Sarcoidosis

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Objectives

Epidemiology & Pathobiology

Manifestations and Diagnosis

Common Treatment Modalities

Sarcoidosis

A granulomatous disease of unknown etiology that effects people throughout the world

Can effect any organ system

Diagnosis involves:

1. Compatible clinical picture
2. Histologic demonstration of non-caseating granulomas
3. Exclusion of other causes

ATS Statement on Sarcoidosis. Am J Resp Crit Care Med 160:736-755, 1999

Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

MAJOR PATHOLOGIC DIFFERENTIAL DIAGNOSIS OF SARCOIDOSIS AT BIOPSY AND SURGICAL PATHOLOGY

Lung	Lymph Node	Skin	Liver	Bone Marrow	Other Sites
• Tuberculosis • Atypical mycobacteriosis • Cryptococcosis • Aspergillosis • Histoplasmosis • Coccidioido-mycosis • Blastomycosis • *Pneumocystis jirovecii* • Mycoplasma, etc. • Hypersensitivity pneumonitis • Pneumoconiosis • Beryllium, titanium, aluminum • Drug reactions • Aspiration of foreign materials • Granulomatous poly-angiitis (sarcoid-type granulomas are rare) • Chronic interstitial pneumonia, such as usual and lymphocytic interstitial pneumonia • Necrotizing sarcoid granulomatosis (NSC)	• Tuberculosis • Atypical mycobacteriosis • Brucellosis • Toxoplasmosis • Granulomatous histiocytic necrotizing lymphadenitis (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)	• Tuberculosis • Atypical mycobacteriosis • Fungal infection • Reaction to foreign bodies: • Beryllium, zirconium, tattooing, paraffin, etc. • Rheumatoid nodule	• Tuberculosis • Brucellosis • Schistosomiasis • Primary biliary • cirrhosis • Crohn's disease • Hodgkin's • disease • Non-Hodgkin's • lymphomas • GLUS syndrome	• Tuberculosis • Histoplasmosis • Infectious mononucleosis • Cytomegalovirus • Hodgkin's Disease • Non-Hodgkin's • lymphomas • Drugs • GLUS syndrome	• Tuberculosis • Brucellosis • Other infections • Crohn's disease • Giant cell myocarditis • GLUS syndrome

Adapted from ATS Statement on Sarcoidosis. *Am J Resp Crit Care Med.* 1999; 160: 736-755

Sarcoidosis - Systemic Disease

Organ system	involvement
Pulmonary	>90%
Ocular	11-83%
GI (liver/spleen)	21-79%
Muscle	25-50%
Skin	20-35%
Cardiac	20-58%
Rheumatologic	10-39%
Renal	7-22%
Hematologic	4-20%
Nervous system	5-16%
Bone	~5%
Genitourinary	rare

Sarcoidosis - Epidemiology

- Morre common in adults younger than 40 years, peaking in the 20-29 years
- A second peak in women older than 50 years
- *Slightly* higher disease rate in women
  - 5.9/100,000 PY in men, 6.3/100,000 PY in women
- Estimates of cumulative lifetime risk:
  - 0.85% for US Caucasians
  - 2.4% for US African-Americans
- Geographic and seasonal clusters suggest person-to-person transmission or shared environmental exposures

Rybicki et al. *Am J Epidemiol* 1997; 145: 234-241.
Henke et al. *Am J Epidemiol* 1986; 123: 840-845.
Hillerdal et al. *Am Rev Respir Dis* 1984; 130: 29-32.

Sarcoidosis - Genetics

- Familial clustering occurs
  - A Case-Control Etiologic Study of Sarcoidosis (ACCESS) trial investigated the familial relative risk of sarcoidosis in 736 age-, gender-, and geographically-matched patients with 10,862 first-degree and 17,047 second-degree relatives
    - The relative risk for development of disease in a first- or second-degree relative was 4.7 after multivariate adjustment

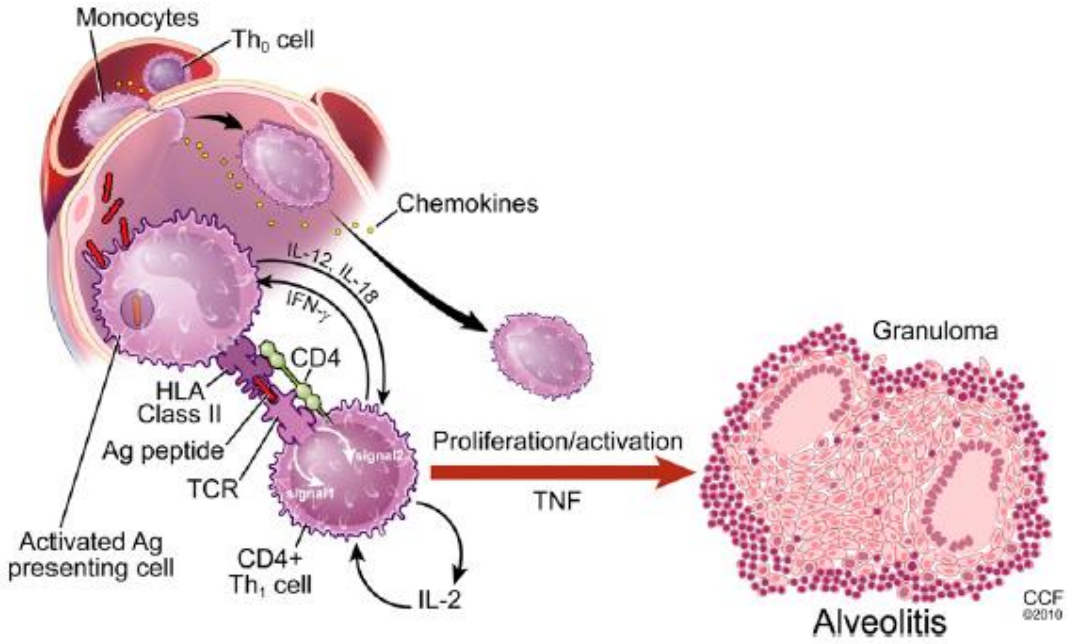
- Sarcoidosis genetic linkage
  - Sarcoidosis genetic analysis study (SAGA): 344 African-American affected sibling pairs evaluating concordance of clinical phenotypes.
    - Odds of ocular and liver sarcoidosis in a second sibling when the first sibling was affected in those organs were 3 and 3.3, respectively
    - Otherwise, phenotypic and clinical outcomes show minimal concordance

Rybicki et al. *Am J Respir Crit Care Med* 2001; 164: 2085-2091
Judson et al. *Chest*. 2006 Sep; 130(3): 855-62

Sarcoid: Pathobiology

Similar to other granulomatous disease

- Antigen processed by APC (MO, dentritic cells)
- Presented by human leukocyte antigen (HLA class II) to
- T-cell Receptors



Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Sarcoid: Antigen Exposure

Exogenous antigen seems to be required

- Reports of case-clustering
- Transmissibility via transplant
- *Propionibacterium acnes*
- Mycobacteria
  - Mycobacterial catalase-peroxidase protein (mKatG)
  - T-cell responses to:
    - mKatG from BAL of sarcoid but not other pulmonary diseases
    - Mycobacterial super oxide dismutase
    - Mycolyl transferaase antigen 85A
- Kveim-Siltzbach agent
- Occupations – Beryllium

Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Sarcoid: HLA Genetic Influence

Numerous lines of varied evidence

- HLA alleles implicated in:
  - Increased or decreased susceptibility
  - Vary depending on the population (other genetics?)
  - Different manifestations
- Importance of accounting for in studies as manifestations may be variable

