

SARCOIDOSIS TREATMENT GUIDELINES

INTRODUCTION

Sarcoidosis is a chronic inflammatory granulomatous disease that primarily affects the lungs, although multi-organ involvement is common. The etiology of sarcoidosis is not clear; however, genetic and environmental factors probably play a role in the development and expression of the disease.

Once thought to be rare, sarcoidosis affects people throughout the world. It can affect people of any age, race, or gender; however, the prevalence is highest among adults between the ages of 20 and 40 and in African Americans and people of European - particularly Scandinavian - descent.

Symptoms and severity can vary by race and gender, with African Americans being more severely affected than Caucasians. Extrapulmonary sarcoidosis is common in certain populations, for example: chronic uveitis in African Americans, painful skin lesions in Northern Europeans and cardiac and ocular involvement in Japanese.

Goals of Sarcoidosis Management

The goals of sarcoidosis management are to prevent or control organ damage, relieve symptoms and improve the patient's quality of life. An evaluation by a pulmonologist is strongly recommended. For patients with extrapulmonary involvement, a multidisciplinary approach may be required. A patient may need to see an ophthalmologist for ocular disease, a cardiologist for cardiac disease, a neurologist for neurological disease, a nephrologist for renal disease, and so forth.

Pharmacologic Treatment

While a significant percentage of sarcoidosis patients never need therapy, there are several groups which require treatment. In this monograph, we will discuss several of the commonly used drugs for sarcoidosis and their potential toxicities, and will provide algorithms for use of these drugs to treat the symptoms associated with specific organ involvement. Treatment algorithms are suggested based on current available evidence but FSR and its members acknowledge that there is no universal agreement on all aspects of most of the treatment algorithms provided in this document.

Corticosteroids

Corticosteroid medications are considered the first line of treatment for sarcoidosis that requires therapy. Oral corticosteroids effectively reduce systemic inflammation in most people, thereby slowing, stopping or even preventing organ damage. Corticosteroids may be prescribed alone or with other medications. In the United States, prednisone is the most commonly used corticosteroid. It is approved by the FDA for treatment of pulmonary sarcoidosis. Although there is no standard dosage or duration of corticosteroid therapy, the charts in this monograph will provide guidelines for individual organ involvement. It is recommended that patients on long term corticosteroids be monitored for osteoporosis and treated appropriately.

Topical corticosteroids or intralesional injections may be prescribed for cutaneous involvement, and eye drops may be prescribed for uveitis. Corticosteroid inhalers may be useful in those with evidence of bronchial hyperactivity.

Hydroxychloroquine. As a treatment for sarcoidosis, the antimalarial drug hydroxychloroquine (Plaquenil®) is most likely to be effective in patients with dermatologic involvement, joint manifestations and hypercalcemia. Due to potential macular toxicity, it is recommended that patients on hydroxychloroquine have an eye examination every 6-12 months.

Methotrexate. Methotrexate is one of the most commonly used corticosteroid-sparing therapies for sarcoidosis, due to its effectiveness, low cost and, at the dosages used to treat sarcoidosis, relatively low risk of side effects compared to other cytotoxic agents. The drug can be given orally or subcutaneously. Due to the potential for hepatic and hematologic toxicity, regular monitoring is required. Since the drug is cleared by the kidneys, one should also monitor renal function. Dosage adjustment may be needed or an alternative corticosteroid-sparing drug may be considered in those with renal insufficiency, e.g. GFR < 50 ml/min). It is recommended that patients have a CBC and hepatic and renal function every 1-3 months. Folic acid supplementation may be prescribed to reduce toxicity.

Azathioprine. What little research has been done on the subject shows that azathioprine (Imuran®) is roughly as effective as methotrexate in treating sarcoidosis. It is often considered when there is a contraindication to methotrexate, such as renal or hepatic function impairment. The most common side effects of azathioprine include diarrhea, abdominal cramping, hair loss, liver enzyme elevation, and bone marrow suppression. Compared to methotrexate, there is also evidence of a higher frequency of opportunistic infections and possibly malignancy with azathioprine use.

Some clinicians measure thiopurine S-methyltransferase (TPMT) levels prior to the first dose to determine if patients have TPMT deficiency and therefore are at increased risk for toxicity. Others measure the CBC 2-4 weeks after the first dosage. It is recommended that patients taking azathioprine have a CBC and hepatic function tests at least every 1-3 three months.

Mycophenolate mofetil. First developed to prevent organ transplant rejection, mycophenolate mofetil (CellCept®) is prescribed for a number of autoimmune and inflammatory diseases, including rheumatoid arthritis and lupus nephritis. Anecdotal reports have suggested it may be effective in treating sarcoidosis. The principal adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis and vomiting. Compared to azathioprine, there is also evidence of a higher frequency of opportunistic infections and malignancy. It is recommended that patients taking mycophenolate have a CBC and hepatic and renal function tests at least every 3 months.

Leflunomide. Leflunomide (Arava®) is a cytotoxic drug that has been used as a single agent or in combination with methotrexate for the treatment of rheumatoid arthritis.. Although experience is limited, it should be considered as an alternative for patients who cannot tolerate or fail to respond to other agents such as methotrexate. It is recommended for the first six months of therapy patients have monthly CBCs. The most common side-effects of leflunomide include liver enzyme elevation, diarrhea, abdominal cramping, and peripheral neuropathy. For patients who experience severe toxicity from leflunomide, cholestyramine therapy may be useful to eliminate its enterohepatic recirculation.

