

SARCOIDOSIS: AN UPDATE

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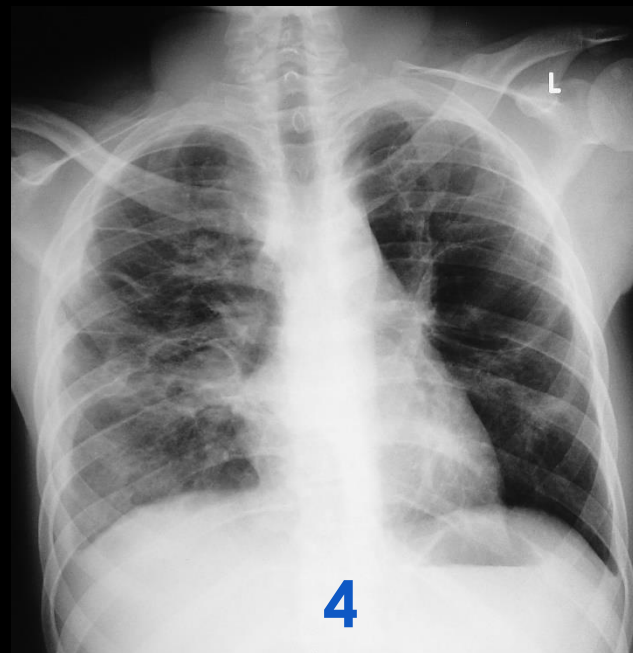
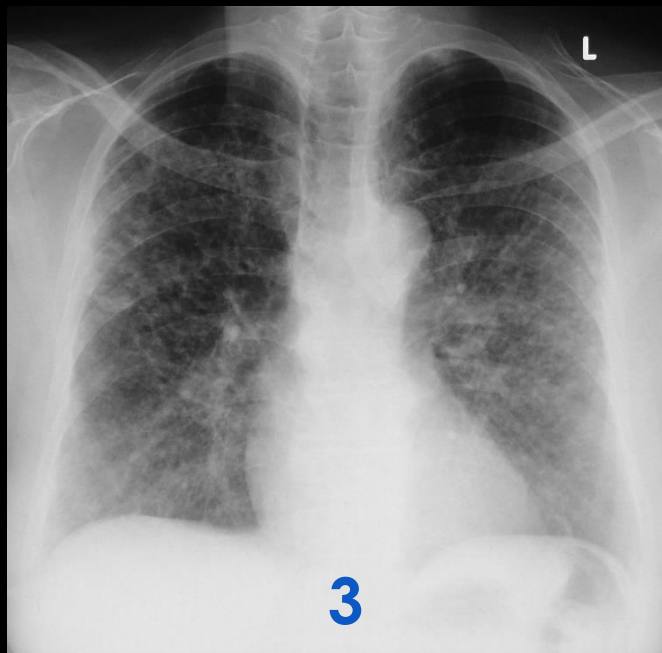
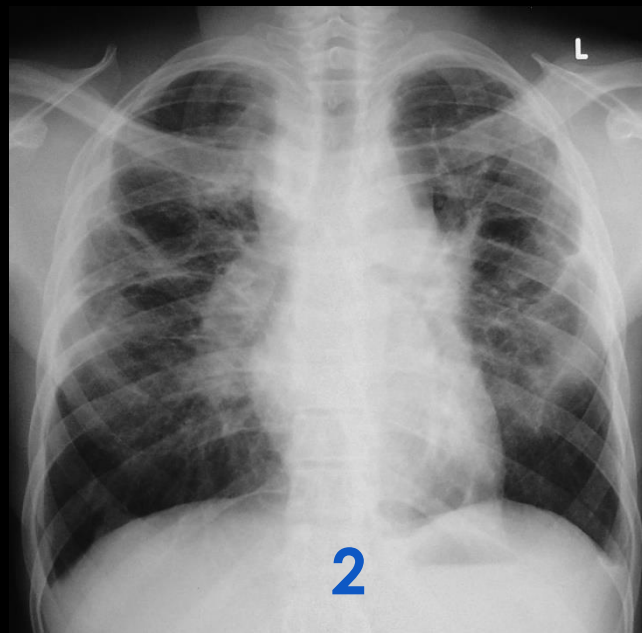
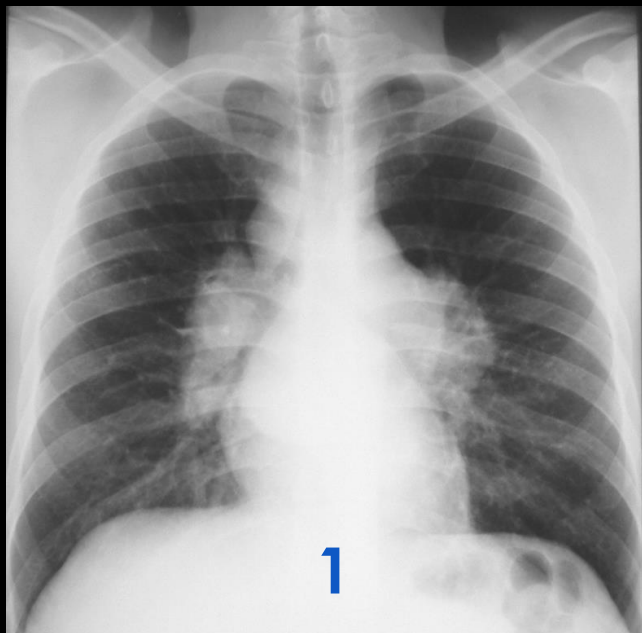
OUTLINE

- Newer diagnostic techniques
 - EBUS-TBNA
 - PET/CT scans
- The patient with persistent respiratory symptoms
- Therapeutic agents
 - Non-steroidal immunosuppressive agents
 - Biologic agents

- ▶ Multisystem disorder

- ▶ Unknown aetiology

- ▶ Diagnosis of exclusion with
 - ▶ compatible clinical and radiological features
 - ▶ tissue biopsy demonstrating non-caseating granulomatous inflammation
 - ▶ absence of any known agents causing granulomatous inflammation