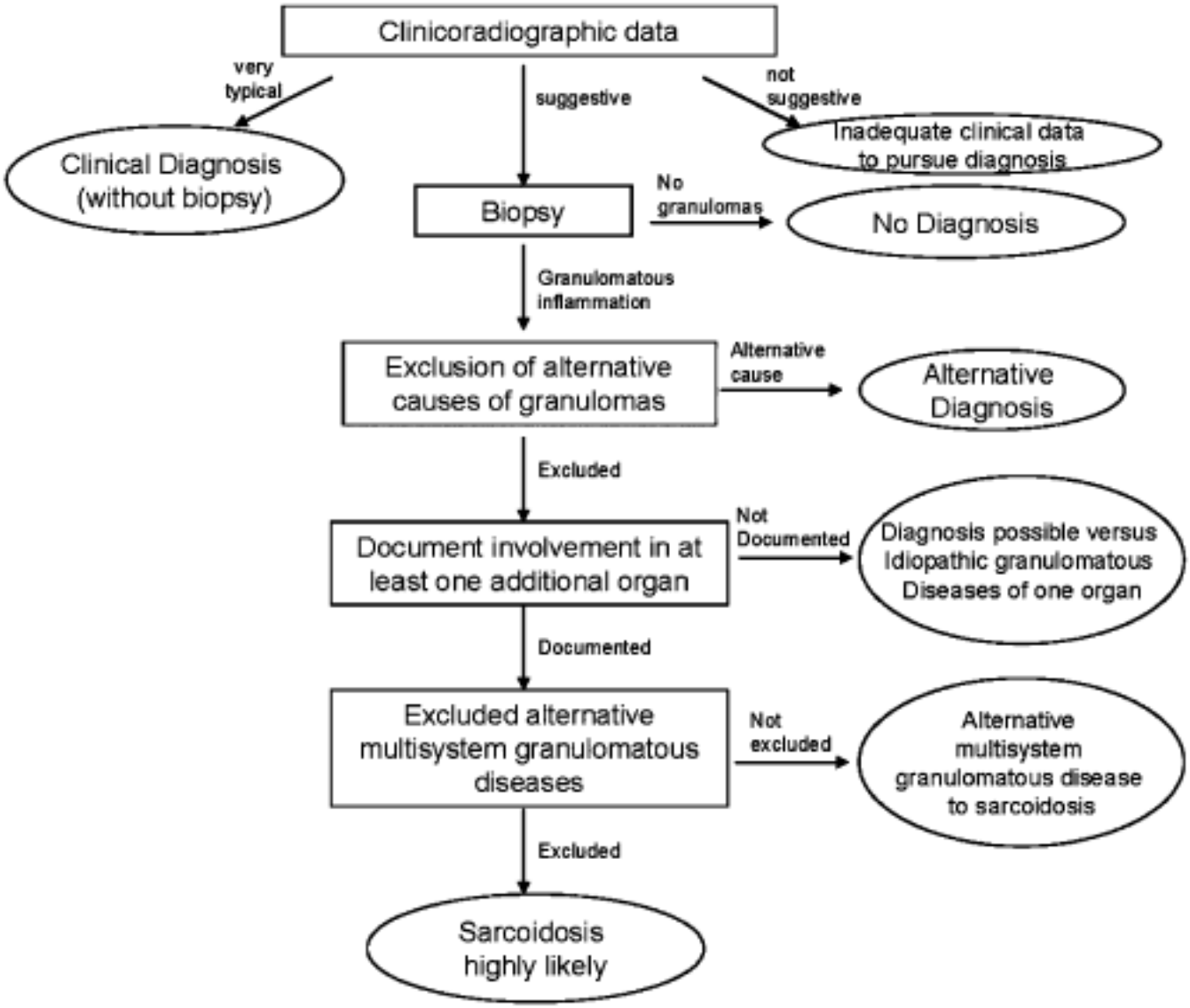
Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Sarcoid: Immune System

Various roles of T-cells

- Majority of cells in granuloma are CD4+ T-cells
- Th1 phenotype
  - INF γ and IL-12
- TNF-alpha
- Functional dysregulation of regulatory T-cells

Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81



Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Sarcoid: Clinical Presentation

Can look like anything

- Lofgren's syndrome – fever, arthralgias, erythema nodosum and hilar adenopathy
- Herford's syndrome – uveitis, parotidis, fever
- Pulmonary
  - Cough, dyspnea
  - PFTs can be normal, restrictive or obstructive
- Cardiac – Chest pain, CHF, arrhythmias, palpitations
- Neurologic – Seizures, Bell's palsy, parasthesias, cranial neuropathies
- Dermatologic – skin rashes, nodules
- Renal – Hypercalcemia, renal insufficiency, nephrolithiasis
- Hepatic – hepatitis, cirrhosis

Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Radiographic Staging (Scadding)

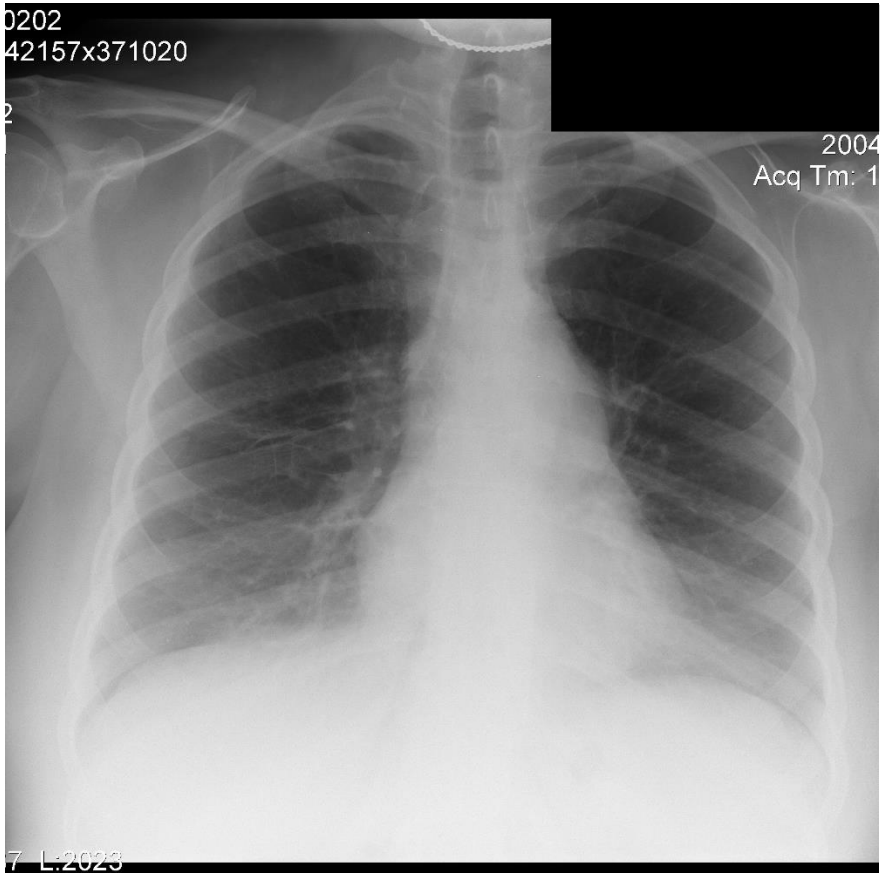
Radiographic staging of sarcoidosis

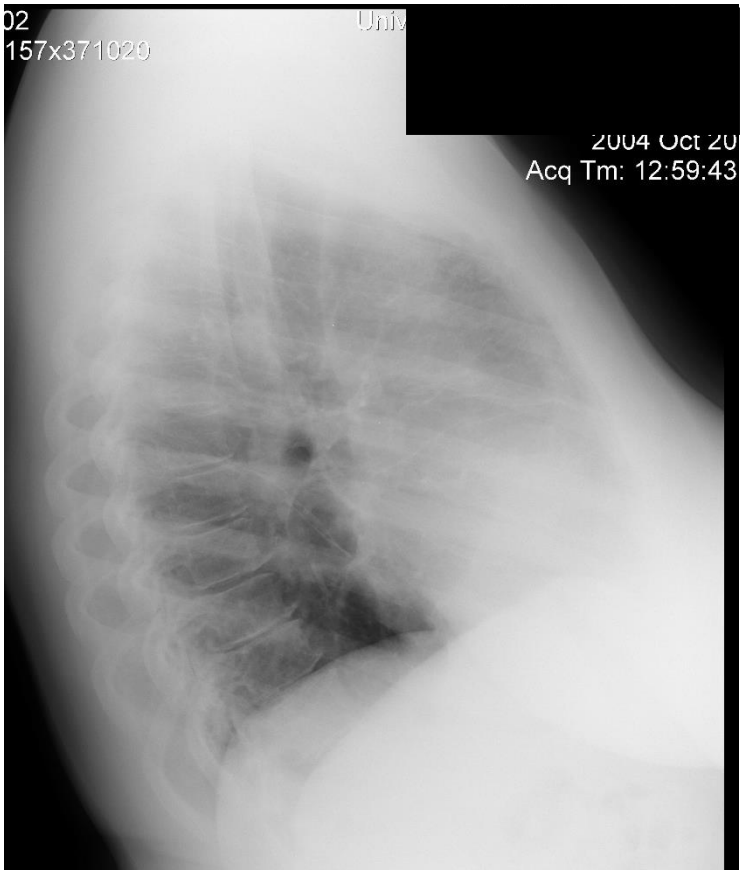
Stage	Radiographic Finding
Stage 0	Normal chest radiograph
Stage I	Bilateral hilar/mediastinal lymphadenopathy
Stage II	Bilateral hilar/mediastinal lymphadenopathy plus interstitial infiltrates
Stage III	Interstitial infiltrates without evidence of hilar/mediastinal lymphadenopathy
Stage IV	Dense fibrosis, bullae formation, architectural distortion

	Diagnostic Reliability	Spontaneous Remission Rate
Stage I	98%	60-90%
Stage II	89%	40-70%
Stage III	52%	10-20%
Stage 0	23%	--

