



Slide 1



Pulmonary Sarcoidosis A-Z

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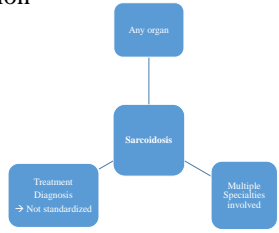
Disclosure

- This presentation has no:
 - Conflicts of interest
 - Off-label promotion of medications

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Introduction



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graph TD; A[Any organ] --- B[Sarcoidosis]; B --- C["Treatment Diagnosis  
→ No standardized"]; B --- D["Multiple Specialties  
involved"]
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Judson MA Am J Med. 2007; May;120(5):400-7.

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Epidemiology

- “Epithelioid cells with large pale nuclei and also a few giant cells” → Sarcoidosis (Boeck, 1899)
- Individuals at all ages (Mainly third and fourth decade)
- Black vs Caucasian:
 - More common (the adjusted annual incidence rate among blacks is roughly 3 times than that among whites)
 - > chronic and fatal
- Prevalence:
 - 59.0-60.1 per 100,000 population overall
 - 141.4 per 100,000 in African-American

* Ramirez MC, Fontana JB. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA. 2011;305(4):391-9.

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Epidemiology


- ? Cause is airborne (Involvement of skin, eyes, and the lungs)
- No single predominant environmental or occupational factor has been identified (large, well-matched, multicenter, etiologic study)

Table 1. - Examples of agents suggested to be involved in the pathogenesis of sarcoidosis

Antigen	Type of agent	Reference
Aluminum	Aluminum	134
Aluminum hydroxide	Aluminum hydroxide	134
Aluminum silicate	Aluminum silicate	134
Aluminum phosphate	Aluminum phosphate	134
Aluminum sulfate	Aluminum sulfate	134
Aluminum hydroxide phosphate	Aluminum hydroxide phosphate	134
Aluminum phosphate sulfate	Aluminum phosphate sulfate	134
Aluminum sulfate octahydrate	Aluminum sulfate octahydrate	134
Aluminum sulfate hexahydrate	Aluminum sulfate hexahydrate	134
Aluminum sulfate monohydrate	Aluminum sulfate monohydrate	134
Aluminum sulfate trihydrate	Aluminum sulfate trihydrate	134
Aluminum sulfate tetrahydrate	Aluminum sulfate tetrahydrate	134
Aluminum sulfate pentahydrate	Aluminum sulfate pentahydrate	134
Aluminum sulfate hexahydrate	Aluminum sulfate hexahydrate	134
Aluminum sulfate heptahydrate	Aluminum sulfate heptahydrate	134
Aluminum sulfate octahydrate	Aluminum sulfate octahydrate	134
Aluminum sulfate nonahydrate	Aluminum sulfate nonahydrate	134
Aluminum sulfate decahydrate	Aluminum sulfate decahydrate	134
Aluminum sulfate undecahydrate	Aluminum sulfate undecahydrate	134
Aluminum sulfate dodecahydrate	Aluminum sulfate dodecahydrate	134

* Ramirez MC, Fontana JB. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA. 2011;305(4):391-9.
* Henschler GW, Casadei E, Ando M, et al. ATXERS/BS/SG: treatment on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffus Lung Dis. 1999;16(2):140-71.

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Mortality and Sarcoidosis

- During the past 20 years sarcoidosis mortality has increased
- Mainly non-hispanic African American
- Age 55 or more
- Cause of death → sarcoidosis itself

* Baker MH, Barrett JS, Briggs DA, White LE, Rosenbly L, Cozier YC. Mortality among African American women with sarcoidosis: data from the Black Women's Health Study. Sarcoidosis Vasc Diffus Lung Dis. 2011;18(2):128-31.
* Sivigri JJ, Olson AL, Hain TE, et al. Sarcoidosis-related mortality in the United States from 1988 to 2007. Am J Respir Crit Care Med. 2011;183(11):1524-8.

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Racial Difference in Sarcoidosis Mortality in the United States

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Method of Research: Cohort; Analytic: Case-Control; Journal: CHEST; Year: 2015; Volume: 148; Issue: 1; Pages: 458-65

CHEST

METHODS:

- Mortality related to sarcoidosis from 1999 → 2010
- Examining data on multiple causes of death from the National Center for Health Statistics.
- Both African Americans and Caucasians.
- Compared sarcoidosis-related deaths vs deaths:
 - Car accidents (previously healthy control subjects)
 - Rheumatoid arthritis (chronic disease control subjects)

RESULTS:

- Sarcoidosis was reported as an immediate cause of death in 10,348 people in the United States
- 6,285 were African American and 3,984 Caucasian

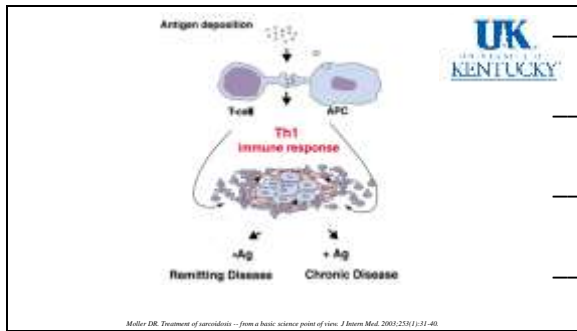
- Age-adjusted mortality rate for African Americans was 12 times higher than for Caucasians
- African Americans died at an earlier age than Caucasians.
- Compared with the control groups, pulmonary hypertension was significantly more common in individuals with sarcoidosis.