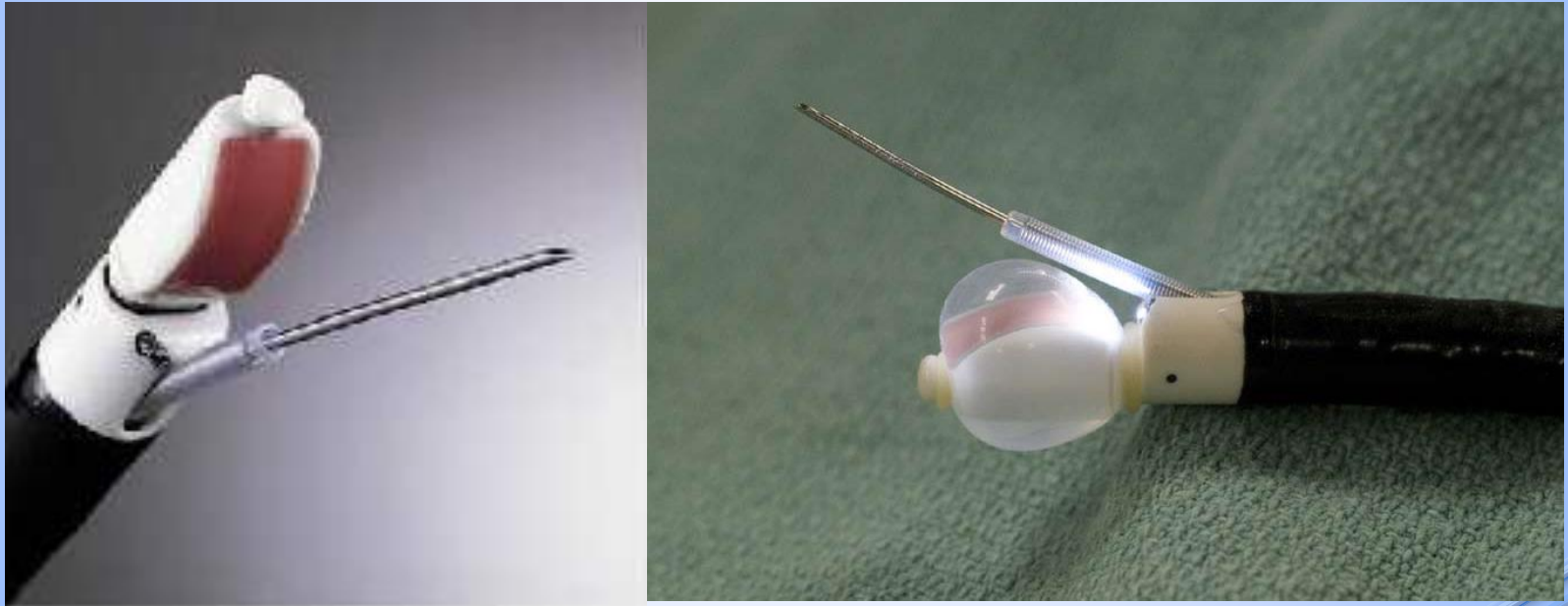


Healthcare use in year prior to diagnosis

	Sarcoidosis	Other respiratory-related diagnosis	
No. of patients	206	2060	
≥ 2 courses of antibiotics	69%	55%	p=0.0020
≥ 2 corticosteroid prescriptions	63%	50%	p=0.0137
Doctor visits (n)	14.7	7.8	p<0.0001
Referrals to specialties (n)	3.9	2.1	p<0.0001
CXR (n)	2.0	1.5	p<0.0001
≥ 2 CXRs	54%	24%	p<0.0001

NEWER DIAGNOSTIC TECHNIQUES

ENDOBONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL FINE NEEDLE ASPIRATION



- ▶ GRANULOMA trial: suspected Stage I or II sarcoidosis
 - ▶ Randomized clinical trial: n=303
 - ▶ Fibreoptic bronchoscopy (EBB and TBLB) vs EUS/EBUS-guided FNA
 - ▶ Yield: EUS/EBUS 80%; bronchoscopy 53% (p<0.001)

- ▶ EBUS-TBNA (cytology and histological core biopsy) vs TBLB/EBB in Stage 1 and II sarcoidosis
 - ▶ n=653
 - ▶ Sensitivity
 - ▶ EBUS-TBNA 82.2%
 - ▶ TBLB alone 43.9%
 - ▶ EBB alone 29.7%
 - ▶ EBUS-TBNA + TBLB/EBB 89%