Lynch and White, *Eur Resp Mon*. 2005, 32:105-129

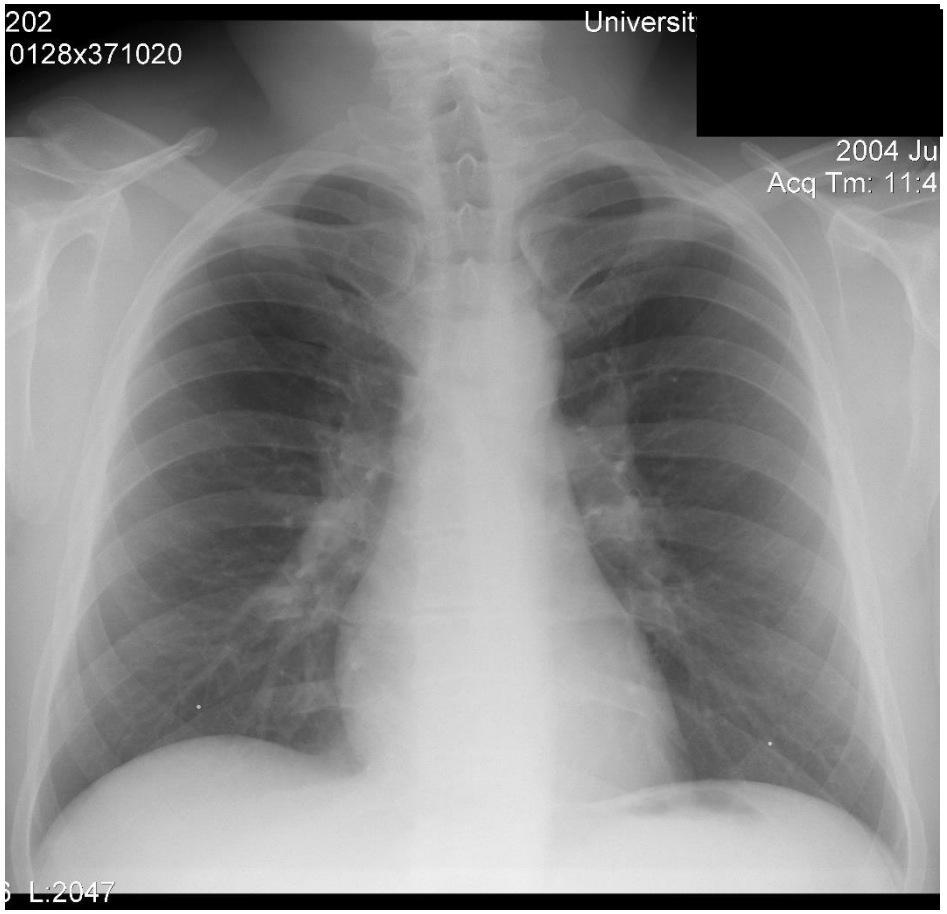
Sarcoid – Stage 0

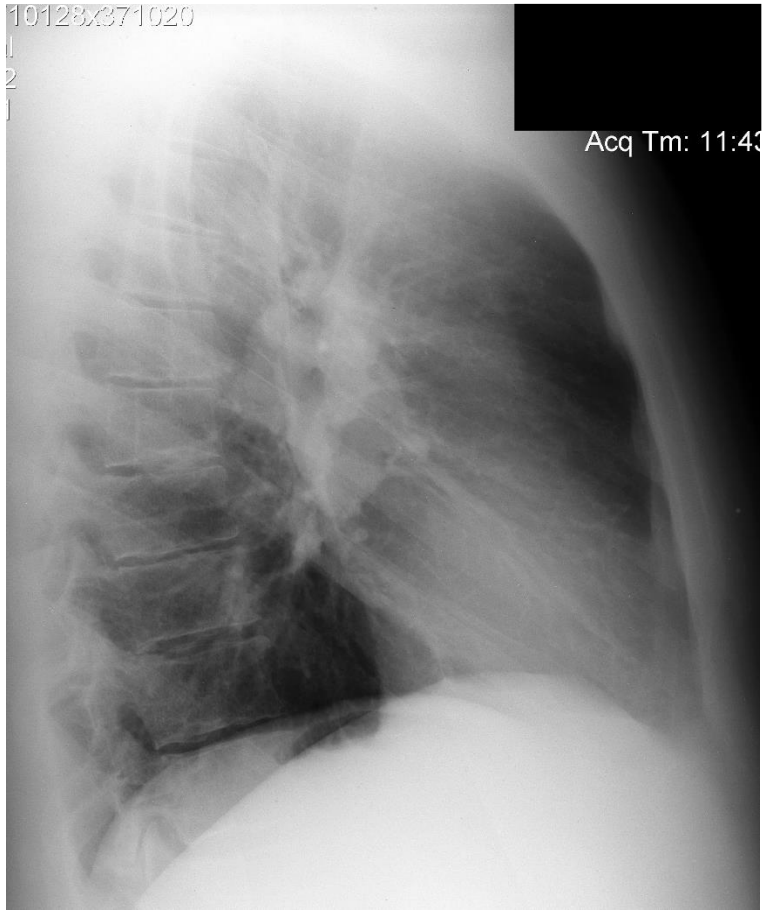




Slide courtesy Eric White MD

Sarcoid – Stage I





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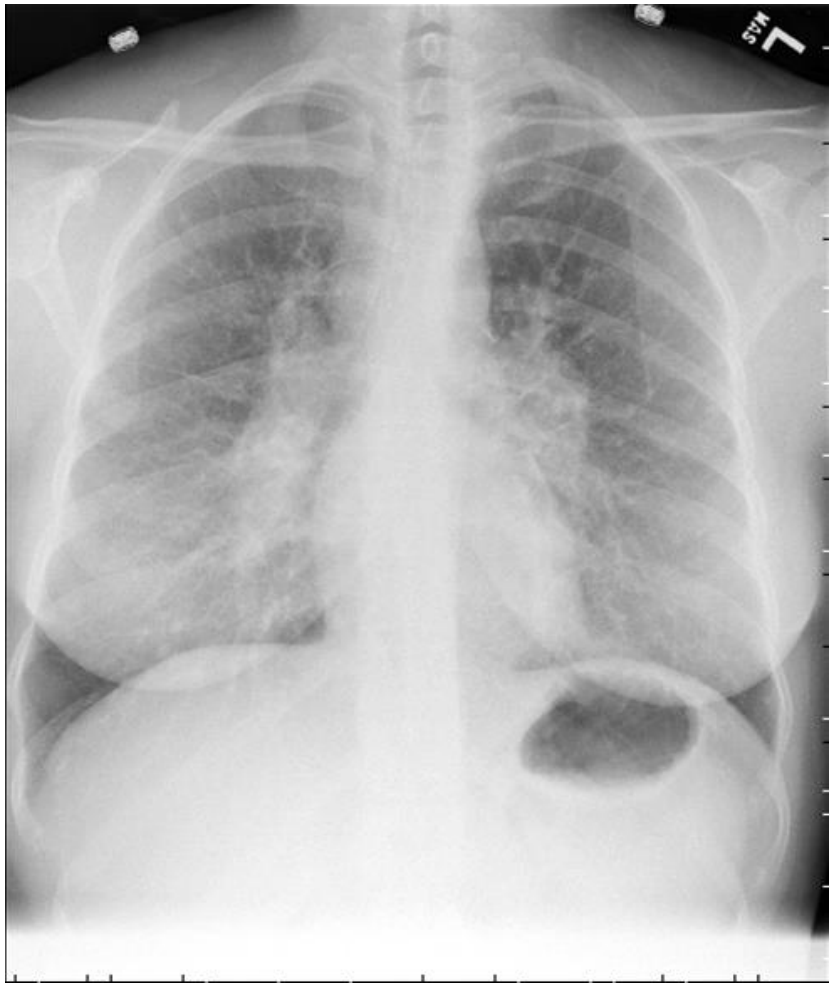
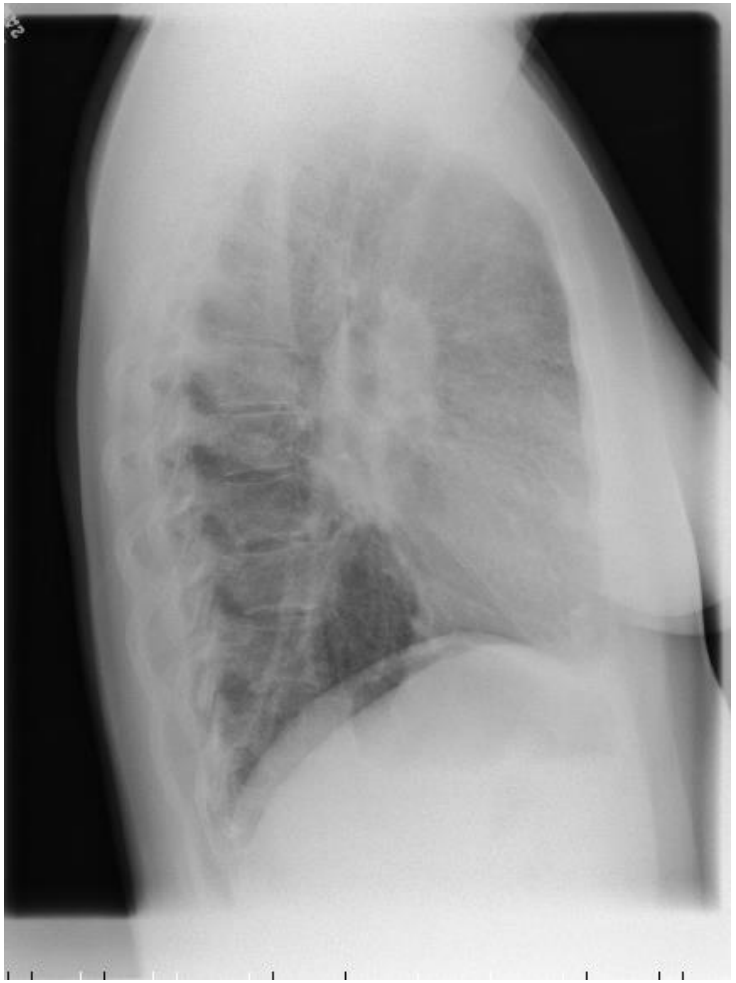
Sarcoid – Stage II