CONCLUSIONS:

- This nationwide population-based study exposes a significant difference in ethnicity and sex among people dying of sarcoidosis in the United States.
- Pulmonary hypertension investigation should be considered in all patients with sarcoidosis, especially African Americans.

Merrill M, Michaels BF, Schoenfeld D, Swartz NJ, Baughman BP. Racial difference in sarcoidosis mortality in the United States. Chest. 2015;147(2):458-65.

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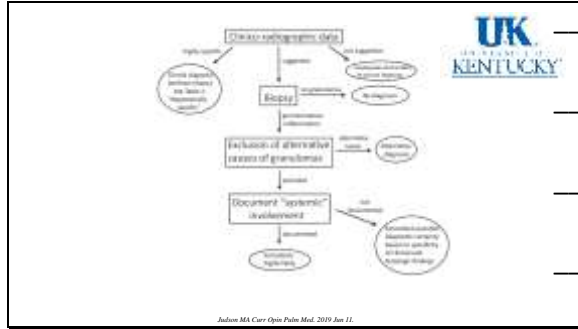
Diagnosis

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- Clinico-Radiologic
- Path: Granuloma
- Other causes excluded

Cahler DA. Sarcoidosis. Immunol Allergy Clin North Am. 2012;32(4):687-511.

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Table 3. The differential diagnosis of granulomatous inflammation other than sarcoidosis, by organ

Organ	Differential diagnosis
Lung	Tuberculosis Atypical mycobacteria Fungi Parasitosis (rare) Mycoplasma Hypersensitivity pneumonitis Pneumoconiosis (beryllium (chronic beryllium disease, silicosis, asbestosis) Aspiration of foreign substances Granulomatosis with polyangiitis Rheumatoid nodules Necrotizing sarcoid granulomatosis Drug reactions including drug-induced sarcoidosis-like reactions

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Julian MA Curr Opin Pulm Med. 2010 Jun 11.

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Diagnosis

- Medical history (Granulomatous disease)
- Tuberculin skin test (Pos ? Tb)

Tuberculosis, other mycobacteria
Fungi
Hypersensitivity pneumonitis
Foreign (eg. Wegener's granulomatosis)
Chronic beryllium disease, other metal exposure
Foreign body reactions
Lymphoma



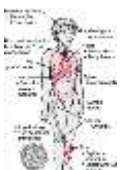
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Julian MA Am J Med. 2007 May;120(5):403-7.


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Diagnosis


- Physical examination:
 - Pulmonary manifestations:
 - Cough
 - Dyspnea
 - Wheezing
 - chest pain
 - Extra-pulmonary manifestations:
 - Red eyes
 - Skin lesions
 - Cardiac rhythm disturbances
 - Neurologic deficits
 - Organomegaly




J Gen Intern Med. 2007;May;22(5):403-7.



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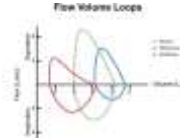
N Engl J Med. 2007; Nov 22;357(23):2355-65.




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Diagnosis

- Pulmonary assessment:
 - Pulmonary function test + diffusing capacity (restrictive, ? Obstructive)
 - Chest radiograph/CT scan of chest
- Extra-pulmonary Assessment:
 - Complete blood count
 - Serum chemistries
 - Urinalysis
 - Electrocardiogram
 - Ophthalmic examination



J Gen Intern Med. 2007;May;22(5):403-7.




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Table 2 - Recommended Initial Evaluation of Patients with Sarcoidosis


1. History (occupational and environmental exposures, symptoms)
2. Physical examination
3. Anteroposterior chest radiography
4. Pulmonary function tests: spirometry, DLCO, and FEV1
5. Peripheral blood counts: white blood cells, red blood cells, platelets
6. Serum chemistry: calcium, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), creatinine, BUN
7. Urine analysis
8. EKG
9. Routine ophthalmologic examination
10. Tuberculin skin test

DLCO = carbon monoxide diffusion in the lung; FEV1 = transfer coefficient; BUN = blood urea nitrogen; EKG = electrocardiogram.
 Reprinted with permission from Henschke CH, Costabel JJ, Asha M, et al. ATS/ERS/ASACI Statement on sarcoidosis. *Semin Respir Crit Care Med.* 1998;9(1):66-175.




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Diagnosis waived



- Lofgren syndrome:
 - Bilateral hilar lymphadenopathy
 - Erythema nodosum
 - Periarticular inflammation (typically of the ankles, not always present)
 - Fever and malaise (usually)
- Heerfordt syndrome
 - Uveitis
 - Parotid swelling
 - Fever and malaise (usually)
- Asymptomatic bilateral hilar lymphadenopathy




Carter DA. Sarcoidosis. *Immunol Allergy Clin North Am.* 2012;32(4):697-721.



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Radiographic Staging



- **Siltzbach/Scadding's Radiographic Staging: (Chest xray)**
 - Stage 0: Normal Chest xray
 - Stage I: Bilateral Hilar Adenopathy
 - Stage II: Bilateral Hilar Adenopathy plus parenchymal abnormalities
 - Stage III: Parenchymal abnormality alone
 - Stage IV: Pulmonary Fibrosis

Guidry C, Fricke RG, Run R, Pandey T, Lambhorst K. Imaging of Sarcoidosis: A Contemporary Review. *Radiol Clin North Am.* 2016;54(3):519-34.