Cyclophosphamide. Due to its toxicity, cyclophosphamide (Cytoxan®, Endoxan®) is usually reserved for severe disease not controlled by immunomodulators such as methotrexate, and when TNF antagonists are not effective or contra-indicated.. Case studies suggest that cyclophosphamide is effective for some people and is perhaps particularly useful in severe disabling neurosarcoidosis that has not responded to other therapies, including intravenous corticosteroids..

Its side effects can include nausea, vomiting, anorexia, alopecia, acne, leukopenia, oral ulcers, skin hyperpigmentation and fatigue. Less common but more severe side effects include hemorrhagic cystitis and an increased risk for cancer. Overall, less toxicity has been reported with intermittent intravenous administration compared to daily oral use of cyclophosphamide. As with other immunosuppressants, monitoring should include CBC and hepatic and renal function tests every 1-3 months. Due to the risk of bladder cancer, urinalysis is needed every month.

Infliximab. An infused TNF inhibitor, infliximab (Remicade®) has been approved for several inflammatory diseases including rheumatoid arthritis and Crohn's disease. Small, short-term studies have shown infliximab to be effective in reducing sarcoidosis symptoms in patients who did not respond to other treatments. Infliximab can cause a variety of side effects, including abdominal pain, nausea, diarrhea, dyspepsia, headache, rash, pruritus, pharyngitis and sinusitis, and sore throat. Infusion reactions, including severe anaphylaxis, can occur. Infliximab also increases the risk of infection and certain types of cancer, autoimmune disease and

demyelinating disease. It is recommended that patients have a PPD or interferon gamma release assay for tuberculosis prior to beginning therapy and that infliximab be withheld in the event of active infection.

Adalimumab. The TNF inhibitor adalimumab (Humira®), given by subcutaneous injection, has been approved for rheumatoid arthritis and several other forms of arthritis. Anecdotal reports have suggested that adalimumab may be effective in reducing sarcoidosis symptoms. Adalimumab can cause a variety of side effects, including abdominal pain, nausea, diarrhea, dyspepsia, headache, rash, pruritus, pharyngitis and sinusitis, and sore throat. Local injection site reactions have been reported. Adalimumab also increases the risk of infection and certain types of cancer, autoimmune disease and demyelinating disease. Adalimumab should be considered for patients who have been treated successfully with infliximab but have developed antibodies. It is recommended that patients have a PPD or interferon gamma release assay for tuberculosis prior to beginning therapy and that adalimumab be withheld in the event of active infection.

Novel agents. The role of novel agents for the management of sarcoidosis is undefined at present, and clinical experience with them is extremely limited. Rituximab is a B-cell depleting monoclonal antibody targeting CD20. It has been described as useful in case series of refractory ocular and pulmonary sarcoidosis. ACTHAR gel is a porcine-derived pituitary extract that was approved by the FDA for the treatment of pulmonary sarcoidosis in the 1950s, on the basis of reports of its efficacy in that era. It has not been prospectively studied for sarcoidosis since then, but several studies are underway. ACTHAR gel is given as a shot under the skin (subcutaneously) or in the muscle (intramuscularly). It works by stimulating the adrenal cortex to release glucocorticoids. It also directly stimulates melanocortin receptors on various inflammatory cells such as T lymphocytes and macrophages. Due to its high cost and need to administer parenterally, it is being studied predominantly in refractory disease.

STANDARD THERAPIES

DRUG	DOSAGE	MAJOR TOXICITY	MONITORING
Prednisone	5-40mg daily	Diabetes, hypertension, weight gain, cataracts, glaucoma	Blood pressure, weight, glucose if clinically indicated. Osteoporosis and bone density checks
Hydroxychloroquine	200-400mg daily	Ocular, hepatic, cutaneous	Eye examination every 6-12 months
Methotrexate	5-20mg weekly	Hematologic, hepatotoxic, pulmonary	CBC, hepatic and renal function every 1-3 months
Acthar gel	40-80 units 1-2 times per week	Diabetes, hypertension, weight gain, cataracts, glaucoma	Blood pressure, weight, glucose if clinically indicated. Osteoporosis and bone density checks
Azathioprine*	50-200mg daily	Hematologic, gastrointestinal	CBC, hepatic and renal function every 1-3 months
Leflunomide*	10-20mg daily	Hepatotoxic, gastrointestinal, neuropathy	CBC, hepatic and renal function every 1-3 months
Mycophenylate	500-1500mg twice daily	Hematologic, gastrointestinal	CBC, hepatic and renal function every 1-3 months
Infliximab	3-5mg/kg initially, two weeks later, then every 4-8 weeks	Increased risk for infections, especially tuberculosis, worsening congestive heart failure, possible increased risk for malignancy	PPD prior to initiating therapy, withhold drug in face of active infection
Adalimumab	40-80mg every 1-2 weeks	Increased risk for infections, especially tuberculosis, worsening congestive heart failure, possible increased risk for malignancy	PPD prior to initiating therapy, withhold drug in face of active infection

Definitions: mg=milligrams; kg=kilogram; CBC=complete blood count; PPD=purified protein derivative, skin test to diagnose tuberculosis.

* See text for initial monitoring

Several other drugs have been used in selected cases. They include the following:

Pentoxifylline. A drug used to treat intermittent claudication, pentoxifylline has been reported to be steroid sparing in some cases of pulmonary sarcoidosis. Its major toxicity is nausea, which is commonly encountered at the doses used for treating sarcoidosis.