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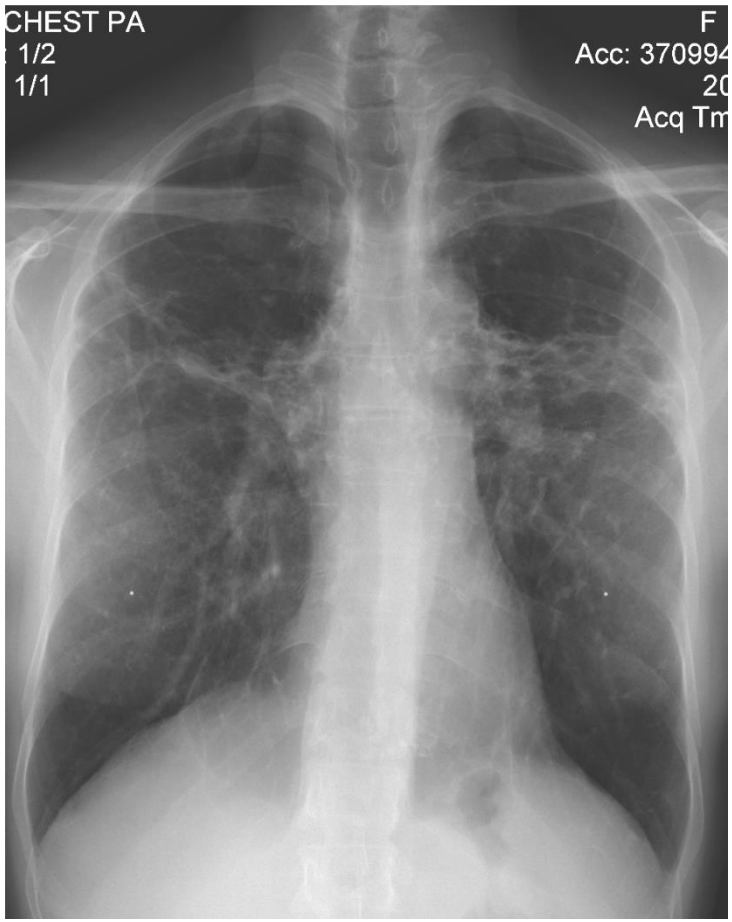
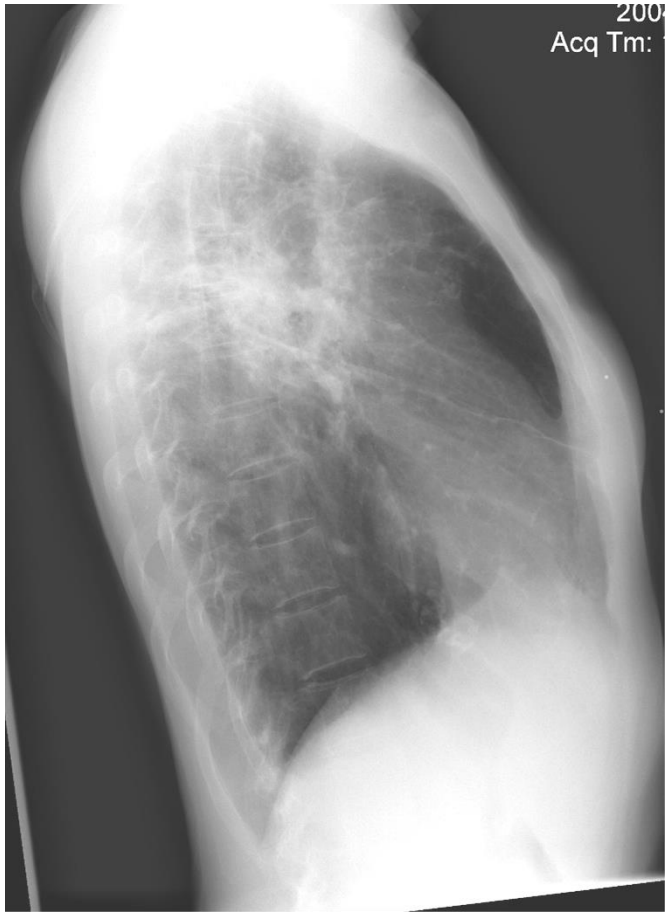
Sarcoid – Stage III





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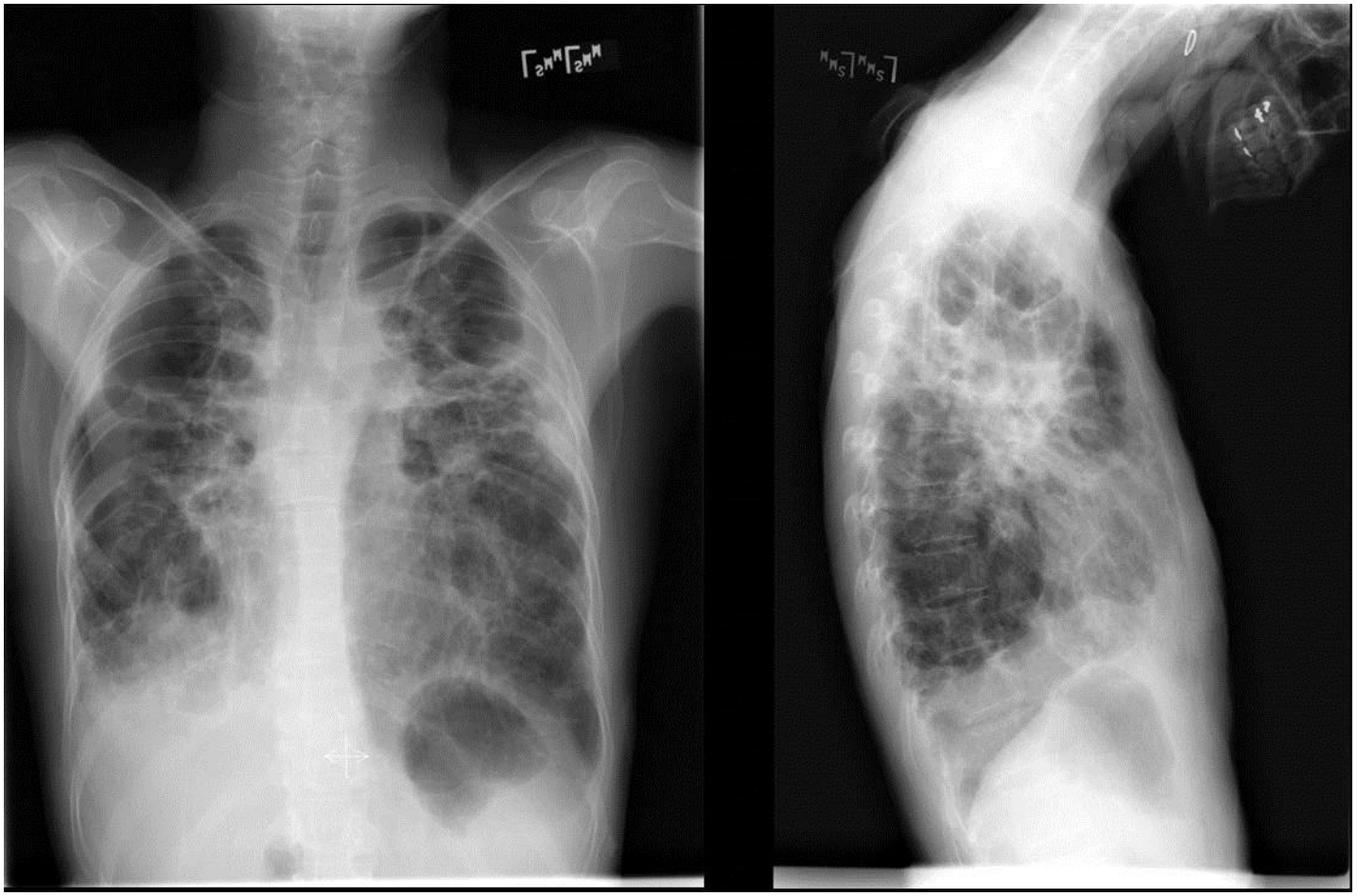
Sarcoid – Stage IV