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Stage I

- Prevalence: 50%
- Resolution: 50-90%

Stage II

- Prevalence: 25-30%
- Resolution: 30-70%

Stage III

- Prevalence: 10-12%
- Resolution: 10-20%

Stage IV

- Prevalence: 5%
- Resolution: 0%

Galvin C, Frick B, Kim R, Pandey T, Jambhekar K. Imaging of Sarcoidosis: A Contemporary Review. Radiol Clin North Am. 2016;54(3):519-34.

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Mortality

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Khalil G, Llover EE, Baughman RP. Chest 2018 Jan;153(1):105-111.

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Mortality



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Khalil G, Llover EE, Baughman RP. Chest 2018 Jan;153(1):105-111.

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Diagnosis

- Role of EBUS:
- EBUS TBNA is a safe procedure and with high diagnostic yield
- EBUS (esp. stage I and II) should be added to conventional bronchoscopy diagnostic criteria.

• Wang M, Yanafuku K, Nakajima T, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Respir J*. 2007;29(6):1132-6
 • Nakajima T, Yanafuku K, Kawanishi K, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis—comparisons with other bronchoscopic diagnostic modalities. *Respir Med*. 2009;103(12):1796-800.

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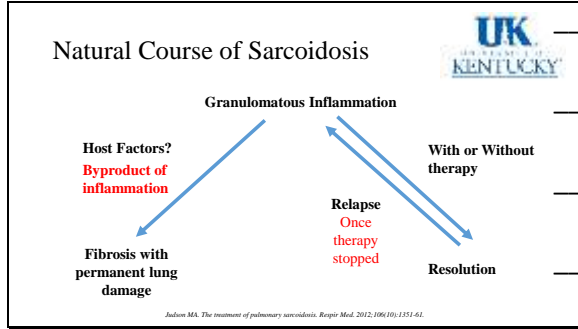
Who has Sarcoidosis?

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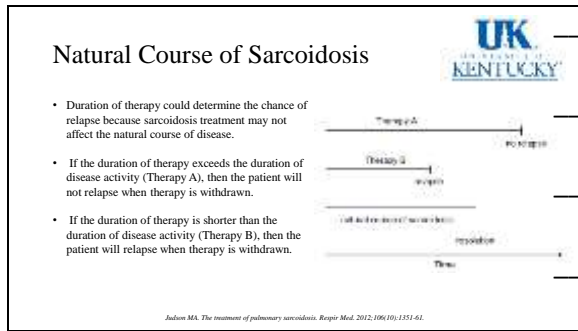
More Likely	Less Likely
African American or northern European Female	Age <18 Age >50 in men Smoking
Symmetric bilateral hilar adenopathy	Exposure to metal dusts, bioaerosols, organic antigens
Asymptomatic presentation	History of exposure to tuberculosis
Peripheral blood lymphopenia	History of recurrent infections
BAL lymphocytes >15% and/or BAL CD4/CD8 ratio >3.5	Hypogammaglobulinemia
Multisystem involvement	Systemic disease capable of inducing granulomatous reactions Malignancy Inflammatory bowel disease Immunodeficiency
Elevated serum ACE	

Culler DA. Sarcoidosis. *Immunol Allergy Clin North Am*. 2012;32(4):487-511.

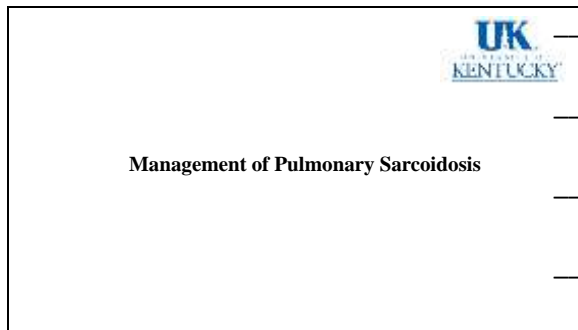
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Who to treat?

- Sarcoidosis patients receiving corticosteroid therapy have a higher rate of relapse
- Higher doses of steroids → higher risk of relapse
- Never been clearly demonstrated that the treatment of sarcoidosis affects the natural course of the disease
- Adequate therapy for sarcoidosis may be more a matter of the duration of therapy than the use of specific medications or specific doses

Judson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Steroids and Relapse?

Study objective:

- Determine the demographic, clinical, and radiographic characteristics of corticosteroid-treated patients with sarcoidosis who developed relapse following a period of clinical stability lasting longer than 1 month, and to compare these characteristics with those of a group of patients with sarcoidosis who were not treated.

Design:

- Historic, concurrent and prospective, nonrandomized, observational study.

Conclusions:

- Relapse occurred frequently treated with steroids
- Rarely occurred in patients who had not been treated with corticosteroids
- Striking difference in relapse rate between treated and untreated:
 - One explanation is that severe presenting symptoms portend a protracted and recurrent course;
 - Alternative explanation is that corticosteroids contributed to the prolongation of the disease by delaying resolution.

Gottlieb JE, Israel HL, Scriver RM, Trinkl J, Patrick H. Outcome in sarcoidosis. The relationship of relapse to corticosteroid therapy. Chest. 1997;111(5):623-31.