Chloroquine. Another antimalarial agent, chloroquine is used for cutaneous and pulmonary sarcoidosis. It has a higher rate of gastrointestinal and ocular toxicity than hydroxychloroquine, so it is used less frequently.

Tetracycline derivatives. Minocycline and doxycycline have been reported as useful for cutaneous sarcoidosis. Both drugs can cause nausea, and minocycline is associated with hepatitis and vertigo.

PULMONARY

Pulmonary involvement, found in over 90 percent of sarcoidosis patients, is the most frequent manifestation of the disease. The assessment of the degree of pulmonary involvement includes pulmonary function tests (PFTs), including at least a forced vital capacity, chest imaging such as a chest x-ray, and ascertaining the level of dyspnea by questioning the patient. Additional tests, such as diffusion capacity (DLCO), chest CT scan, and 6-minute walk, may be useful for individual patients.

As shown in the figure, the treatment approach depends on whether the disease is asymptomatic or has minimal symptoms versus those with moderate or severe symptoms and functional impairment.

For asymptomatic patients with Stage 0 or I chest x-ray, therapy is not likely to offer benefits. For patients with mild symptoms, such as a cough, treatment should begin with inhaled corticosteroids. If there is no response, oral corticosteroids can be considered. While not specifically studied, asymptomatic patients with a significant drop in pulmonary function should be considered for therapy.

For those with dyspnea, corticosteroid therapy has been shown to improve lung function for both the short term and up to five years after therapy has been discontinued. Less clear is whether to recommend an 18-month course of corticosteroids for patients with Stage II-IV disease and no dyspnea. If pulmonary function tests are normal to mildly abnormal, the patient can be observed. About 70 percent of these patients will either remain the same or improve spontaneously.

For patients with Stage 0 or I and dyspnea, an echocardiogram may be useful to identify other causes of dyspnea, such as cardiac disease. A high-resolution CT may also identify parenchymal lung disease not seen on a chest x-ray. If there is no evidence of congestive heart failure or pulmonary hypertension, a trial of treatment with corticosteroids may be considered.

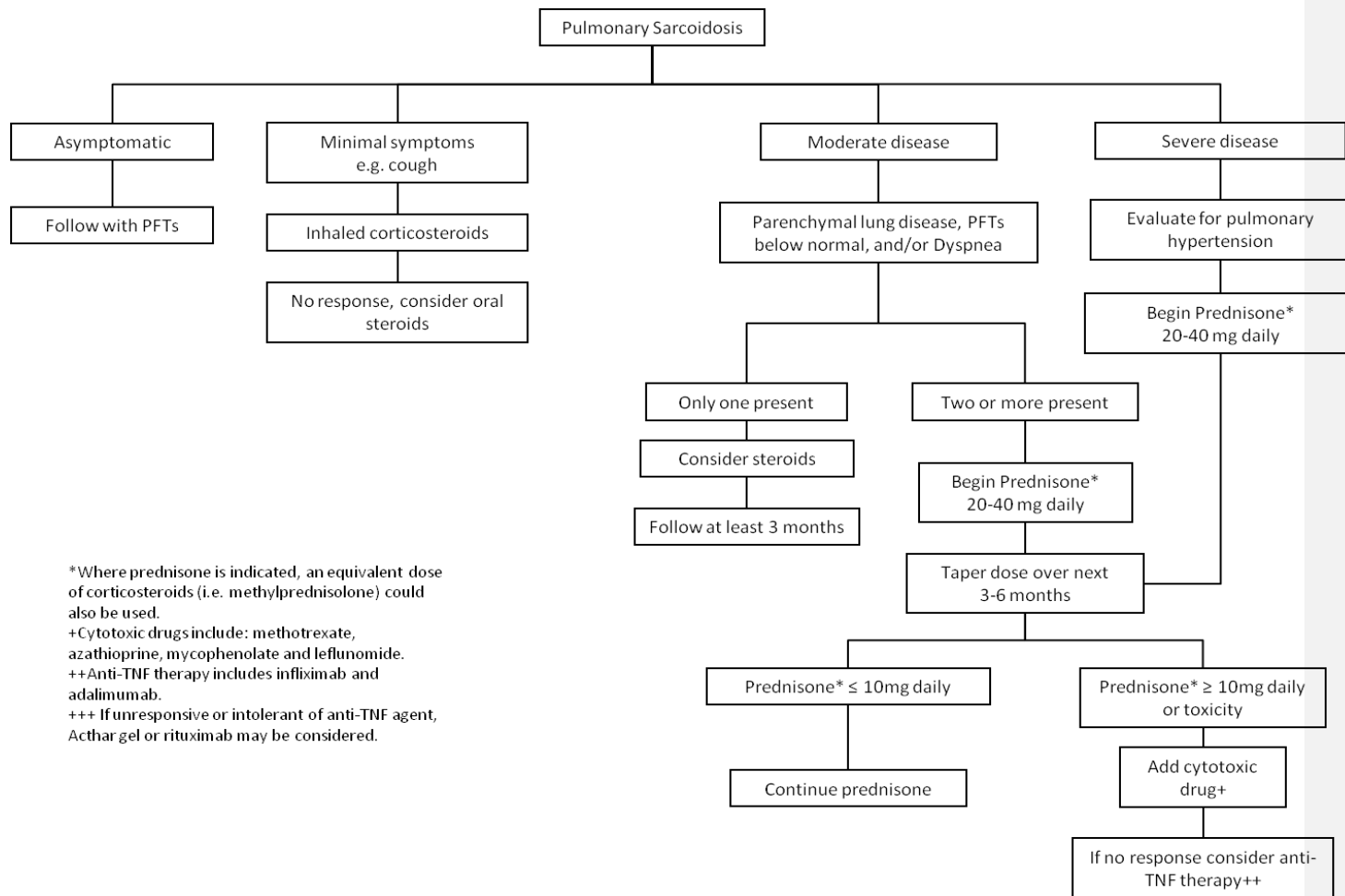
Corticosteroids remain the standard initial drug of choice for treatment of parenchymal lung sarcoidosis. A starting dosage is 20 - 40 mg prednisone or its equivalent. Once corticosteroids have been started, the patient is usually reassessed after 1-3 months. Depending on the patient's condition, the dosage can be tapered at those visits. After 3-6 months, the dose should be tapered to physiologic levels - for example, 10 mg of prednisone per day or less and below the threshold associated with toxicity in that individual. If such a taper is not successful, or there is toxicity from the corticosteroids, one should consider the addition of a steroid-sparing agent, such as methotrexate or azathioprine. Both of these agents may require up to 6 months to demonstrate effectiveness and are effective in only about two-thirds of patients. There is some evidence that combining two cytotoxic agents may be useful. Leflunomide has also been used in combination with methotrexate.