Slide courtesy Eric White MD

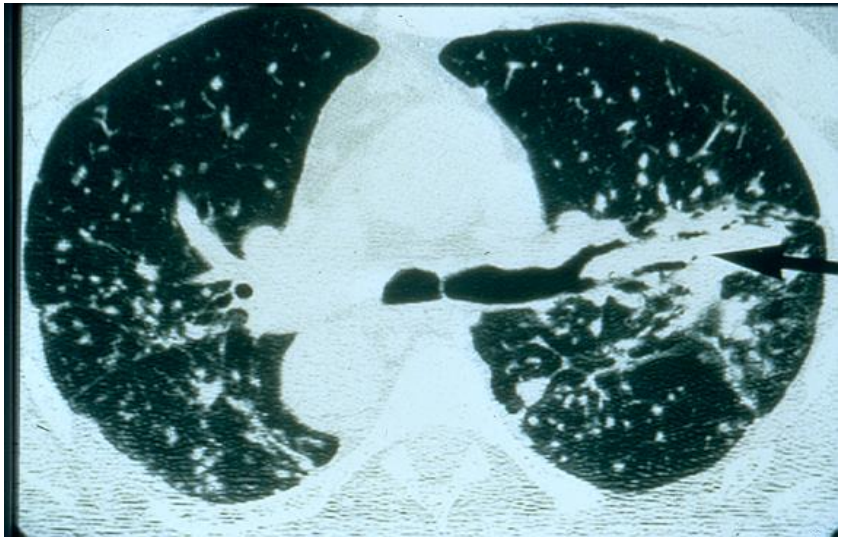
Sarcoidosis - HRCT

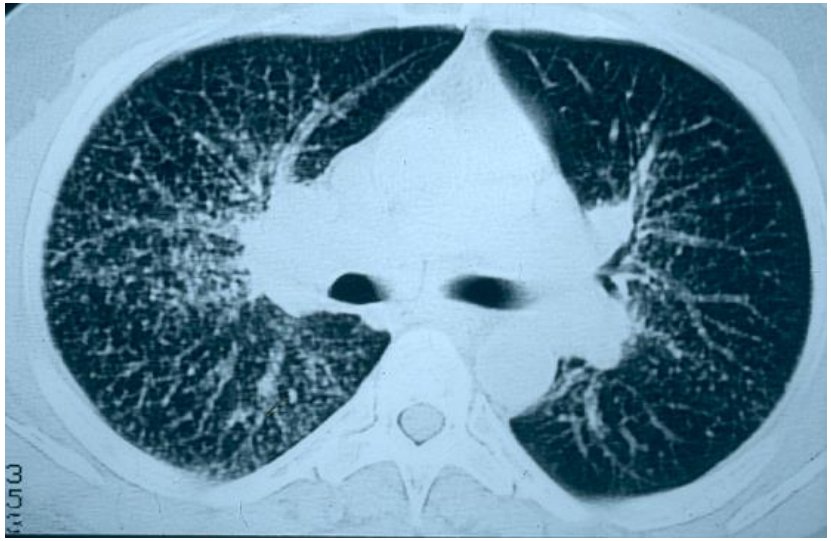
Pattern:

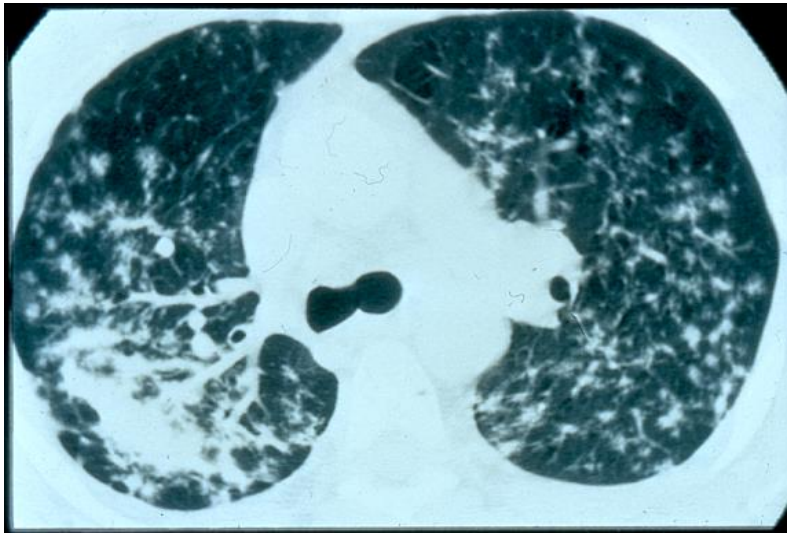
- Nodules
- Confluent alveolar spaces
- Distortion, fibrosis, cysts

Distribution:

- Upper lobe
- Central/bronchovascular







Sarcoidosis – Histologic Confirmation

Biopsy where it is easiest

- Skin (not E. nodosum)
- Conjunctiva, lip
- Peripheral lymph node

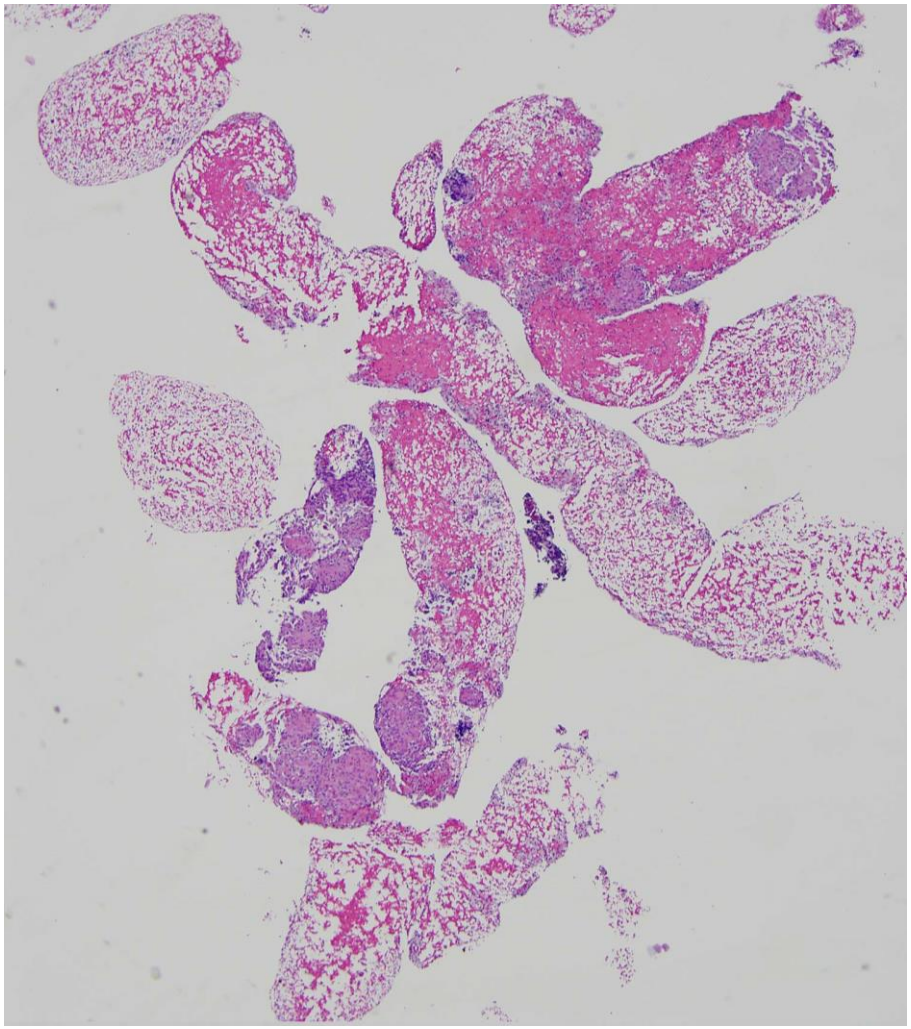
Bronchoscopy

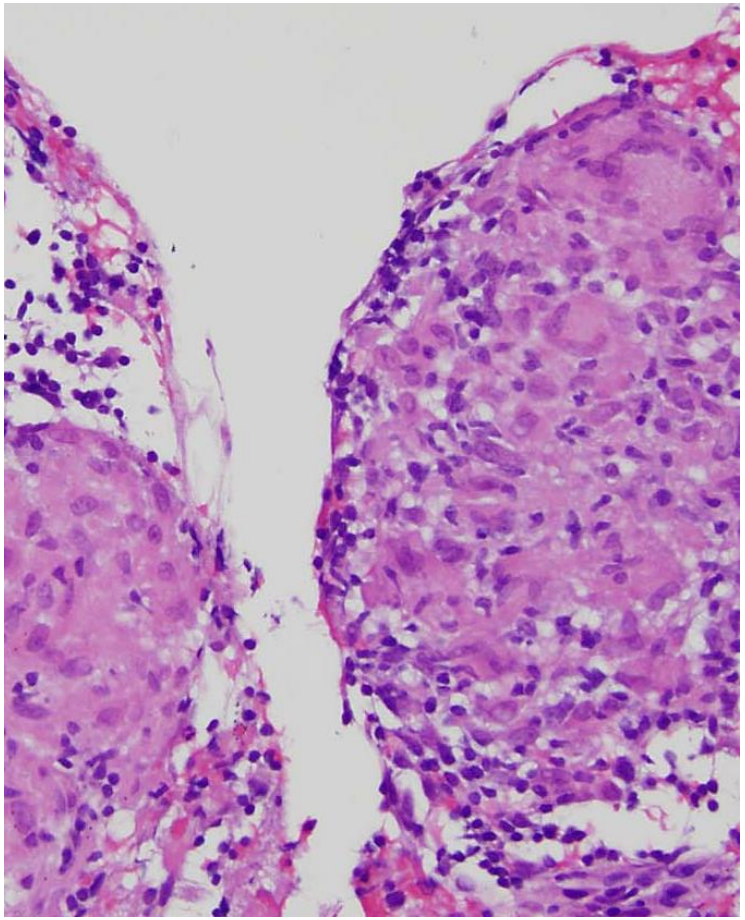
- Transbronchial lung biopsy
  - ~ 80% yield with parenchymal disease, 40-60% in stage I disease
  - risk of complications low
- Endobronchial (mucosal) biopsy
  - Easily obtained during bronchoscopy
  - Histologic granulomata in 40-60%, even when mucosa appears normal
  - May increase yield by 20% when added to TBBx
- Transbronchial needle aspirate
  - helpful if multinucleated giant cells or granulomas are found
  - often helpful when excluding malignancy
  - EBUS improves yield significantly (83% vs. 54% for TBNA)

Medianstinoscopy and surgical lung biopsy less common

Shorr et al. *Chest*. 2001; 120(1): 109-114.
von Bartheld et al. *JAMA*. 2013; 309(23): 2457-2464.

