About right

D. Sarcoidosis does not affect the heart

Cardiac Sarcoidosis

- 2.5% in the US
  - 25% on autopsy in USA[1]
  - 58% on autopsy in Japan[2]
- Affect any part of the heart
- Heart block, fibrosis, and arrhythmias
- Syncope, heart failure, and sudden death

[1]*Circulation* 1978; 58:1204-11.
[2]*Am Heart J* 2005; 150: 459-63.

Cardiac Sarcoidosis

- EKG
  - Cheap, easy, low sensitivity
  - First to use as screening tool
- Holter monitor
  - Sensitivity 67%; specificity 80%[1]
- TTE
  - Insensitive during early stages
  - Wall motion abnormalities; systolic/diastolic dysfunction
  - Thinning of LV and septum[2]
  - Pulmonary hypertension

[1]Chest 1994; 106: 1021-4.
[2]Am J Cardio 1998; 82: 537-40.

Cardiac Sarcoidosis

- Cardiac MRI → Diagnosis
  - Capture structural and functional abnormalities
  - Late gadolinium enhancement: fibrosis
  - Less; no radiation

- PET → Monitor response to treatment
  - Better than radionuclide imaging: Gallium/Thallium
  - Unclear compared to cardiac MRI [1]
  - Detect inflammation
  - High cost; radiation; difficult preparation

[1] *Eur J Nucl Med Mol Imaging* 2008; 35: 933-41.

Endomyocardial Biopsy

- High risk; low yield
- Low sensitivity ~ 20-30%
- Electrogram mapping increased sensitivity ~50%[1]
- Reserved for “pure” cardiac cases

[1] *JACC* 2004; 2: 466-73.

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]

Heart Rhythm 2014; 11: 1304-21.

CS Treatment

- Immunosuppressive Rx
- Heart failure
  - ACEi/ARBs; β blockers; diuretics
- Arrhythmias[1]
  - Complete heart block: pacemaker (1C)
  - Spontaneous sustained VT/VF: ICD (1C)
  - LVEF < 35% despite therapy: ICD (1C)
- Cardiac transplant

[1]*Cardiovasc Diagn Ther* 2016; 6: 50-63.

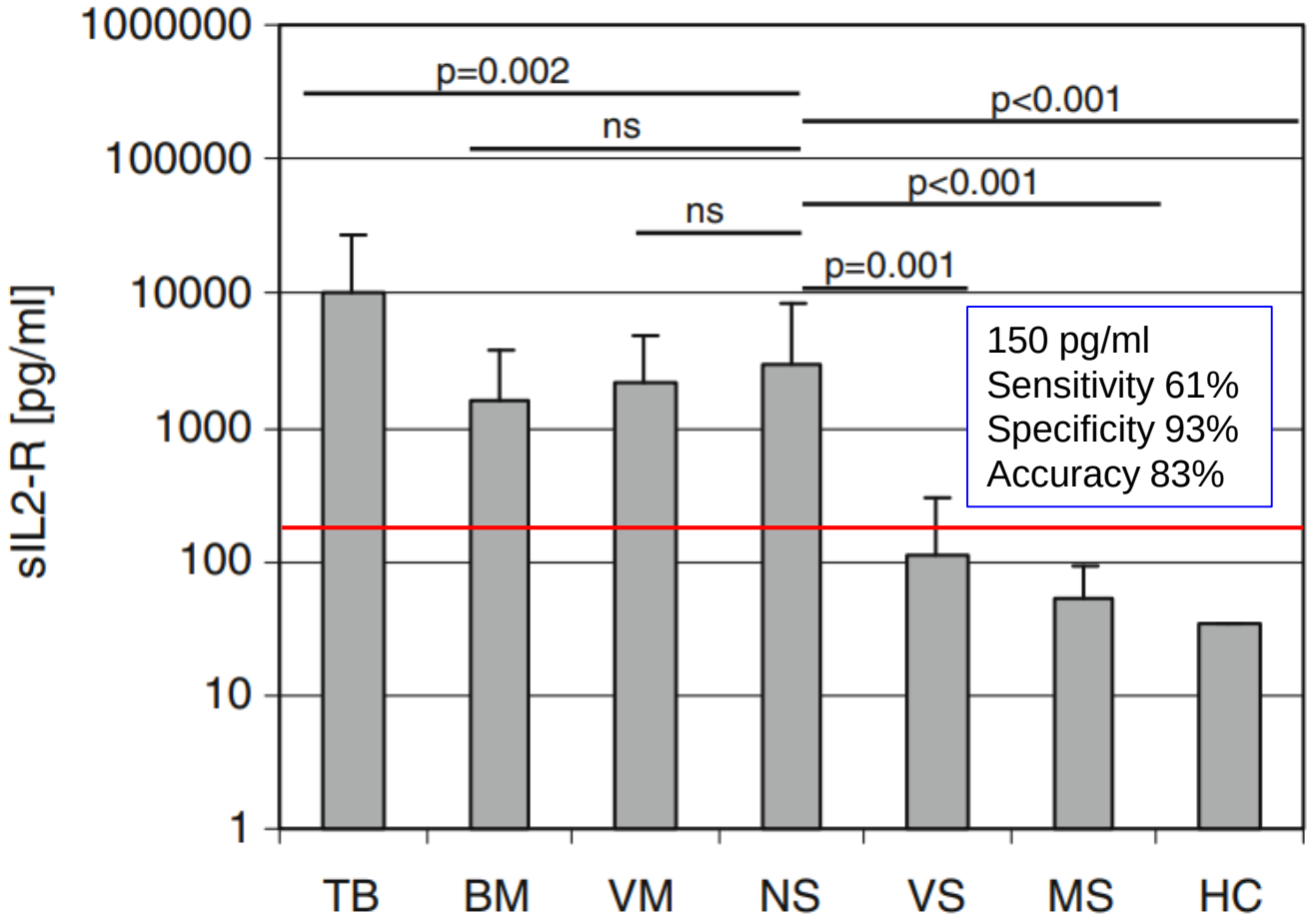
Neurosarcoidosis

- Cranial nerves – facial and optic
- Spinal cord—para/quadriplegia
- Seizures
- Weakness, ataxia, cognitive impairment

Neurosarcoidosis

- Difficult to biopsy
- MRI/PET
- Lumbar puncture

CSF sIL2-R



Legends:
TB: Neurotuberculosis
BM: Bacterial meningitis
VM: Viral meningitis
NS: Neurosarcoidosis
VS: Vasculitis
MS: Multiple sclerosis
HC: Healthy control

J Neuro 2010; 257: 1855-63.

Neurosarcoidosis Rx

"HEART TRANSPLANTS, YES. BRAIN TRANSPLANTS, NO."

Research

Disease	Sarcoidosis	HP	IPF	AAT
NIH Funding	$	$	$$$$	$$$$$

Conclusions

- Low threshold for sarcoidosis; cardiac and neurological are easily missed
- Immunopathogenesis is multifactorial
- Current therapy are non-specific
- Sarcoidosis research is becoming active

Acknowledgment

Crouser Lab

- Mark Julian, MS

Schlesinger Lab

OSU Collaborators

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- Peter White, PhD
- Evelyn Caceres, PhD
- Audrey Papp, CLSp
- Wolfgang Sadee, PhD

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Foundation for Sarcoidosis Model Grant

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T32-HL007946 (Van Le)

Thank You!