If a patient does not respond to the combination of prednisone and a cytotoxic agent, the clinician has to decide whether or not the patient has a reversible disease process (granuloma versus fibrosis) in the lung. In addition, the clinician should rule out pulmonary hypertension as a cause of dyspnea. There are also non-pulmonary causes of dyspnea, including anemia, heart failure, obesity, other systemic diseases

and fatigue that should be considered. A 6-minute walk or a cardiopulmonary exercise test may help identify what is happening during exercise. It may identify patients who require oxygen supplementation. It may also identify other potential causes of dyspnea, such as cardiac causes, muscle strength impairment or deconditioning.

If no alternative cause of dyspnea is identified, an anti-TNF agent can be considered. Infliximab has been widely studied, although adalimumab at higher doses may be effective. These agents have proved effective for treating inflammatory changes in the lung but will not reverse fibrosis. Benefits are usually seen within 2-6 months of starting one of these agents. For required monitoring for these agents, see Table 1.

For patients who are intolerant to, have contraindications for, or have been non responsive to anti-TNF agents, other agents may be considered; these include Acthar gel and rituximab, but experience with them is extremely limited at this time.



CARDIAC

Cardiac involvement is estimated to occur in up to 25 percent of sarcoidosis patients in the United States, but it is clinically silent in the majority.

Common manifestations of cardiac sarcoidosis include arrhythmias, conduction abnormalities, and cardiomyopathy due to granulomatous inflammation of the myocardium and/or conducting system. Rarer manifestations include valvular dysfunction, ventricular or atrial mass lesions, pericardial disease, myocardial infarction or sudden death.

It is not clear how to best screen for cardiac sarcoidosis. An EKG or echo may provide useful information. If concerns about possible cardiac involvement remain, advanced cardiac imaging such as cardiac perfusion imaging, MRI or cardiac PET scanning have greater sensitivity and specificity than an echocardiogram and are recommended. However, the implications of a positive test in a patient with no symptoms or dysrhythmias remain unclear.

A diagnosis of cardiac sarcoidosis is usually established by a non-cardiac biopsy that confirms systemic sarcoidosis together with consistent cardiac imaging and/or dysrhythmias/heart block.

There are no prospective clinical trials of medical regimens for cardiac sarcoidosis. Current treatment recommendations are based on several retrospective studies from Japan (where cardiac manifestations may be present in approximately 50 percent of sarcoidosis patients) and accumulated experience from referral centers in the U.S. and Europe. These studies suggest that survival correlates with left ventricular function and severe ventricular dysrhythmias with no difference in 5-year survival rates for patients treated with prednisone >30 mg/day vs. <30 mg/day. The usual initial dose of prednisone for cardiac sarcoidosis is 30-40 mg a day. In refractory cases, higher doses have been used.