EBUS Guided TBNA





Images courtesy of Doug Arenberg, MD

Sarcoidosis – Initial Evaluation

All Cases

- History
  - Symptoms, comorbidity, medications
  - Occupational, environmental, travel
- Physical examination
- PA chest x-ray → HRCT
- Pulmonary function studies (spirometry, D_LCO)
- Complete blood count with platelets
- Serum chemistry (Calcium, LFTS, creatinine, BUN)
- Urinalysis
- ECG
- Ophthalmologic evaluation
- Tuberculin skin test / QuantiFERON GOLD

As Needed by Findings

- Bone Marrow Biopsy
- Cardiac Evaluation
- Neuro Imaging

ATS Statement on Sarcoidosis. *Am J Resp Crit Care Med* 160:736-755, 1999

Sarcoidosis - Cardiac

Clinically evident in 2-7% (occult involvement much higher >20%)

Can occur at any time during disease course

High attributable mortality (50-85%) → arrhythmias, CHF

Can be isolated but most will have extra-cardiac manifestations

ECG – Appropriate for screening

ECHO – Evaluate overall fxn, pulm HTN, “speckled snowstorm pattern” (insensitive)

Thallium ^{201} – “Reverse” improvement in perfusion with exercise

^{18}FDG-PET/CT – Sensitivity 89%, Specificity 78% - may improve with therapy

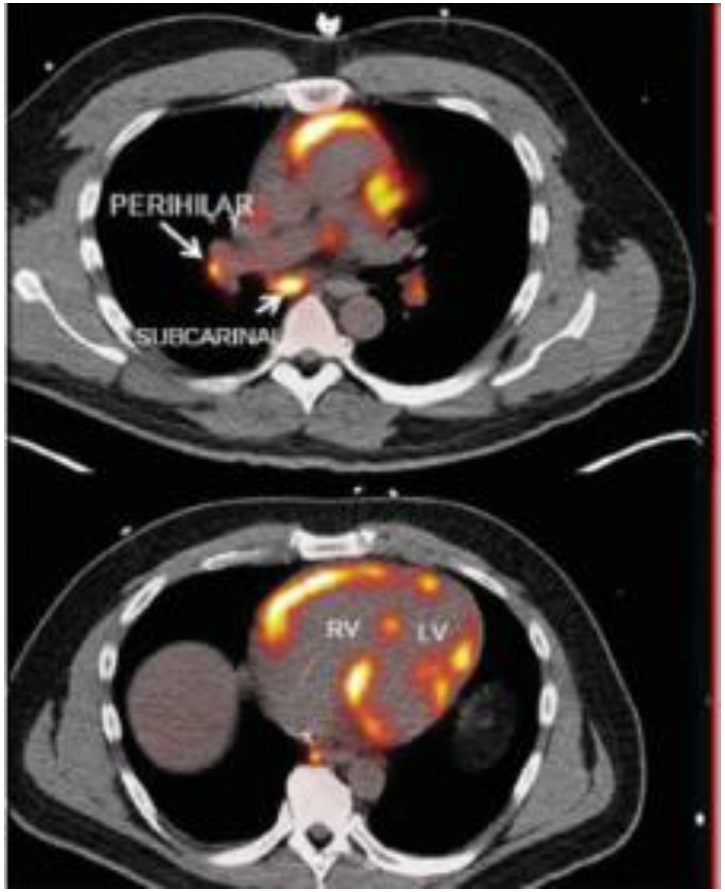
Gadolinium-enhanced C-MRI – Enhancement related to edema, inflammation, scaring

Endomyocardial Bx – Low sensitivity due to patchy disease involvement

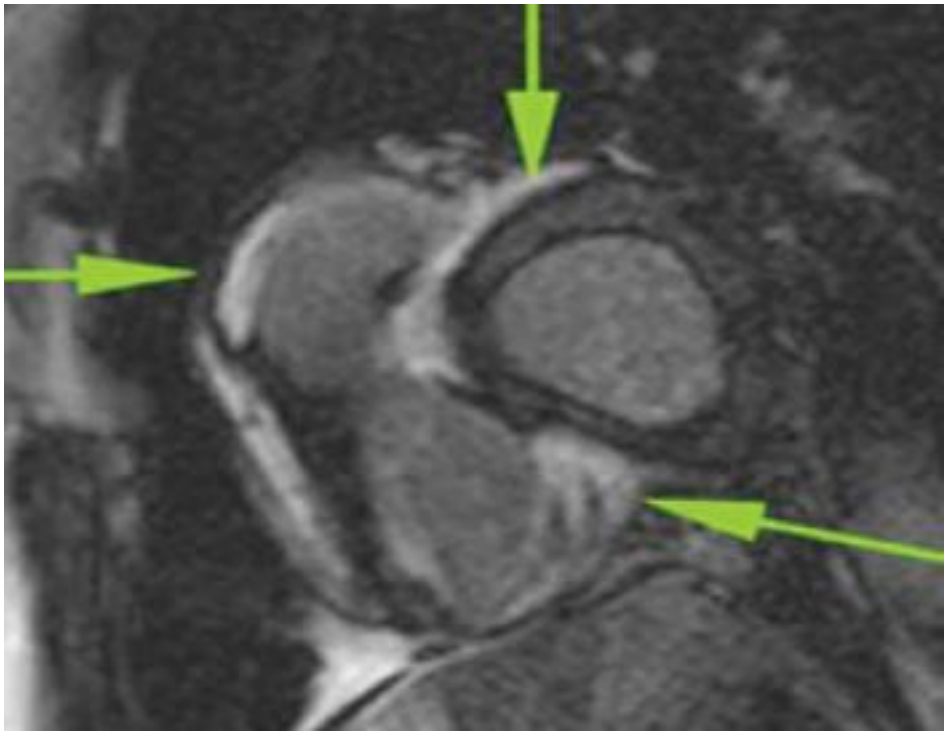
Treatment – Steroids + Immunosuppresant + hydroxychloroqine for 2-3 years, if in remission can monitor PET/CMR every 6-12 months for recurrence

Lynch et al, *Semin Resp Crit Care Med* 2014; 35:372-90

Sarcoidosis - Cardiac



18FDG-PET/CT
Hilar node uptake / patchy
Cardiac update



Cardiac MRI
With Increased Enhancement

Lynch et al, *Semin Resp Crit Care Med* 2014; 35:372-90

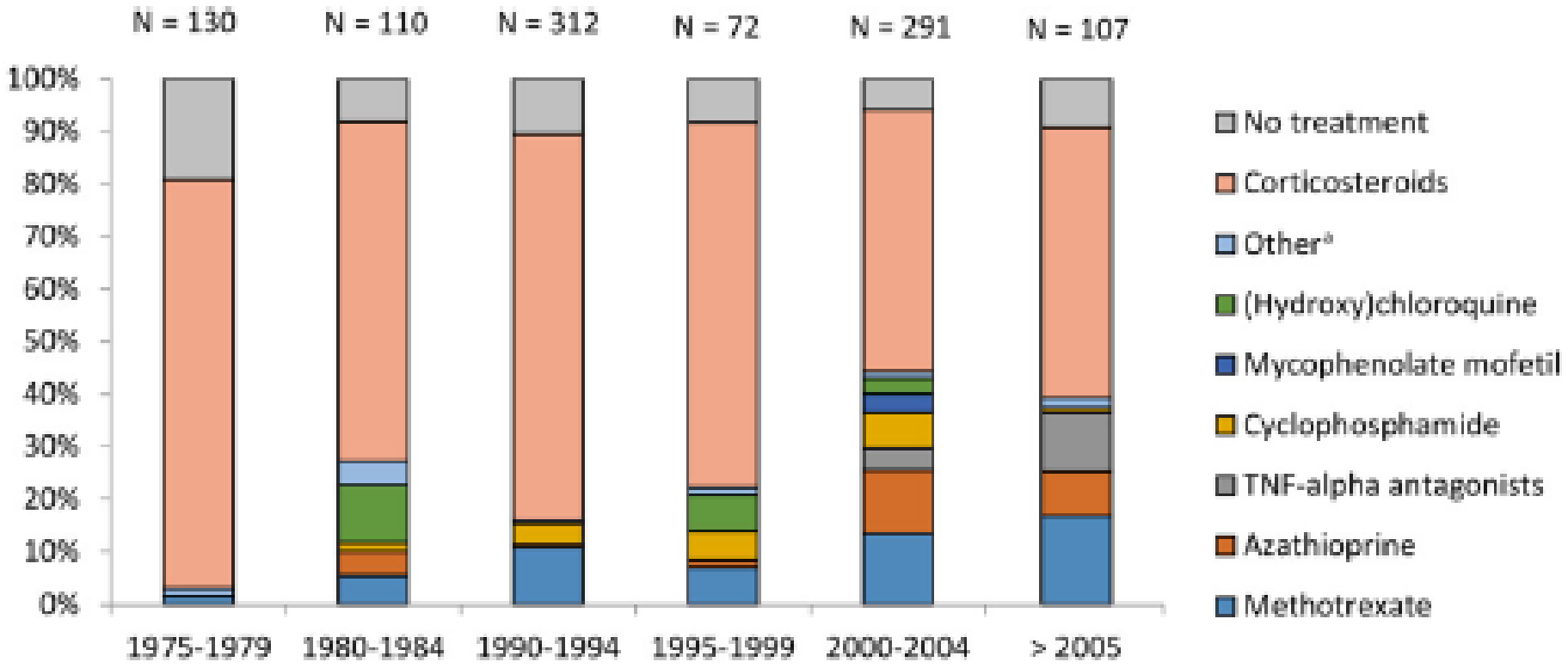
Sarcoidosis - Neurology

Systematic Review/Meta-analysis

- 1980 – 2016, 29 studies, 1088 patients
- 5% with neurosarcoid, mean age 43, Neuro 1st Symptom in 52%
- Manifestations
  - Cranial neuropathy (facial, optic) 55%, Headach 32%
  - Abnormal CSF 63%, MRI abnormal 70%
- Treatment – Steroids 81%, 2nd agent 27%, 3rd agent 9%
- Response – Complete (27%), Partial (32%), Stable (24%), Worse (6%), Death (5%)