Choose Wisely

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Sarcoidosis

Atul C. Mehta, MBBS, FCCP

Francisco A. Almeida, MD, FCCP

Cleveland, OH

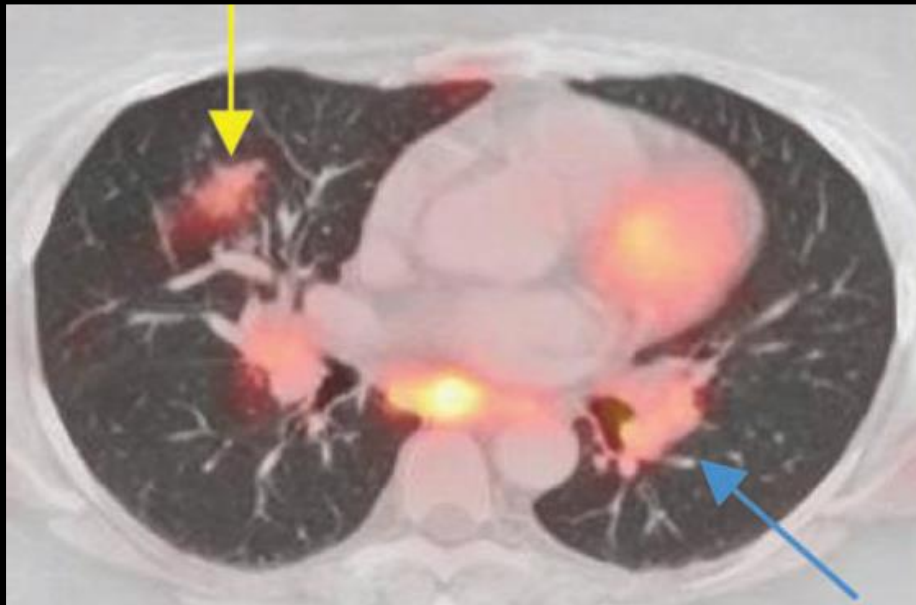
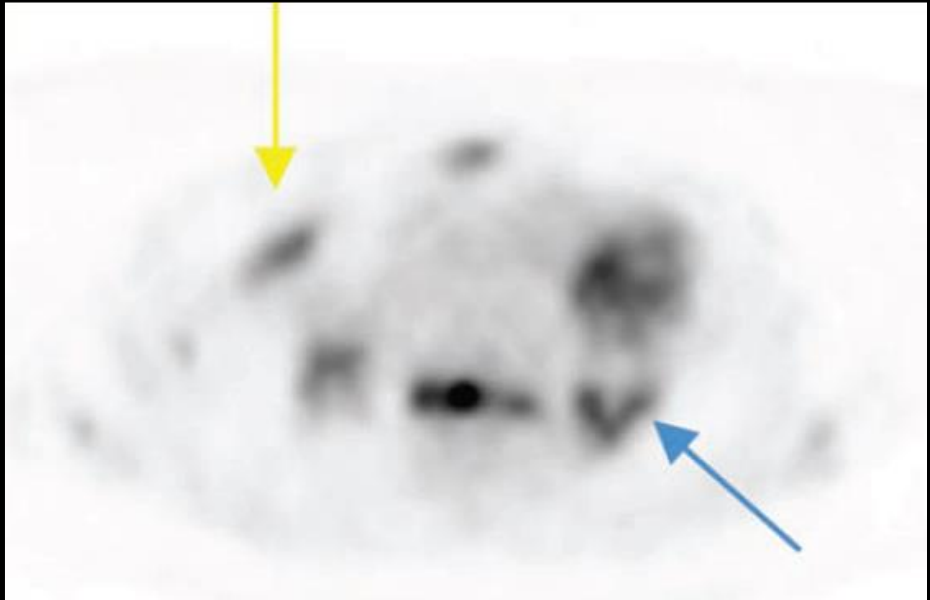
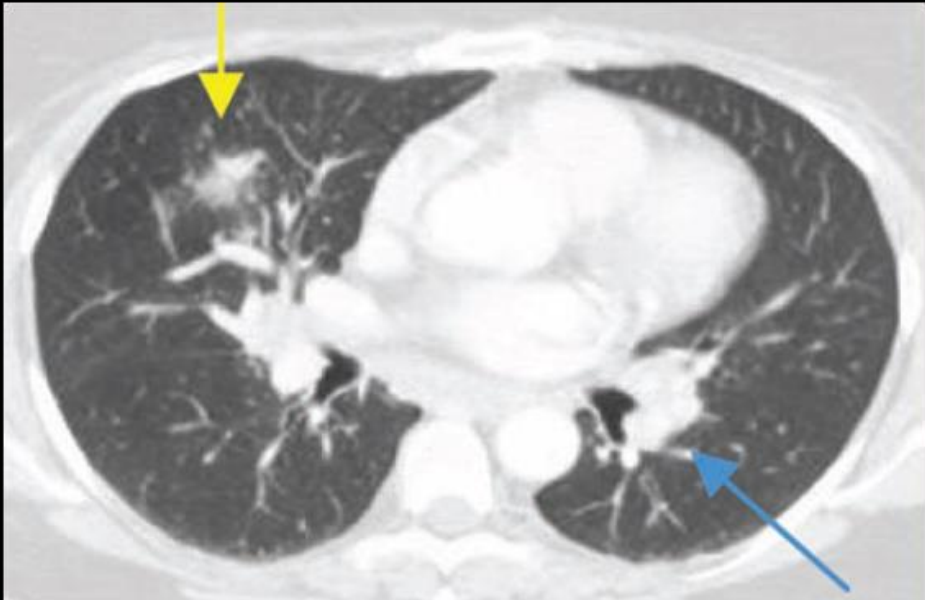
You must choose. But choose wisely.

Indiana Jones and the Last Crusade¹

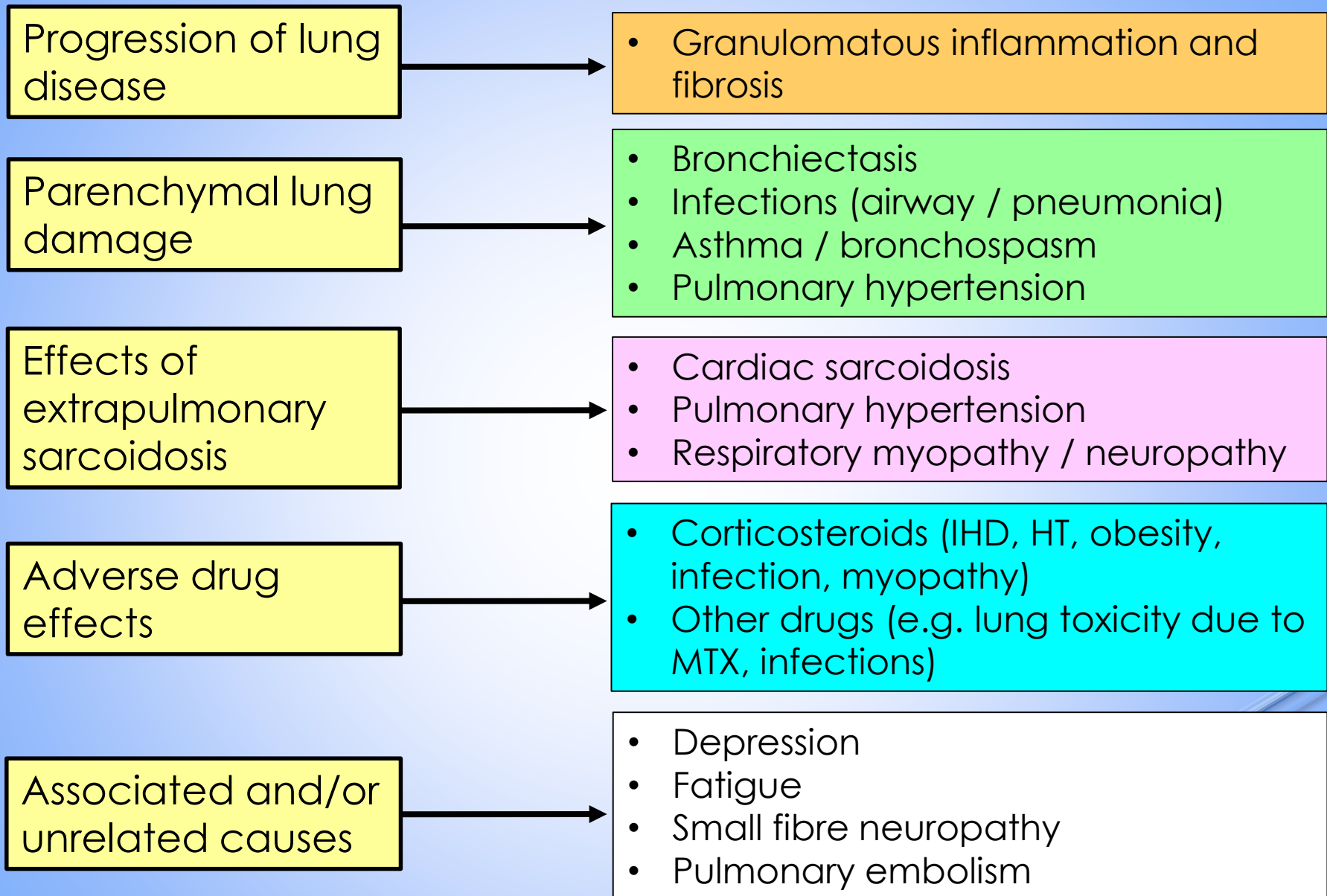
- ▶ Stage 1 sarcoidosis
 - ▶ > 10 000 invasive procedures to diagnose 5 alternative diagnoses
 - ▶ Clinical follow-up can establish diagnosis
 - ▶ No treatment required
- ▶ EBUS-TBNA
 - ▶ availability, affordability, safety, operator competence
 - ▶ best combined with TBLB for optimal yield in patients with pulmonary infiltrates
- ▶ Study: suspected sarcoidosis in patients with indication for TBNA (n=130)
 - ▶ TBLB/EBB + cTBNA or TBLB/EBB + EBUS-TBNA
 - ▶ Diagnostic yield similar (85.5% vs 92.7%; p=0.34)
 - ▶ Procedure time longer for EBUS-TBNA (33.5 ± 5.6 mins vs 22.9 ± 3.9 mins; p=0.0001)