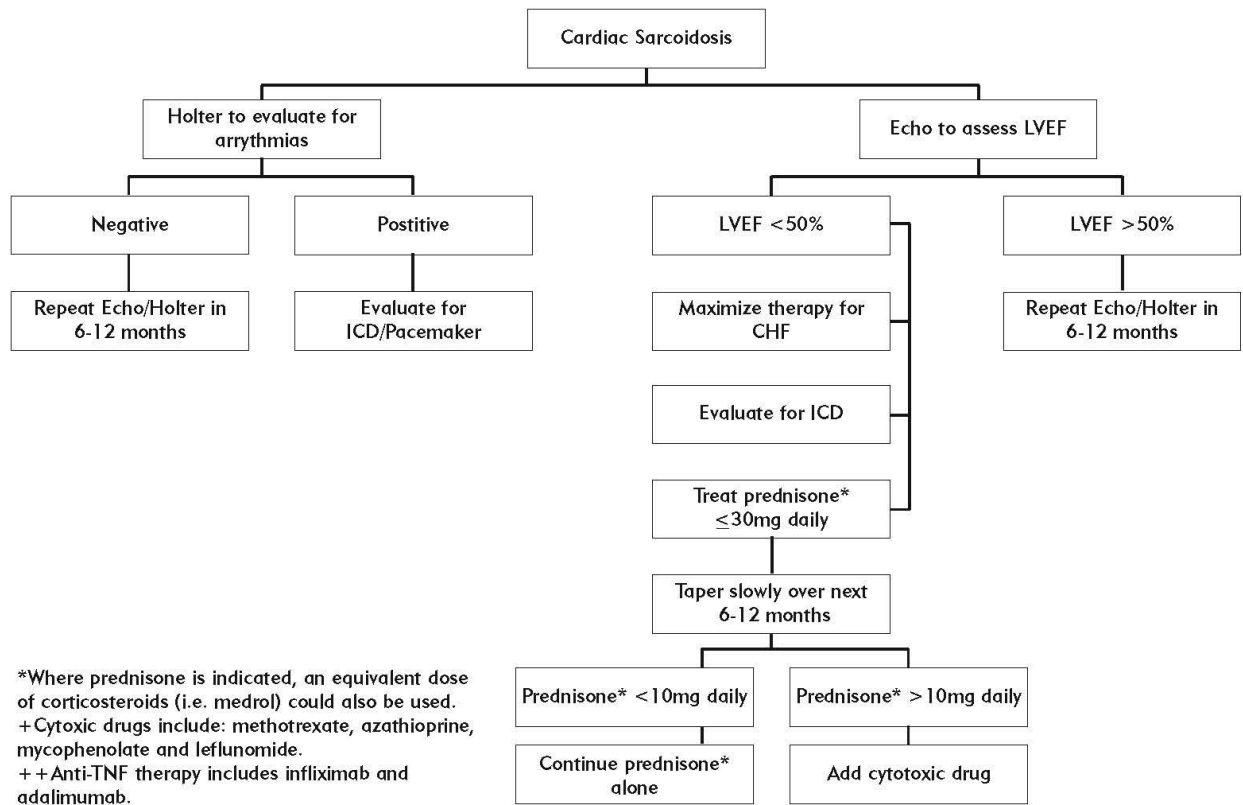
Many patients with significant cardiomyopathy and chronic sarcoidosis require long-term treatment to minimize progressive cardiac dysfunction. Cytotoxic drugs are often added to prednisone as additional therapy or subsequently added as steroid-sparing agents in patients with left ventricular ejection fraction (LVEF) <50% who require ongoing prednisone therapy to maintain stable cardiac function.

The role of TNF inhibitors remains undefined since these therapies have been shown to worsen congestive heart failure (CHF) in non-sarcoidosis cardiomyopathy; however, small case series suggest these therapies may be beneficial in some patients with cardiac sarcoidosis, assuming that the treatment of systemic sarcoidosis also benefits the cardiac involvement.

Indications for prophylactic insertion of an implantable cardioverter defibrillator (ICD) or pacemaker are evolving. Currently, common practice is to recommend prophylactic ICD insertion for patients with LVEF<35% or for serious dysrhythmias and to recommend against

prophylactic ICD insertion when there is normal cardiac function. In those patients with an LVEF between 35-50%, further evaluation including EPS or Holter monitoring may be helpful to identify those patients who could benefit from ICD placement. The effectiveness of radiofrequency ablation for prevention of arrhythmias in cardiac sarcoidosis is uncertain, given limited experience. Since cardiac sarcoidosis is often diffuse, it is unusual that ablation of a single focus can provide long-term control of ventricular dysrhythmias. Permanent pacemakers are suggested for high-degree heart block.

Cardiac transplantation is an option for patients with advanced cardiac sarcoidosis with survival rates better than those with other causes of heart disease despite reports of recurrent granulomatous inflammation in the allograft.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. medrol) could also be used.
 +Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.
 ++Anti-TNF therapy includes infliximab and adalimumab.

OCULAR

Ocular manifestations are frequent in sarcoidosis, affecting 11 percent of patients in a recent U.S. study. Sarcoidosis can affect virtually any part of the eye, including the lacrimal gland, ocular surface, and anterior and posterior segments. Treatment depends on the specific manifestation and its severity.

Lacrimal gland granulomas can lead to keratoconjunctivitis sicca, which is best managed with artificial tears to keep the conjunctiva moist, lacrimal punctal plugs and/or topical cyclosporine. Occasionally surgery or injection of the lacrimal glands with corticosteroids is used.

Involvement of the ocular surface can include conjunctival granulomas that may not require treatment. Symptomatic conjunctivitis, episcleritis or keratitis may be managed with corticosteroid eye drops. Scleritis is typically managed with corticosteroids and/or cytotoxic drugs.