Fritz et al, *BMC Neurol.* 2016; 16:220

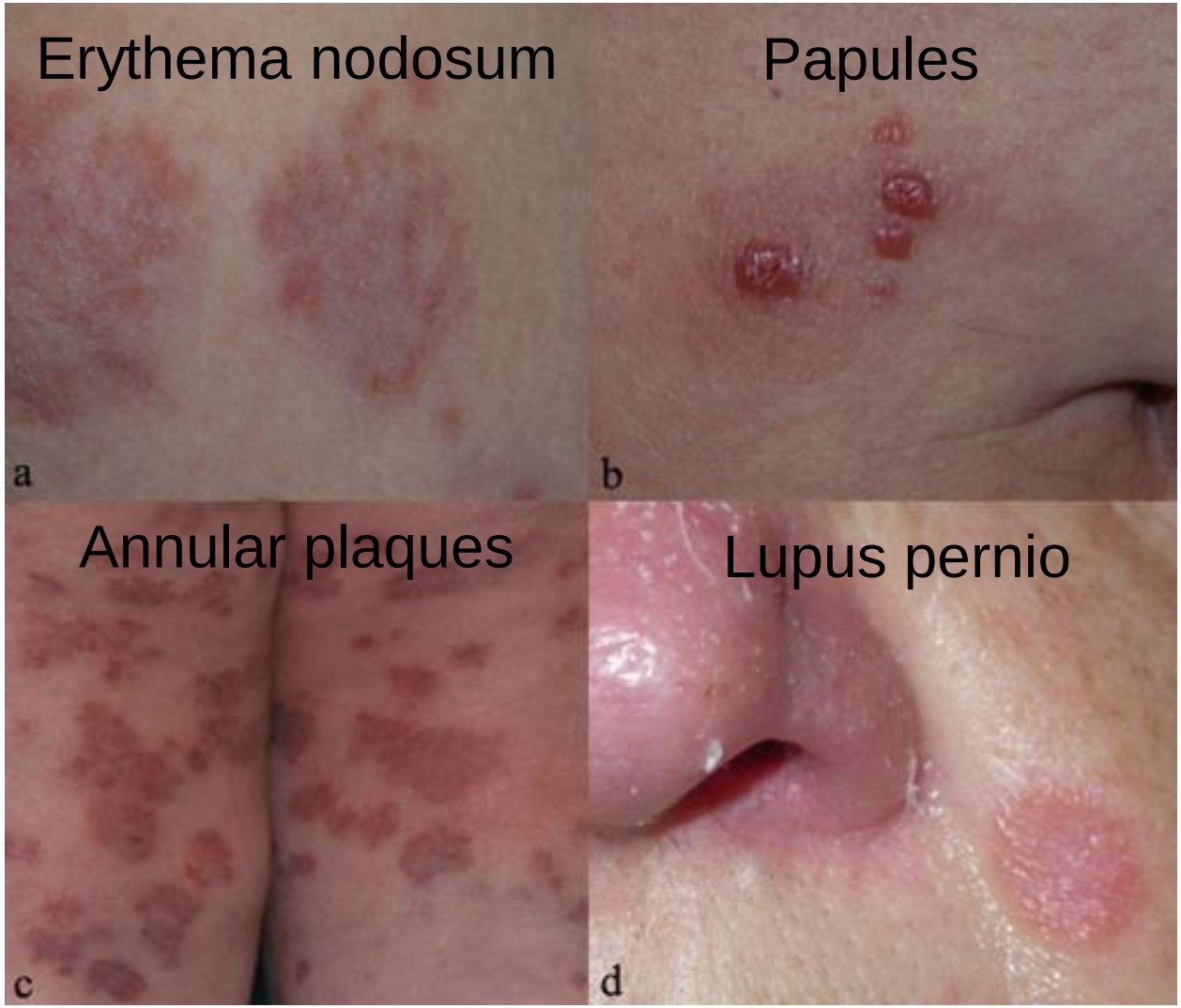
Sarcoidosis - Neurology



Types of treatment over time

Fritz et al, *BMC Neurol.* 2016; 16:220

Sarcoidosis - Cutaneous



Palmucci et al, *Insights Imaging.* 2016;7:571-87

Sarcoidosis – Treatment

- Immunosuppression is the basis of therapy
- Typically limited to the symptomatic patient
- ~ 50% do not require long-term therapy
- Organ specific therapy may be possible
  - Topic steroid creams
  - Steroid eye drops
  - Local steroid skin injections
  - Inhaled corticosteroids for cough

- Evaluating therapy complicated by variable disease course

Baughman et al, *Am J Resp Crit Care Med* 2011; 183:573-81

Sarcoidosis – Treatment

Mild disease

- Most patients require no therapy
- NSAIDs are appropriate first-line therapy for both EN and migratory arthralgias
- Occasionally, a short course (2-4 weeks) of mid-range prednisone (i.e. 20 mg orally per day) may be necessary if NSAIDs ineffective
- For single joint involvement, intra-articular corticosteroids may be beneficial

Other options

- Pharmacologic treatment
  - Corticosteroids
  - Hydroxychloroquine
  - Methotrexate
  - Azathioprine
  - Leflunomide
  - Mycophenolate
  - Infliximab
  - Others

Sarcoidosis – Corticosteroids

Topical

- May take weeks for improvement to be noticed

Intralesional

- Monthly injections of corticosteroids may be beneficial for single or few lesions

Systemic

- Initial dosing: 20-40 mg/day for 2-6 weeks
- Taper to maintenance by 5-10mg every 2-4 weeks
- Continue maintenance dose at 5-15mg/day for 6-9 months
- Treat relapse by increase dose 10-20 mg above maintenance for 2-4 weeks then taper

Sah et al, *Pharmacology & Therapeutics* 2016; 1-9

Sarcoidosis – Corticosteroids

Cochrane Review

- 13 Randomized trials with 1066 participants
- OCS dose of 4-40mg/day

- Improved CXR over 3-24 months (RR 1.46 (95% CI 1.01, 2.09)
- No other significant differences on secondary outcomes
- 2 studies showed improved lung function

Paramothayan et al, *Cochrane Database Syst Rev. 2005 Apr 18;(2):CD001114.*

Sarcoidosis – Hydroxychloroquine

Hyddroxychloroquine

- Dose 200 mg orally twice daily
- basic amine that inhibits protein degradation by acidic hydrolases within lysosomes
- also inhibits the assembly of MHC-peptide complexes and transport to cell surfaces
- Ophthalmologic follow-up every 6-12 months while on drug
- Appears fairly effective for cutaneous, ocular, hepatic, possibly pulmonary disease
  - Pulmonary responses may take 4-6 months

Sarcoidosis – Methotrexate

Methotrexate

- Dose 0.3 mg/kg per week (5-15mg)
- folic acid analogue that inhibits dihydrofolate reductase
- interferes with purine metabolism and polyamine synthesis
- inhibits TNFa, IL-6, and IL-8, release of ROS, LTB_4, and suppresses lymphocyte proliferation
- Increases concentration of adenosine → anti-inflammatory effects
- bone marrow suppression, hepatotoxic → labs must be followed regularly
- Requires daily folic acid supplementation (1 mg), may increase for toxicity

Prospective Data are Sparse

- 24 Patients with new onset, symptomatic disease within 4 weeks of starting prednisone
- Randomized to methotrexate or placebo for the next year → outcome steroid dose
- Only 15 received at least 6 months of therapy and evaluated
- Prednisone decreased for both groups:
  - 1st 6 months methotrexate - Median 26mg/day (Range 15-37) vs placebo 28 (24-33)
  - 2nd 6 months methotrexate – Median 8mg//day (Range 1-22) vs placebo 16 (11-22)
  - There was less weight gain for those patients receiving methotrexate. There was no difference in toxicity between methotrexate and placebo. The difference between methotrexate versus placebo was not seen when all patients (including the dropouts) were analyzed.