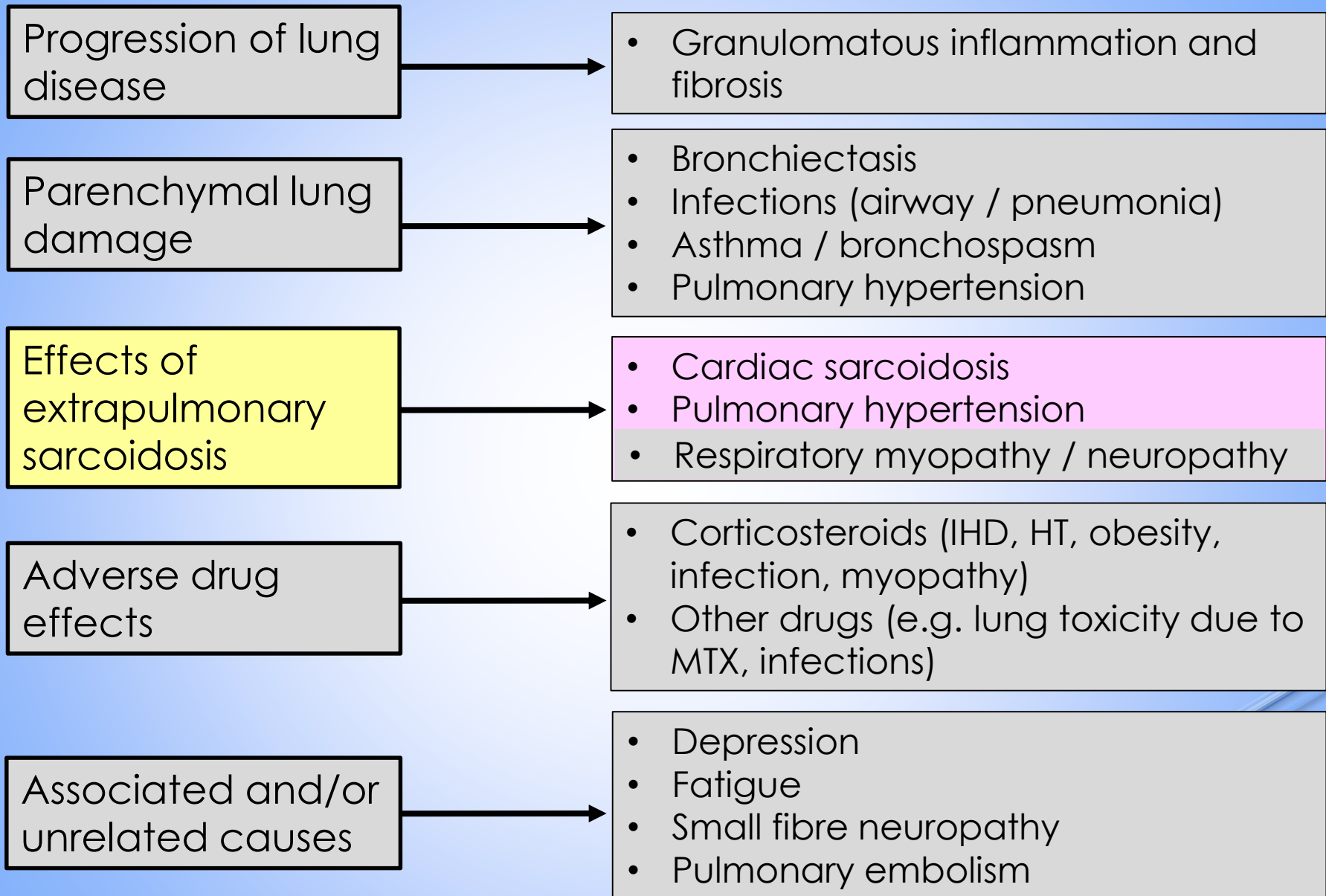
^{18}F -FDG PET/CT SCAN

- ▶ Functional imaging modality
- ▶ Increased ^{18}F -FDG uptake in areas of increased metabolic activity
- ▶ Not specific
- ▶ Sensitivity for detecting active sarcoidosis: 80 – 100%
- ▶ ^{18}F -FDG PET/CT improves accuracy in assessment of active disease
- ▶ Can identify potential sites for biopsy
- ▶ Useful in assessing residual activity in fibrotic pulmonary sarcoidosis
- ▶ Specific pattern in cardiac sarcoidosis