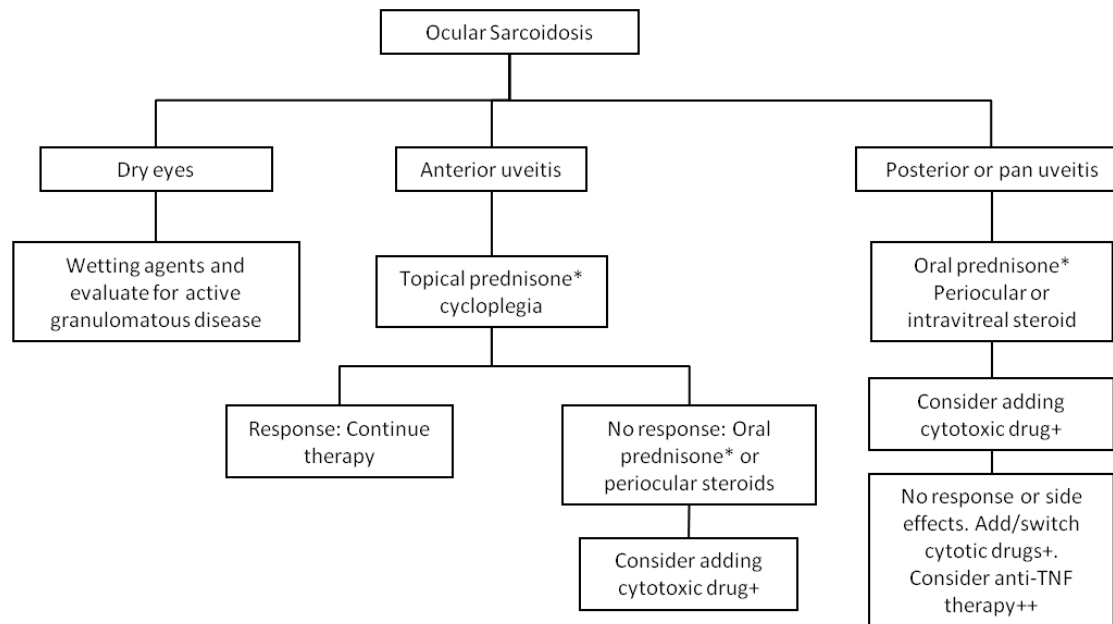
The anterior segment is involved most frequently with a chronic granulomatous uveitis that is characterized by "mutton fat" keratic precipitates and iris nodules. Posterior segment disease occurs in the form of vitritis and periphlebitis and can sometimes be the sole manifestation of ocular disease. Severe vasculitis can be associated with exudates that give the appearance of "candle wax drippings." Frequently there is involvement in the anterior segment when there is posterior segment disease. Although these are not the most classic presentations of sarcoidosis-related uveitis, sarcoidosis is a potential cause of nearly any form of uveitis.

Management of uveitis is frequently carried out by an ophthalmologist in collaboration with the pulmonologist or rheumatologist treating the systemic manifestations of sarcoidosis. Anterior uveitis usually can be managed with local therapy using corticosteroid eye drops to suppress inflammation and cycloplegic eye drops to suppress pain and avoid intraocular scarring. In some cases, periocular corticosteroid injections and long-term intraocular corticosteroid implants also have been used; however, implants have been associated with a significantly higher rate of cataracts and glaucoma and are still being studied in chronic inflammatory conditions such as sarcoidosis. For severe cases, infliximab has been useful. Due to its flexibility, effectiveness and the ability to provide ongoing therapy and treat extraocular aspects of sarcoidosis simultaneously, cytotoxic therapy (e.g. methotrexate) has been the mainstay of therapy.

For posterior uveitis or panuveitis, systemic therapy is usually used. Systemic corticosteroids are usually effective in controlling inflammation in both the short and long term. However, due the risks of systemic corticosteroids - especially with long-term use - some physicians use periocular injections of corticosteroids in the posterior or sub-Tenon's space, or in the orbital floor. Intravitreal corticosteroids, used since the 1990s, are useful for controlling acute exacerbations but are probably not appropriate for chronic therapy.

For severe disease, the typical initial dosage of prednisone is 20-40 mg/day, while some use as much as 1 mg/kg/day. If immediate therapy is needed, intravenous corticosteroids in 1-gram pulses are given. If greater than 10 mg prednisone is needed to control the disease, then corticosteroid-sparing drugs should be used. Cytotoxic drugs such as methotrexate, azathioprine, leflunomide, and mycophenolate mofetil have been used with success. In some cases, cytotoxic agents alone are used with local therapy. Recent experience suggests that the biologic agents infliximab or adalimumab, both anti-TNF monoclonal antibodies, are also effective. In uveitis in general - including uveitis related to sarcoidosis - either infliximab or adalimumab has been useful in refractory cases.

For patients who are intolerant to, have contraindications for, or have been non responsive to anti-TNF agents, other agents may be considered, possibly including Acthar gel and rituximab.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.

+Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.

++Anti-TNF therapy includes infliximab and adalimumab.

+++ If unresponsive or intolerant of anti-TNF agent, Acthar gel or rituximab may be considered.

NEUROSARCOIDOSIS

Approximately 5-15 percent of patients have neurologic disease. Neurologic manifestations of sarcoidosis include cranial neuropathies, meningeal disease [acute and chronic meningitis, mass lesion(s)], hydrocephalus, CNS parenchymal disease [endocrinopathies, mass lesion(s), encephalopathy/vasculopathy, seizures, and spinal cord abnormalities], peripheral neuropathies and myopathy.

Treatment decisions depend, in part, on the certainty of diagnosis, the patient's clinical status, the anticipated clinical course and contraindications to a particular intervention. Because of the rarity of neurosarcoidosis, there have been no rigorous clinical trials to guide treatment; management is predicated principally on clinical series and "expert opinion."