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Factors involved in the treatment decision

Granulomatous Activity

Development of granulomas, mediators

Radiographic imaging
Nuclear imaging
BAL cell counts
Serum ACE

Physiological Impact

Derangement of pulmonary physiology

FVC
FEV1
DLCO
6MWT

Functional Impact

Functional impairment, symptoms

Pulmonary Symptoms
HRQoL

Judson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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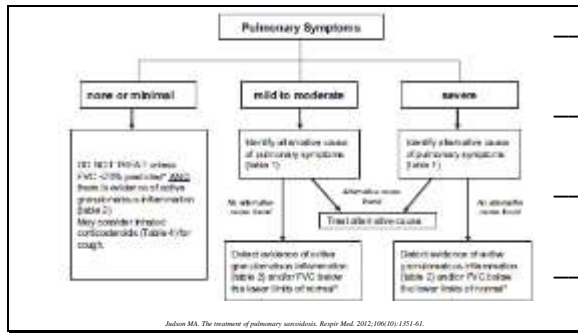


Who to treat?

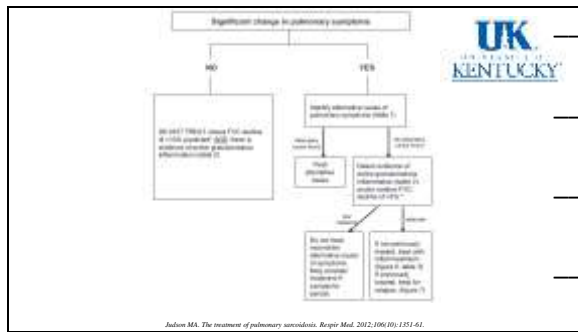
Established versus newly Diagnosed

Judson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

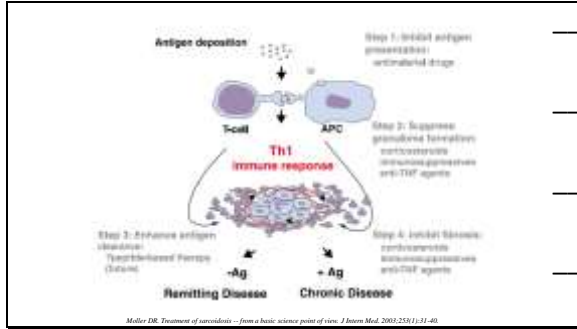
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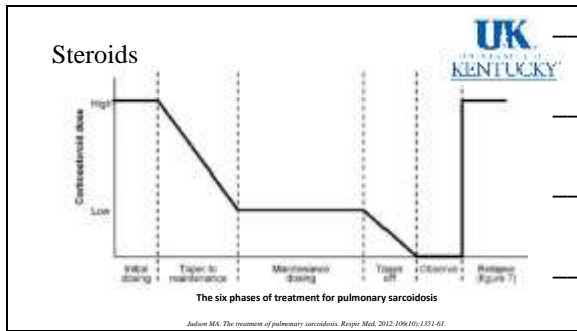
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6 Phase Treatment for Pulmonary Sarcoidosis

Phase	Daily Dose	Period
Initial dosing	20 – 40 mg	2-6 weeks
Taper to maintenance	N/A	6 weeks- 6 month
Maintenance dosing	5-15 mg	5-9 months
Taper off corticosteroid therapy	N/A	1-6 months
Monitor while not receiving therapy	N/A	N/A
Treatment of relapse		

Judson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Relapse

- 20 -70 % of patients in whom steroids are discontinued
- Steroid for relapses may be used identically as for the initial treatment of pulmonary sarcoidosis
- Sensitive to corticosteroids compared to other forms of sarcoidosis (20 mg of daily prednisone equivalent)
- Toxicities:
 - side effects from corticosteroids are cumulative (e.g., weight gain, osteoporosis, cataracts)

Julson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Efficacy of Short-Course, Low-Dose Corticosteroid Therapy for Acute Pulmonary Sarcoidosis Exacerbations

Julson P, McClean P, Harris D, Pinsky B, Bullington WM, Mazer JE, and Moore J, Indiana, WI, IJCCP

Methods:

- Reviewed the short-term treatment outcome (median duration 21 days)
- 36 patients with acute exacerbations of pulmonary sarcoidosis
- Low-dose corticosteroid therapy (20 mg or less of daily prednisone equivalent)

Conclusions:

- Treatment of acute exacerbations of pulmonary sarcoidosis with 20 mg prednisone for a median of 21 days improved spirometry back to baseline and improved clinical symptoms.
- These data suggest that this corticosteroid dose can be safely used initially, and an attempt at tapering can be considered within the first month.

McKinnic BP, Bullington WM, Mazer JE, Julson MA. Efficacy of short-course, low-dose corticosteroid therapy for acute pulmonary sarcoidosis exacerbations. Am J Med Sci. 2010;340(1):1-4.

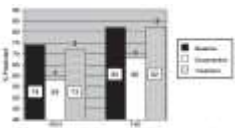



FIGURE 1. Patients' absolute FEV₁ and FVC at baseline (the low-intensification), during tapering, and after maintenance, short-course corticosteroid therapy for pulmonary sarcoidosis. *P < 0.0001 (compared with baseline), †P < 0.0001 (compared with tapering), ‡P (compared with baseline).