THE SARCOIDOSIS PATIENT WITH PERSISTENT RESPIRATORY SYMPTOMS





CARDIAC SARCOIDOSIS

- ▶ Symptoms and signs recognized in only 5%
- ▶ Autopsy studies suggest involvement in 20 – 30% of cases
- ▶ Older Japanese females have highest incidence (~ 80%)
- ▶ Often occurs in absence of apparent disease elsewhere

► Autopsy studies

	n	Antemortem diagnosis	Sudden death
Matsui et al. 1976	42	11.9%	38.0%
Roberts et al. 1977	113	21.2%	53.0%
Fleming, 1988	138	64.4%	55.8%

CLINICAL MANIFESTATIONS

- ▶ conduction abnormalities
- ▶ ventricular and atrial arrhythmias
- ▶ heart failure (25 – 75% of deaths)
- ▶ papillary muscle dysfunction
- ▶ mitral regurgitation
- ▶ myocardial infarction
- ▶ ventricular aneurysm
- ▶ sudden death (presenting feature in up to 65%)

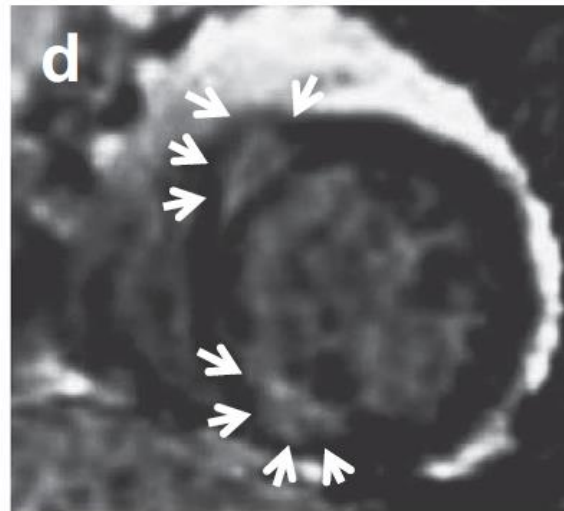
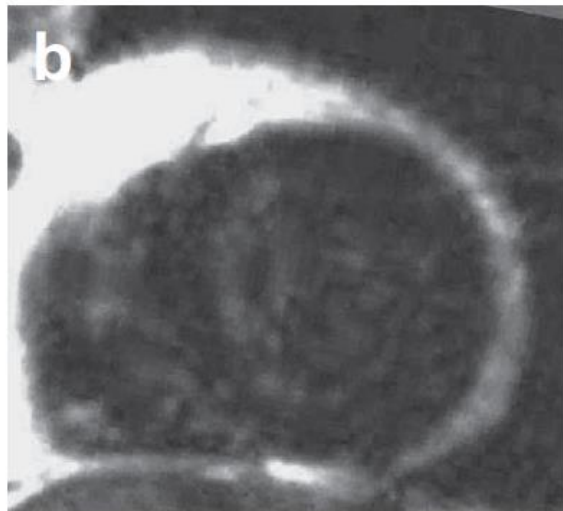
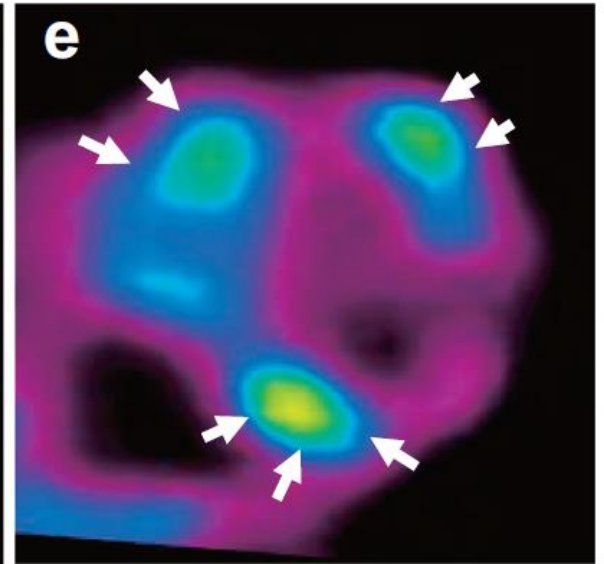
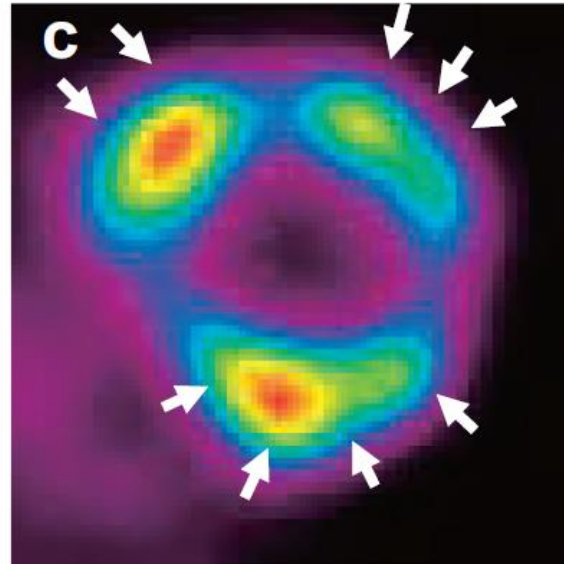
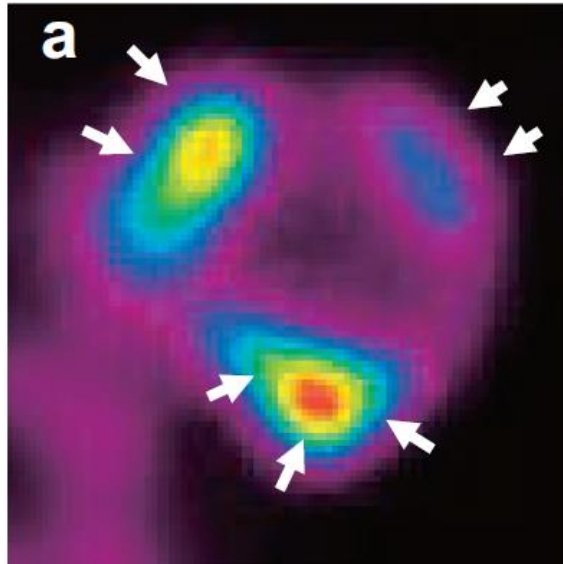
DIAGNOSIS