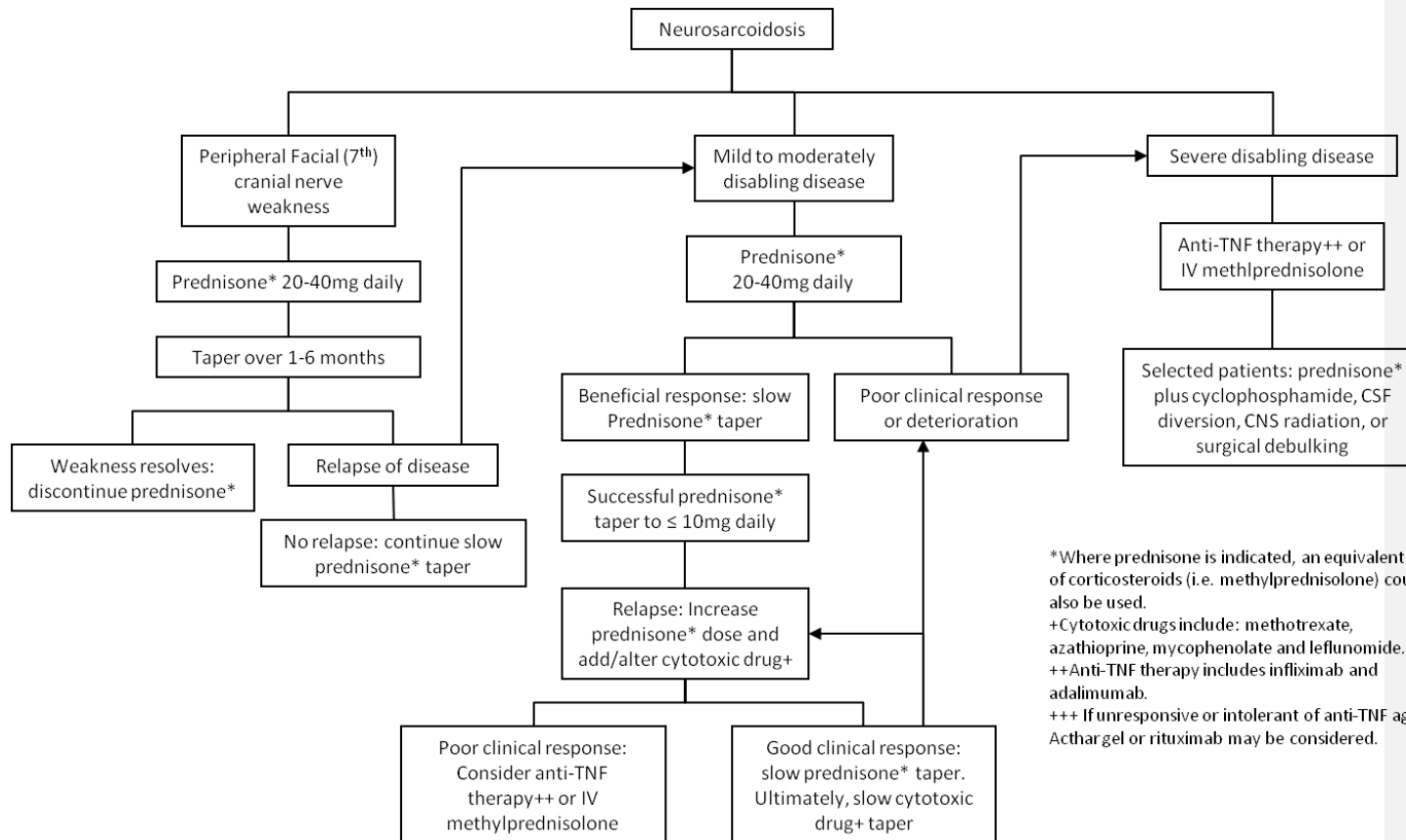
Corticosteroid treatment is recommended as the first line of therapy for neurologic involvement. In order to avoid the long-term complications of corticosteroid therapy, use of adjuvant cytotoxic therapy is recommended early in the clinical course of patients who are likely to require prolonged treatment.

The most common neurologic manifestation of neurosarcoidosis is peripheral facial nerve palsy. A limited course of prednisone 20-40 mg daily is recommended for these patients. The dosage should be tapered over 1-6 months and can be discontinued if weakness resolves. A similar course may be sufficient to treat patients with acute sarcoidosis-associated aseptic meningitis.

It is suggested that patients with mild to moderately disabling disease (cranial nerves II and VIII, meningeal mass lesions, hydrocephalus, CNS parenchymal disease, neuropathies and generalized myopathies) be treated with 20-30 mg prednisone daily for at least one month. However, the initial dose of prednisone for neurologic sarcoidosis is often higher than 40 mg a day; in some centers, a dose of 1 mg/kg is used.

If the patient improves, the dose can be decreased by 5 mg every two weeks as the clinical course is monitored. Patients may require a maintenance dose of 10 mg or lower daily even if they are treated with adjuvant drugs.

For patients who are acutely and severely ill, intravenous methylprednisolone for three days or anti-TNF therapy is recommended. Infliximab can also be used for chronic treatment or to "bridge" a patient until an immunosuppressive drug's benefit becomes evident, typically in 2-3 months. Infusions of infliximab can be administered every 2-8 weeks, or at longer intervals, as clinically indicated. Mycophenolate and cyclophosphamide have been reported as useful for refractory neurosarcoidosis in selected cases.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.
 +Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.
 ++Anti-TNF therapy includes infliximab and adalimumab.
 +++ If unresponsive or intolerant of anti-TNF agent, Acthar gel or rituximab may be considered.

SKIN

One in four sarcoidosis patients will have cutaneous involvement. Although sarcoidosis of the skin is almost never life-threatening, it can cause significant cosmetic problems that may have a major impact on the patient's quality of life.