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Steroid sparing agents

- Rarely effective alone for the treatment of sarcoidosis
- Allow for a reduction in the maintenance corticosteroid dose (steroid sparing)
- Require 3 to 9 months to reach peak efficacy for the treatment
- Steroids slowly tapered after an alternative agent added

Julson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Steroid sparing agents

- Add of an alternative agent be for the initial treatment of pulmonary sarcoidosis ?
- Large percentage of treated patients will not relapse and, therefore, will avoid the potential toxicity of a second agent if they are treated with corticosteroid alone

Austin MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Steroid sparing agents

- Second line agent: **Methotrexate**
- Most well studied
- Only non-corticosteroid therapy demonstrated equivalence to corticosteroids as a single agent for acute disease
- A consensus of sarcoidosis experts (25/30, 83%) selected methotrexate as the preferred second line agent for pulmonary sarcoidosis

Austin MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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KEYWORD DEFINITIONS

Prolonged Use of Methotrexate for Sarcoidosis

Hiro E, Lerner AH, Rubin F, Baughman EP

Table 1. Characteristics of Patients Treated With Methotrexate

Characteristic	No. (%)
Age, y	50 (57)
Female	35 (63)
Median duration of disease, mo	100
Median duration of treatment, mo	100
Median duration of follow-up, mo	100
Median duration of follow-up, mo	100
Median duration of follow-up, mo	100
Median duration of follow-up, mo	100
Median duration of follow-up, mo	100
Median duration of follow-up, mo	100

Table 2. Reasons for Initiating Methotrexate Therapy

Reason	No.	%
Worsening symptoms on corticosteroids	10	100
Relapse	0	0
Adverse effects of corticosteroids	0	0
Other reasons for therapy	0	0

Table 3. Reasons for Discontinuing Methotrexate Therapy in 20 Patients

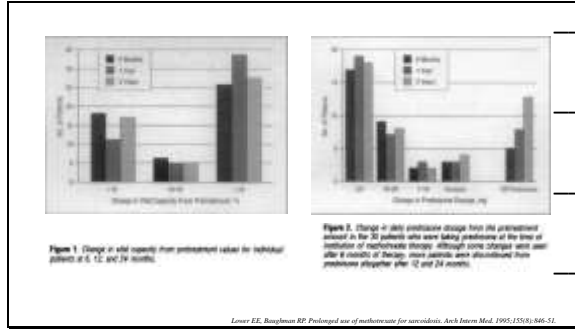
Reason	No.	%
Adverse effects	10	50
Relapse	10	50
Other reasons	0	0

Table 4. Reasons for Discontinuing Methotrexate Therapy in 20 Patients

Reason	No.	%
Adverse effects	10	50
Relapse	10	50
Other reasons	0	0

Lerner EE, Baughman EP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med. 1995;155(9):846-51.

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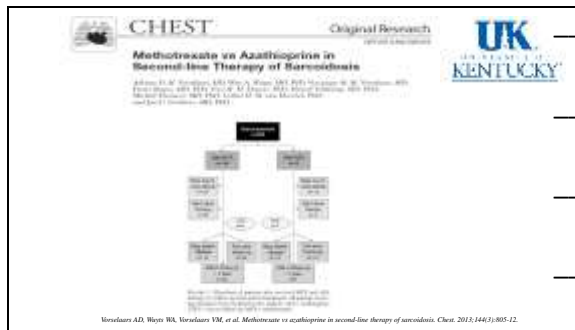
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Table 4. Liver Function Tests for Patients Requiring Liver Biopsy

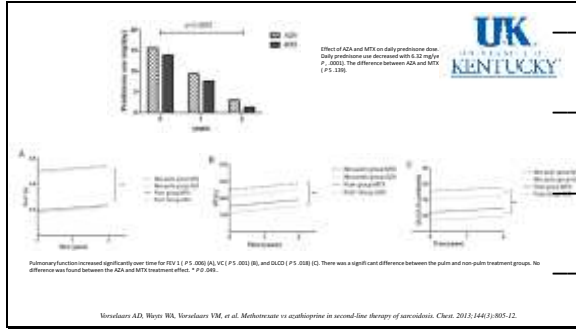
Measure	Methotrexate 20-40 mg/week	Methotrexate 0.5-5.4 mg	Methotrexate 24 mg/week 0.4-1.1 mg/kg	Azathioprine 50 mg weekly	Azathioprine 50 mg weekly
Results of Biopsy					
Biopsy (13 patients)					
- Significant values	11(83.3%)	2(14.3%)	10 (100%)	10(100%)	11(84.6%)
- None	2(15.0%)	12(85.7%)	0	0	2(15.4%)
- Total	13	14	10	10	13
Biopsy (10 patients)					
- Significant values	10(100%)	10(100%)	10(100%)	10(100%)	10(100%)
- None	0	0	0	0	0
- Total	10	10	10	10	10
Methotrexate only (16 patients)					
- Significant values	14(87.5%)	2(12.5%)	14(100%)	14(100%)	14(87.5%)
- None	2(12.5%)	16(100%)	0	0	2(12.5%)
- Total	16	16	14	14	16

Lower LE, Bagheri RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med. 1995;155(9):846-51.