- Endomyocardial biopsy (positive in < 10%)
- Imaging techniques
 - ▶ echocardiography (sensitivity may be as low as 14%)
 - ▶ gallium-67 scan (false negative with chronic corticosteroid Rx)
 - ▶ thallium-201 and technetium-99m scintigraphy (reverse distribution)
 - ▶ ¹⁸F-FDG-PET scan (sensitivity 82–100%, but relatively poor specificity)
 - ▶ delayed gadolinium-enhanced cardiac MRI
- ▶ NT-proBNP may be useful, but non-specific

1st workup in 2005

2nd workup in May, 2006

3rd workup in August, 2006



▶ Management

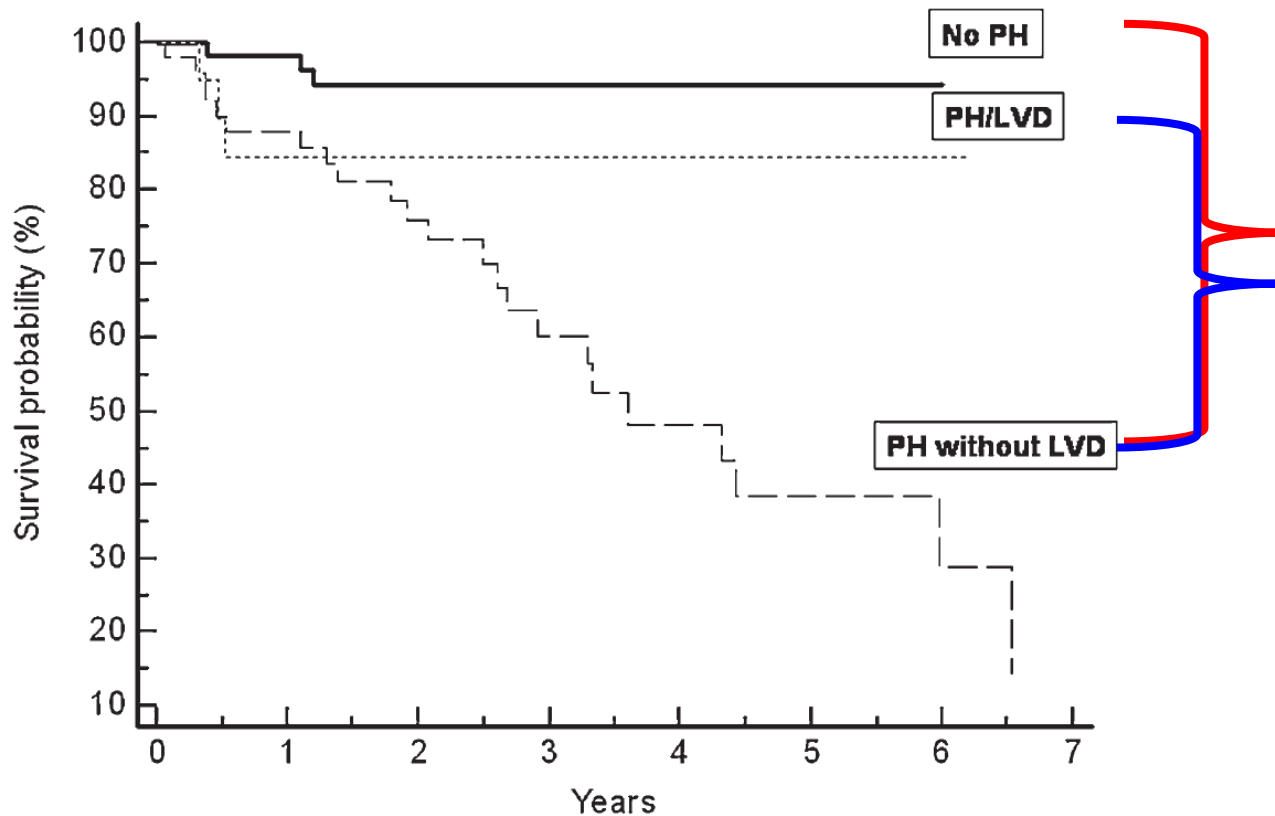
- ▶ corticosteroids
- ▶ alternative drugs (chloroquine, cyclosporin, methotrexate)
- ▶ anti-arrhythmic drugs
- ▶ permanent pacemaker
- ▶ implantable cardiac defibrillator
- ▶ cardiac transplantation

PULMONARY HYPERTENSION

PULMONARY HYPERTENSION

- ▶ Reported overall prevalence 5 – 15%
- ▶ Prevalence in symptomatic patients > 50%
- ▶ Causes
 - ▶ destruction of pulmonary arterial and venous beds by granulomas or fibrosis
 - ▶ pulmonary arterial vasoconstriction
 - ▶ pulmonary veno-occlusive disease
 - ▶ pulmonary artery compression by lymph nodes
 - ▶ LV systolic and diastolic dysfunction
 - ▶ (portopulmonary hypertension)

- ▶ Retrospective review of 22 patients with sarcoidosis and PAH
 - ▶ 2 patients with Stage 0 CXR
 - ▶ Mortality correlated with NYHA functional class IV, but not with lung function, CXR or haemodynamic parameters
 - ▶ Survival 59% at 5 years



- ▶ Median survival for PH without LVD: 4.2 yrs
- ▶ Hazard ratio for death
 - ▶ PH without LVD vs no PH: 10.39
 - ▶ PH without LVD vs PH/LVD: 3.14

TREATMENT OF PULMONARY HYPERTENSION

- ▶ Corticosteroids or alternative drugs for active sarcoidosis
- ▶ Endothelin receptor antagonists (bosentan)
- ▶ Nitric oxide / selective PDE-5 inhibitors (sildenafil)
- ▶ Prostanoid analogues (epoprostenol, inhaled iloprost)
- ▶ Lung transplantation