Baughman et al., *Sarcoidosis Vasc Diffuse Lung Dis*. 2000;1:60-6

Sarcoidosis – Azathioprine

Azathioprine

- Purine antagonist that interferes with DNA, RNA synthesis
- Inhibits T- and B-cell proliferation and cytotoxic T-cell function
- Common AEs - Nausea, vomiting, diarrhea, myalgia, fever, rash, infections
  - Bone marrow suppression/hepatotoxicity - monitor CBC and LFTs every 4-6 wks
  - Check baseline red cell TPMT enzyme activity at baseline

Retrospective Study of Methotrexate (n=145) or Azathioprine (n=55)

- Linear mixed models of change over time – similar between agents
  - FEV1 increased 52 mL/year, p=0.006
  - FVC increased 95 mL/year, p=0.001
  - DLCO increased 1.23%/year, p=0.018
  - Prednisone decreased 6.3 mg/yr, p<0.0001
- Higher infections on azathioprine (n=35) vs MTX (n=18), p=0.01

Sah et al, *Pharmacology & Therapeutics* 2016; 1-9
Vorselaars et al., *Chest* 2013;144(3):805-12

Sarcoidosis – Mycophenolate

Mycophenolate mofetil

- Inosine monophosphate dehydrogenase inhibitor that prevents purine synthesis and subsequent T-cell and B-cell proliferation
- Dose is usually no greater than 1500 mg BID
- Common AEs – nausea, diarrhea
- Monitor CBC every 4-6 weeks for leukopenia

Restrospective Evaluation (n=10)

- 5/10 due to side effects prednisone; 5/10 due to lack of prednisone response
- Median treatment duration 31 months (range 8-66)
- Steroid dose decreased from 14 → 6 mg/day
- PFTs better in 4/10, stable in 6/10
- Change in FVC + 8.5% (range -2, 16)

Sah et al, *Pharmacology & Therapeutics* 2016; 1-9
Brill et al., *Respiration* 2013;86(5):376-83

Sarcoidosis – Leflunomide

Leflunomide

- Blocks proliferation of activated lymphocytes by inhibiting de novo pyrimidine and thus DNA synthesis
- Consider loading dose 100 mg/day x 3 days, then 10-20 mg/day
- $t_{1/2}$ is greater than 2 weeks, and is contraindicated in pregnancy
- Lab monitoring - CBC, LFTs, electrolytes every 2-6 weeks
- Common side effects include GI symptoms, hepatotoxicity, peripheral neuropathy
- Hypersensitivity reactions (erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis) have been reported

Retrospective study of 76 patients

- Primarily progressive or intolerant of other therapy
- Some improvement in pulmonary/extrapulmonary manifestations after 6 mo
  - mean (sd) change in FVC was -0.1 $\pm$ 0.3 L; after starting the medication, there was a mean gain of 0.09 $\pm$ 0.3 L (p=0.01, paired t-test)

Sah et al, *Pharmacology & Therapeutics* 2016; 1-9
Sahoo et al., *Eur Respir J.* 2011 Nov;38(5):1145-50.

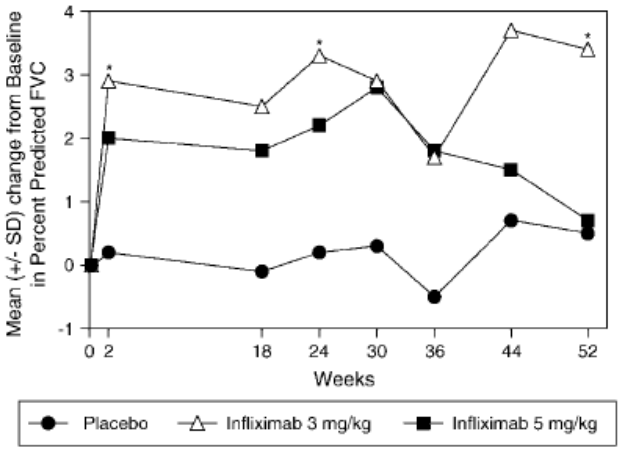
Sarcoidosis – Infliximab

Infliximab

- chimeric mouse monoclonal antibody against TNFa, prevents binding of TNFa to the cell surface receptor
- may result in development of anti-mouse antibodies which requires MTX to suppress
- increased risk of infection
- Numerous case reports of efficacy including lupus pernio and CNS involvement

Randomized placebo controlled trial (1:1:1 – 3mg/kg : 5mg/kg : placebo)

- 138 patients, chronic progressive pulmonary sarcoidosis despite steroid treatment
- Treated for 24 weeks, followed for 52 weeks, Primary endpoint FVC at 24 weeks
- FVC improved 2.5% in Tx groups vs 0% in placebo p=0.038
- No differences in other secondary endpoints
- Post-hoc analysis suggested greater benefit in those with worse baseline disease



Sah et al, *Pharmacology & Therapeutics* 2016; 1-9
Baughman et al., *Am J Respir Crit Care Med*. 2006; 174:795-802

Sarcoidosis – Treatment

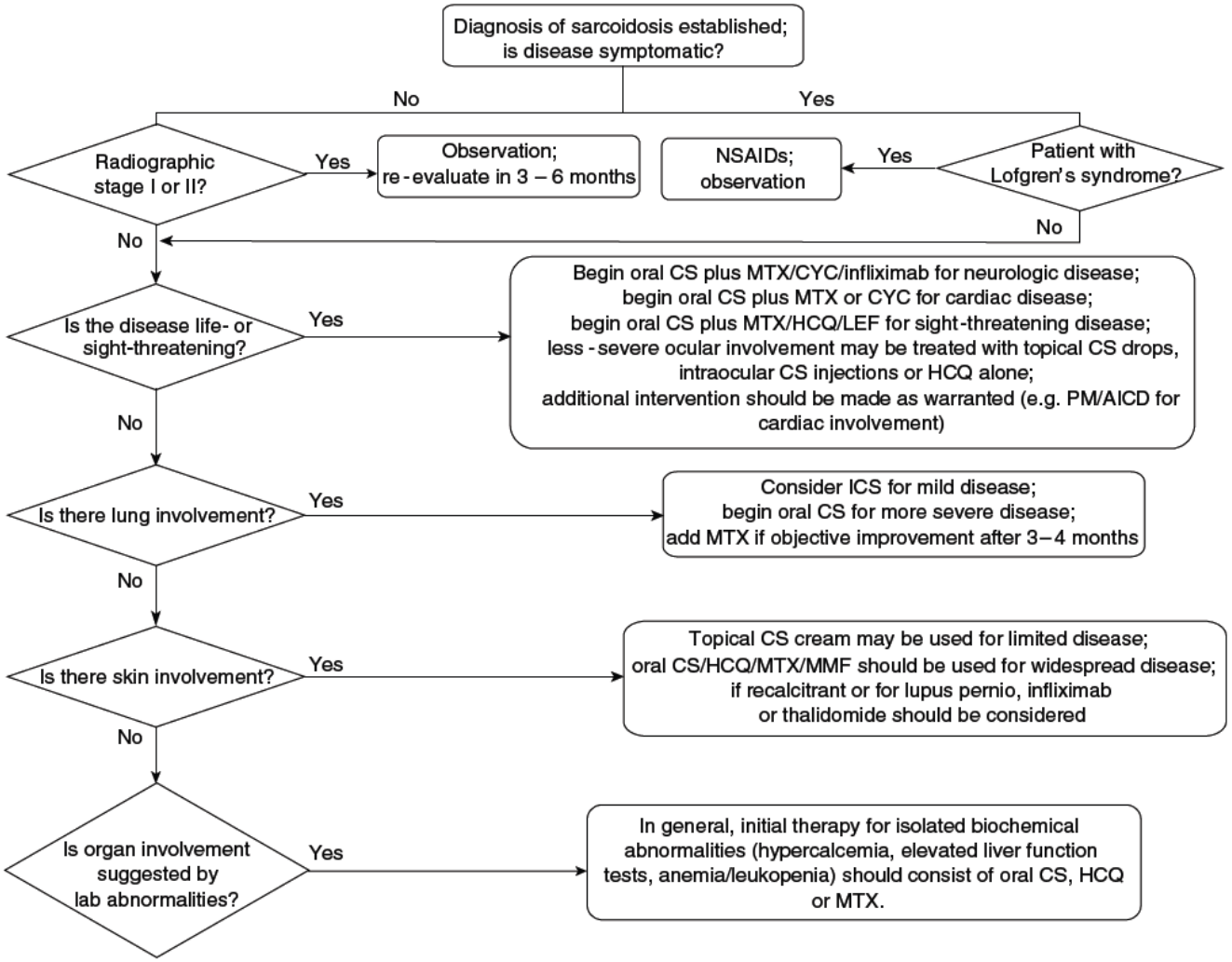
Rituximab

- Monoclonal antibody against CD20 on B-cells
- FDA approved for RA, NHL, CLL, GPA
- Case reports of efficacy in refractory sarcoidosis involving lung, skin, brain, eye
- Hypotension, infusion reactions, diaphoresis, muscle stiffness all common side effects
- Given as 2-infusion cycle 1000 mg 15 days apart, every 6 months

Thalidomide

- inhibits TNFa production by mononuclear cells
- alters expression of pro-inflammatory cytokines
- anti-angiogenic
- teratogenic and induces peripheral neuropathy
- Usual dose is 200 mg orally daily, STEPS program enrollment mandatory
  - Not beneficial in pulmonary disease
  - May be beneficial for CNS or skin involvement

One approach to sarcoidosis management



White and Lynch, *Expert Opin. Pharmacother.* 2007, 8(9):1293-1311

Sarcoidosis – Summary

- The diagnosis of sarcoidosis should be entertained in all patients with symptoms of unclear etiology.
- In all patients with sarcoidosis, cardiac, ophthalmic, dermatologic, and neurologic evaluation should be performed (EKG, full neurologic examination, slit-lamp and dilated exam).
- Serologic, radiographic, and bronchoscopic studies may be supportive but are never diagnostic. Non-caseating epithelioid granulomas must be observed on a biopsy specimen.
- Diagnosis is one of exclusion.
- Treatment based on symptoms and severity of manifestations