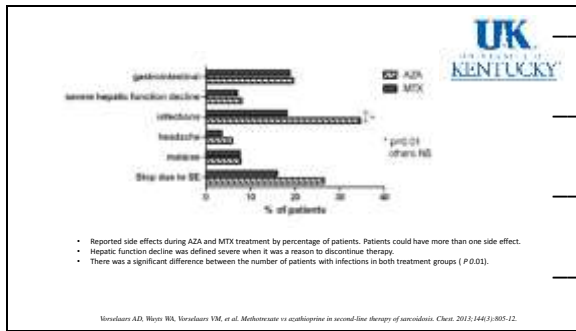
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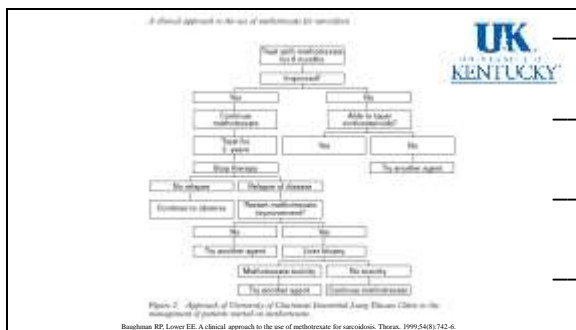
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Third line agent

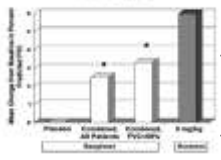
- **Infliximab:**
 - Cost
 - Difficulties of intravenous administration

Johnson MA. The treatment of pulmonary sarcoidosis. *Respir Med*. 2012;106(10):1351-61.

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Infliximab

- The mean change from baseline in the percent predicted forced vital capacity (FVC) 6 months after starting therapy, derived from two randomized trials of infliximab.
- Baughman and colleagues :
 - 138 patients
 - Three treatment groups (placebo, 3 mg/kg, and 5 mg/kg)
 - Significant improvement in percent predicted FVC for patients treated with 3 or 5 mg/kg compared with placebo (P<0.05).
 - Difference was larger for those who had a pretreatment FVC less than 69% (the median of all patients in the study) (P<0.05)
- Rossman and colleagues:
 - 19 patients with chronic pulmonary sarcoidosis who received 5 mg/kg infliximab either initially (13 patients) or delayed (6 patients).
 - Mean FVC percent predicted before therapy (59.6%).
 - Improvement in FVC percent predicted 22 weeks after two treatments with infliximab

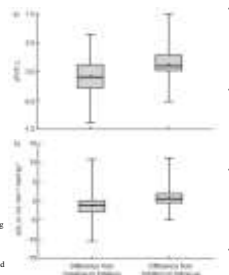


• Rossman MA, Newman EA, Baughman RP, et al. A double-blind, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffus Lung Dis*. 2006;23(3):201-8.
 • Baughman RP, Davis M, Kazem M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med*. 2006;174(7):795-802.

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How about Leflunomide?

TABLE 3. Outcomes for patients with pulmonary sarcoidosis	
Number of patients	35
Mean age (range) at study enrollment	56 (39-78)
Female:male	23:12
Duration of disease	45 (0-108)
Median steroid therapy	11 (3-33)
Patients progressing to organ involvement	6 (17)
% of all the disease episodes	33 (33)



- Median corticosteroid dose at initiation was 10 mg (interquartile range 5-20) mg at baseline, and 0 (0-10) mg at the 6-month follow-up (p<0.001).
- Leflunomide is a viable alternative agent for pulmonary and extrapulmonary sarcoidosis.
- Leflunomide appears to facilitate reduction of steroid dose and can be considered as monotherapy or as add-on therapy in cases of progressive disease.


Sobue DH, Bando-Yoshitani D, Ito M, et al. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. *Eur Respir J*. 2011;38(3):1145-50.

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Inhalers

- Inhaled corticosteroids:
 - Cough
 - High doses

Johnson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.




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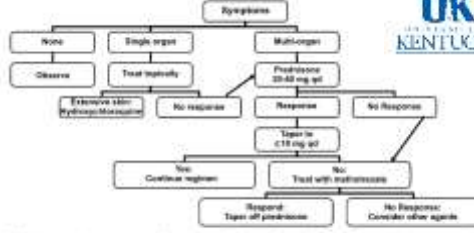
Classification of Sarcoidosis

- Acute disease:
 - Resolves within 2 to 5 years of time of diagnosis residual defects are fibrosis, not ongoing inflammation
- Chronic disease:
 - Persists beyond 5 years after diagnosis
- Refractory disease:
 - Chronic disease that worsens despite adequate systemic therapy


Baughman RP, Costabel U, Du Bois RM. Treatment of sarcoidosis. Clin Chest Med. 2008;29(1):53-65, ix-x.



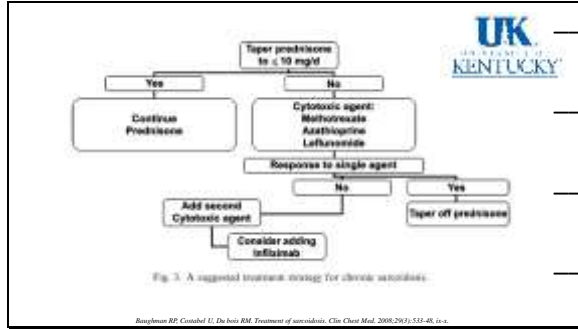
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Baughman RP, Costabel U, Du Bois RM. Treatment of sarcoidosis. Clin Chest Med. 2008;29(1):53-65, ix-x.