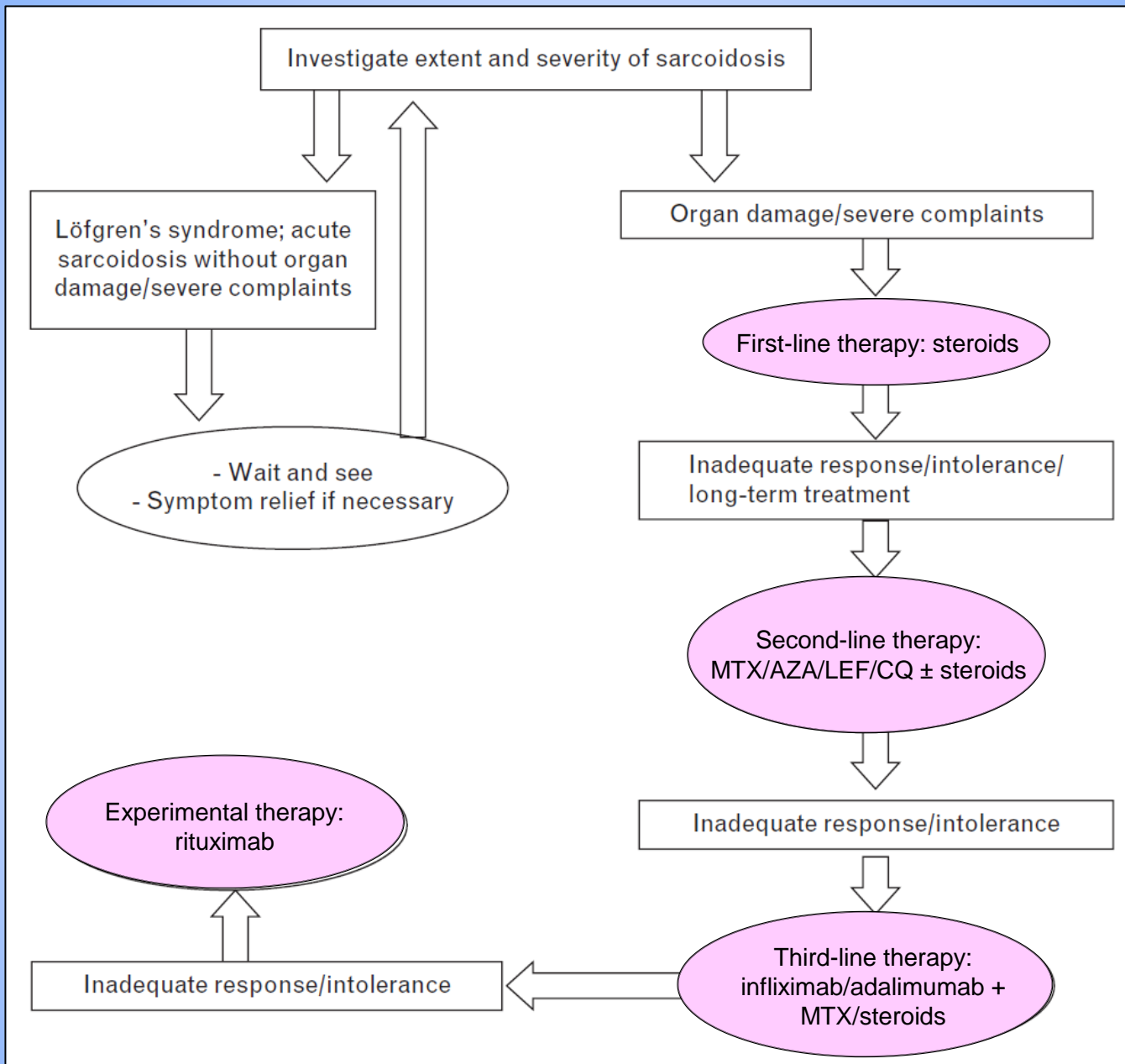
BOSENTAN

- ▶ DBPCT of sarcoidosis-associated PH: n=35
- ▶ Bosentan 62.5 mg bd for 1 month, then 125 mg bd or placebo
- ▶ At 16 weeks, within and between groups
 - ▶ Bosentan: significant fall in PA mean pressure (-4 ± 6.6 mm Hg, $p=0.0105$) and PVR (-1.7 ± 2.75 Wood units, $p=0.0104$).
No significant change in placebo group.
 - ▶ No difference in 6MWD or FVC
 - ▶ No significant difference in Borg score, FAS, SF-36 score, SGRQ
 - ▶ 2 patients in Bosentan group required increase in supplemental O₂ by > 2 L/min

THERAPEUTIC AGENTS

INDICATIONS FOR SYSTEMIC TREATMENT

- ▶ significant or worsening organ dysfunction
- ▶ hypercalcaemia and/or hypercalciuria
- ▶ cardiac involvement
- ▶ neurological involvement
- ▶ posterior uveitis or panuveitis
- ▶ eye involvement not responsive to topical Rx
- ▶ disfiguring skin lesions
- ▶ “bulky” disease
- ▶ prominent constitutional symptoms



DRUG THERAPY: ALTERNATIVES TO CORTICOSTEROIDS

SECOND- AND THIRD-LINE AGENTS

- ▶ Disease-modifying anti-sarcoid agents
 - ▶ Methotrexate
 - ▶ Azathioprine
 - ▶ Leflunomide
 - ▶ Mycophenolate mofetil
 - ▶ (Hydroxy)-chloroquine
- ▶ Biologic agents
 - ▶ TNF- α inhibitors (adalimumab, infliximab, golimumab)
 - ▶ Ustekinumab
 - ▶ Rituximab

WASOG RECOMMENDATIONS FOR METHOTREXATE

- ▶ MTX should be regarded as
 - ▶ 2nd line Rx
 - ▶ Steroid-refractory disease
 - ▶ Steroid side-effects
 - ▶ Steroid-sparing agent
 - ▶ 1st line Rx with or without steroids
 - ▶ Uveitis non-responsive to topical steroids
 - ▶ Neurosarcoidosis
 - ▶ Cardiac sarcoidosis
 - ▶ Diabetes and/or obesity
- ▶ Recommended initial dose: 5 – 15 mg weekly
- ▶ Folic acid supplementation: at least 5 mg weekly or 1 mg daily

- ▶ Monitor ALT ± AST, creatinine and FBC
- ▶ GIT side-effects
 - ▶ Divide oral dose but ensure that total dose ingested within 12-hour period
- ▶ Acceptable safety profile, can be used long-term
- ▶ Avoid in males and females for at least 3 months before planned pregnancy

METHOTREXATE VS AZATHIOPRINE

- ▶ Retrospective cohort study
 - ▶ MTX (n=145) vs AZA (n=55) as 2nd line therapy in refractory sarcoidosis
 - ▶ 2-year follow-up
- ▶ No difference between two arms
 - ▶ decrease in Prednisone (mean 6.32 mg/yr)
 - ▶ increase in FEV₁ by 52 ml/yr
 - ▶ increase in VC by 95 ml/yr
 - ▶ increase in DLCO by 0.107 mmol/kPa/s
- ▶ More infections in AZA group (34.6% vs 18.1%)