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Therapy for Pulmonary Fibrosis

- Treatment decisions based on the propensity to develop pulmonary fibrosis rather than the duration of disease
 - Respiratory failure
 - Pulmonary hypertension
 - Mycetoma
- Taper off → High rate of relapse
- Taper to 10 mg a day (successful taper)

Johnson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Drug	Indication	Contraindications	Precautions	Adverse Effects
Hydrocortisone	10-15 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation
Methylprednisolone	16-24 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation
Dexamethasone	4-8 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation
Triamcinolone	4-8 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation
Beclothemide	4-8 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation
Fluocortidone	4-8 mg daily	Systemic infection, osteoporosis, hypertension, diabetes, peptic ulcer disease, glaucoma, cataracts, hypothyroidism, adrenal insufficiency, pregnancy, lactation	Monitor for hypotension and electrolyte imbalance	Weight gain, fluid retention, hypertension, diabetes, osteoporosis, cataracts, glaucoma, peptic ulcer disease, hypothyroidism, adrenal insufficiency, pregnancy, lactation

Johnson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Drug	Level of evidence*	Standard dose	Site of use†	Monitoring	Comments	Reference
Trimethoprim	III	150-300 mg/kg	Respiratory tract, systemic, topical, intravitreal, ocular, intravenous	None	Monitoring should include monitoring of renal function, especially in the elderly. Also for phenytoin. Not usually for culture-proven cases. Not recommended as a single agent for culture-negative pulmonary sarcoidosis.	19, 20
Inhaled corticosteroids	III	High dose (e.g., budesonide 800, fluticasone propionate 1000 mg/day)	Inhalation	None	Not usually for culture-proven cases. Not recommended as a single agent for culture-negative pulmonary sarcoidosis.	21-23, 26


* Level of evidence: I, Randomized controlled trial; II, Randomized controlled trial with some limitations; III, Cohort study or case-control study; IV, Case series or case report; V, Expert opinion. † Site of use: I, Systemic; II, Topical; III, Inhaled; IV, Intravitreal; V, Intravenous.

Author MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(9):1351-61.

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Acthar gel

- 1950s corticotrophin (Acthar) reported effective in treating sarcoidosis
- First drug approved for treatment of pulmonary sarcoidosis by the FDA (limited number of case reports)
- FDA approved the drug for pulmonary sarcoidosis without new studies examining the effectiveness of Acthar gel in sarcoidosis.
- Fell out of favor:
 - Cost
 - Convenience of an oral versus injected route of delivery
 - Local reactions at the site of injection
 - Question that Acthar may have been less effective (Dosing)



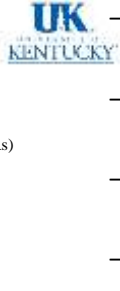
Baughman RP, Barnes JB, O'Han L, Lerner EE. A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients. Respir Med. 2016;110:66-72.

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Acthar gel

Mechanism of action:

- Corticosteroid secretion by the adrenal glands
- Endocrine and immune effects outside the adrenal axis
- Stimulation of alternative melanocortin receptors (MCRs)



https://www.actharpharmacology.com/potential-mechanism-of-action

Baughman RP, Barnes JB, O'Han L, Lerner EE. A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients. Respir Med. 2016;110:66-72.

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Respiratory Medicine

A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients

Robert F. Baughman^{1,2}, Joseph B. Ransley³, Lasey O'Hare¹, Elyse E. Lower¹

¹University of Michigan Medical Center, Division of Pulmonary and Critical Care Medicine
²Department of Internal Medicine, University of Michigan
³Department of Internal Medicine, University of Michigan

Category	Number
Total patients	100
Patients on Acthar gel	50
Patients not on Acthar gel	50
Patients included in study	25
Patients excluded from study	25
Reasons for exclusion	10 (40%)

Baughman RF, Ransley JB, O'Hare L, Lower EE. A retrospective pilot study examining the use of Acthar gel in sarcoidosis patients. Respir Med. 2016;110:66-72.

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INTERSTITIAL LUNG DISEASE

Repository corticotropin for Chronic Pulmonary Sarcoidosis

Robert F. Baughman¹, Nadere Swain², Ruth Keijzers³, Srinidhi S. Biringi⁴, Ralph Skjoly⁵, Lasey Ann Salathies⁶, Elyse E. Lower¹

Category	Number
Total patients	100
Patients on corticotropin	50
Patients not on corticotropin	50
Patients included in study	25
Patients excluded from study	25
Reasons for exclusion	10 (40%)

Baughman RF, Swain N, Keijzers R, et al. Repository corticotropin for Chronic Pulmonary Sarcoidosis. Lung. 2017.

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Fig 1. FEV1 (L) over time. The y-axis represents FEV1 in liters, ranging from 0 to 2.0. The x-axis represents time in months, ranging from 0 to 24. Two lines represent the corticotropin group (n=25) and the placebo group (n=25). The corticotropin group shows a higher and more stable FEV1 over time compared to the placebo group.

Fig 2. FEV1 (% predicted) over time. The y-axis represents FEV1 as a percentage of predicted, ranging from 50 to 120. The x-axis represents time in months, ranging from 0 to 24. Two lines represent the corticotropin group (n=25) and the placebo group (n=25). The corticotropin group shows a higher and more stable FEV1 (% predicted) over time compared to the placebo group.

Baughman RF, Swain N, Keijzers R, et al. Repository corticotropin for Chronic Pulmonary Sarcoidosis. Lung. 2017.

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Acthar Gel




- **Conclusion:**
- Regardless of dose that the patient received:
 - Significant reduction in the dosage of prednisone
 - Significant improvement in their DLCO (Despite withdrawal of prednisone)
 - Significant improvement in the health-related quality of life

Boughton RP, Swales N, Keijzers R, et al. Respiratory corticosteroids for Chronic Pulmonary Steroidoids. *Lancet*. 2007.