BIOLOGIC AGENTS

▶ Anti-TNF- α agents

- ▶ recombinant inhibitors: etanercept (not effective)
- ▶ monoclonal antibodies
 - ▶ infliximab (chimeric)
 - ▶ adalimumab (humanized)
 - ▶ golimumab (humanized)

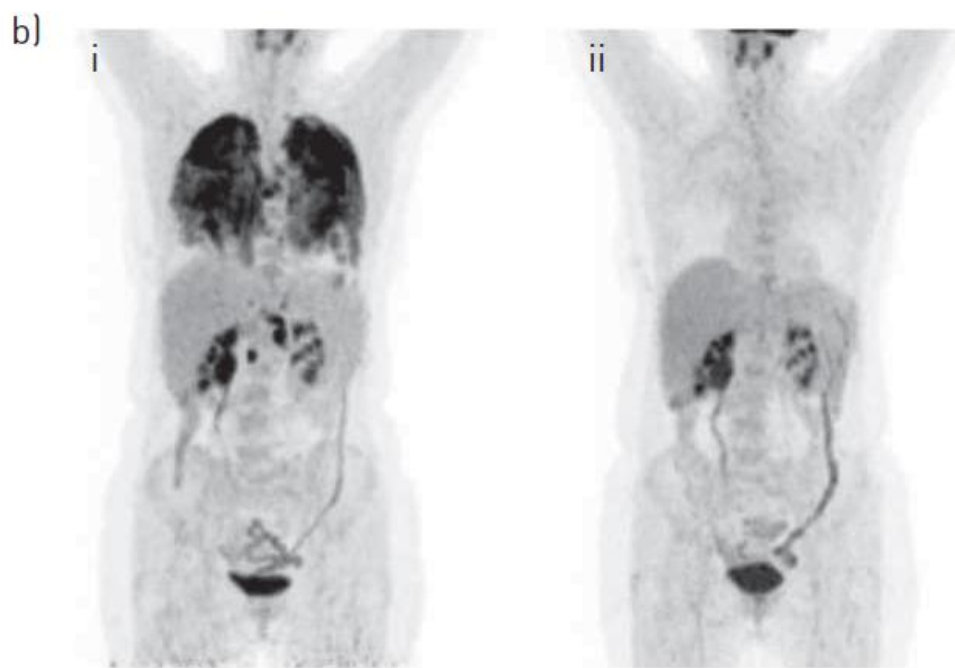
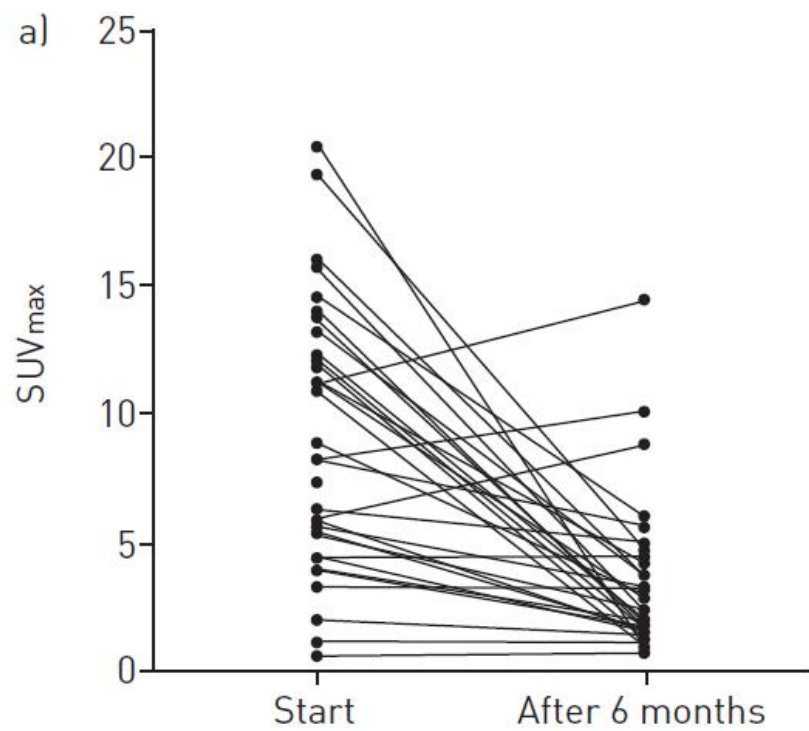
INFLIXIMAB

- ▶ Useful in
 - ▶ FVC \leq 70% pred
 - ▶ reticulonodular infiltrate
 - ▶ lupus pernio
 - ▶ neurosarcoidosis
- ▶ Can cause sarcoid-like granulomas
 - ▶ median interval between drug and diagnosis 18 mo
 - ▶ manifestations mainly pulmonary and cutaneous

INFLIXIMAB: PROSPECTIVE TRIALS

- ▶ RDBPCT: 138 patients with chronic pulmonary sarcoidosis
 - ▶ Stable disease, continued background treatment
 - ▶ Follow-up for 24 weeks
 - ▶ Improvement in FVC % predicted by 2.5% in infliximab group (p=0.038)
 - ▶ No difference in SGRQ, 6MWD or Borg dyspnoea score

- ▶ Prospective trial of 56 patients with refractory sarcoidosis
 - ▶ Unresponsive to 1st and 2nd line agents
 - ▶ Active disease (PET/CT scan, sIL-2R, ACE)
 - ▶ Infliximab administered over 6 months
 - ▶ Significant increase in FVC (6.64% pred), FEV₁ (5.80% pred), DLCO (4.12% pred)
 - ▶ Significant decrease in SUV_{max} of mediastinum and lung parenchyma on PET/CT scan
 - ▶ Significant decrease in sIL-2R and ACE levels



USTEKINUMAB AND GOLIMUMAB

- ▶ Chronic pulmonary and/or cutaneous sarcoidosis
 - ▶ Phase II multicentre RDBPC trial with 3 arms (ustekinumab, golimumab, placebo): n=173
 - ▶ Neither drug showed efficacy with regard to change in
 - ▶ FVC % pred
 - ▶ 6MWD
 - ▶ SGRQ
 - ▶ Skin Physicians' Global Assessment (SGPA) score
 - ▶ Trend towards improvement with golimumab in
 - ▶ Skin sarcoidosis group
 - ▶ Lower BMI

Thank you