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Acthar Gel




- **No placebo group:**
- Can't be sure that reduction in prednisone dose due to effect of repeat study visits and effort to reduce prednisone.
- The reduction of prednisone dose may have also been due to stimulation of glucocorticoid release

Boughton RP, Swales N, Keijzers R, et al. Respiratory corticosteroids for Chronic Pulmonary Steroidoids. *Lancet*. 2007.

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Thank you



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Acthar Gel


- We were unable to demonstrate
- that the reduction in prednisone dosage during the short
- course of this study was associated with lessening of the
- toxicities associated with high-dose prednisone such as
- weight gain and diabetes. However, patients reported an
- improved quality of life while receiving RCI.
- A change in FVC percent predicted is a



Baughman RP, Swain N, Keijzers R, et al. Respiratory corticosteroids for Chronic Pulmonary Sarcoidosis. *Lancet*. 2017.

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- there was no
- significant change in weight during the course of the study.
- There was also no change in hemoglobin A1c levels or
- treatment for diabetes or hypertension. Eight patients complained
- of anxiety and fluid retention on the day of drug
- administration



Baughman RP, Swain N, Keijzers R, et al. Respiratory corticosteroids for Chronic Pulmonary Sarcoidosis. *Lancet*. 2017.

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Table 3. Prednisone dosage during baseline and after 7 and 24 weeks of therapy

	Week 0	Week 7	Week 24
PVE, mean	2.82 (0.34-2.32)*	2.95 (0.38-3.05)	2.47 (1.25-3.65)
Change in PVE from Week 0		-0.89 (-0.11, -1.68)	-0.89 (-0.32, -1.45)
PVE % predicted	66 (30-96)	60 (30-96)	61 (30-96)
Change in PVE % predicted from week 0		-5.2 (-9.0, -1.1)	-2.9 (-6.6, -0.6)
FVC, L, mean	1.00 (0.80-1.21)	1.00 (0.79-1.20)	1.00 (0.86-1.15)
Change in FVC % from week 0		-0.82 (-0.11, -1.54)	-0.22 (-0.88, -0.44)
FVC % predicted	66 (36-96)	61 (36-96)	61 (36-96)
Change in FVC % predicted from week 0		-5.2 (-9.0, -1.1)	-3.4 (-7.1, -0.3)
FEV1, L, mean	0.50 (0.40-0.60)	0.50 (0.40-0.60)	0.50 (0.40-0.60)
Change in FEV1 % from week 0		0.00 (-0.20, -0.20)	-0.82 (-1.11, -0.54)
FEV1 % predicted	63.7 (30-100)	63.1 (37-100)	62.1 (30-100)
Change in FEV1 % predicted from week 0		-0.6 (-0.9), -0.3	-0.4 (-0.8), -0.1
FEV1 % predicted	60 (22-93)	58 (33-93)	57 (28-93)
Change in FEV1 % predicted from week 0		-2.0 (-3.8, -0.2)	-1.0 (-2.2, 0.2)
DMED, n	544 (212-834)	488 (239-737)	588 (312-864)
Change in DMED, n		0 (-46 to 46)	0 (-11 to 11)

*Values from week 0, p < 0.001.

Baughman RP, Swain N, Keijzers R, et al. Respiratory corticosteroids for Chronic Pulmonary Sarcoidosis. *Lancet*. 2017.

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Jansz MC, Fontana JB. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA. 2011;305(4):391-9

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Who to treat?

- Duration of an anti-sarcoidosis regimen exceeds the presence of the antigen in the host, the therapy will be “effective.”
- If the regimen is discontinued while the antigen is still present, the patient will “relapse”

Judson MA. The treatment of pulmonary sarcoidosis. Respir Med. 2012;106(10):1351-61.

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Table 2. Clinical features identifying the likelihood of sarcoidosis

Significant sarcoidosis associated by	Features that offer granulomatous infectious disease
Anterior uveitis	Urgent treatment and a rapid response including facial cellulitis
Extrapulmonary disease	High fever, weight loss, hemoptysis
Neurologic	High response to steroids (up to the usual initial corticosteroid dose)
Response to therapy	High response to steroids (up to the usual initial corticosteroid dose) with rapid resolution of symptoms
Demographics	Age of onset less than 18 years old

Judson MA. Curr Opin Pulm Med. 2019 Jun 11.

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Table 4 Cardiovascular complications associated with drug administration during surgery

Drug	Pharmacologic action on myocardium	Effect on heart rate	Effect on stroke volume	Effect on systemic pressure	Effect on myocardial oxygen demand	Effect on myocardial oxygen supply
Propofol	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Etomidate	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Halothane	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Isopropyluride	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Barbiturates	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Local anesthetics	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase

[Judson MA Curr Opin Pulm Med, 2019 Jun 11.](#)

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Table 4 (Continued)

Drug	Pharmacologic action on myocardium	Effect on heart rate	Effect on stroke volume	Effect on systemic pressure	Effect on myocardial oxygen demand	Effect on myocardial oxygen supply
Propofol	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Etomidate	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Halothane	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Isopropyluride	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Barbiturates	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase
Local anesthetics	Myocardial depression, peripheral vasodilation, decrease in SVR	Decrease	Increase	Decrease	Decrease	Increase

[Judson MA Curr Opin Pulm Med, 2019 Jun 11.](#)