Sarcoidosis skin lesions are classified in two groups: sarcoidosis-specific skin lesions and non-granulomatous lesions. The former represent true sarcoidosis of the skin. That is, the skin contains granulomas, the pathological lesions of sarcoidosis. The latter are inflammatory reactions of the skin but are non-granulomatous.

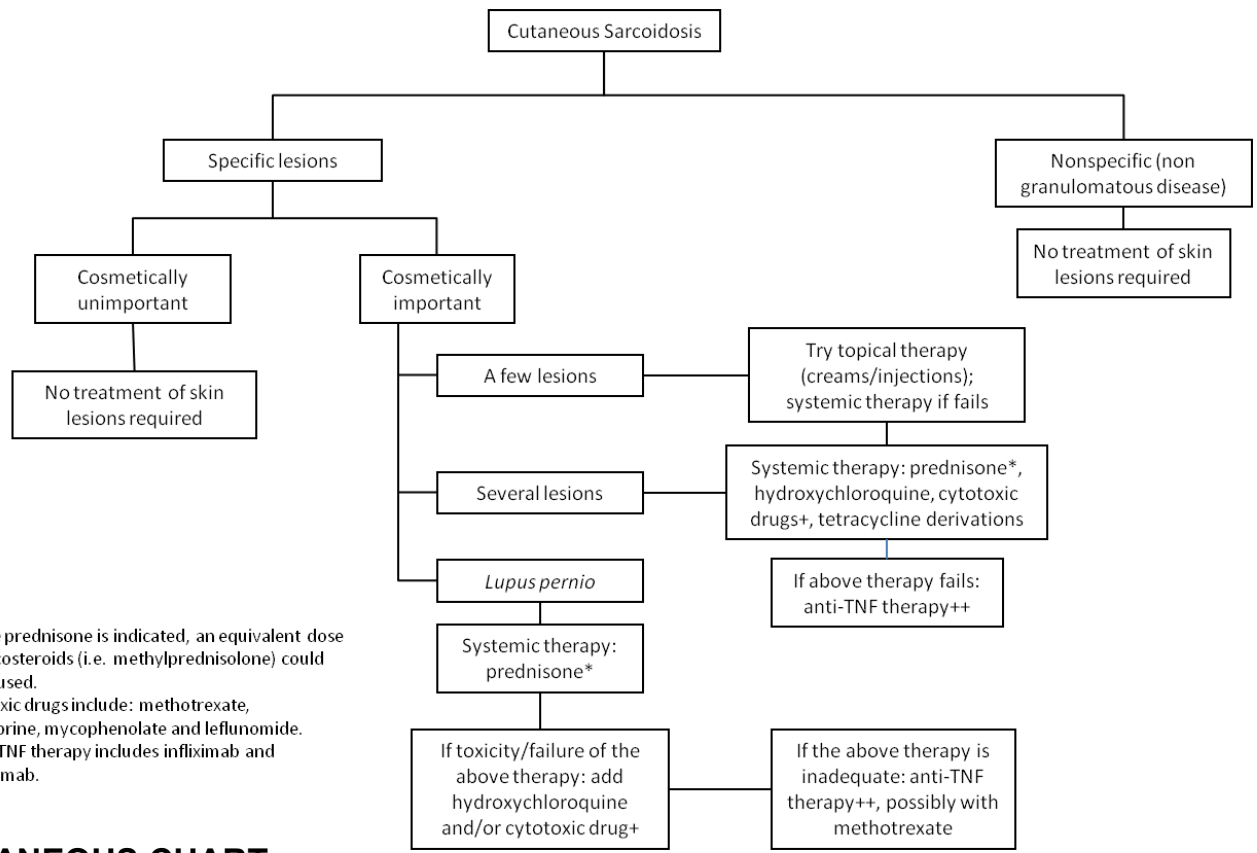
Specific sarcoidosis skin lesions include thick, raised skin lesions that have an apple jelly color. They may be scaly, and occasionally they are yellow to violet in color. Other specific skin lesions include skin nodules that develop on old scars and tattoos; lesions that look like ulcers; lesions that may be mistaken for psoriasis; and *lupus pernio*, potentially disfiguring lesions that occur on the face, particularly on or around the nose, around the eyes or mouth.

These specific lesions almost never cause pain or itching and are not life-threatening. For that reason, they should be treated only if they are of cosmetic importance to the patient. If the patient has very few localized lesions, they may respond to application of a corticosteroid cream or intralesional injections. If lesions do not respond to local therapy or if skin disease is more generalized, some type of pharmacotherapy is required. Systemic corticosteroids are usually used at least for the short term, but because of their many potential side effects, other agents should be considered for longer-term treatment.

Hydroxychloroquine is often the first steroid-sparing drug used. Among the cytotoxic drugs, methotrexate seems to have a better response rate than other agents. In some cases, derivatives of tetracycline have been helpful in mild disease. For very severe cases, anti-TNF therapy, such as infliximab may have a role. In selected patients chloroquine and thalidomide have been used.

Non-granulomatous lesions are very common with acute initial presentations of sarcoidosis. Also, they are associated with a good prognosis of sarcoidosis in that the disease often goes away within a few months when non-granulomatous lesions occur. The most common non-granulomatous sarcoidosis lesion is erythema nodosum. These lesions - which are thick, slightly raised and often painful - are often seen with an acute presentation of sarcoidosis called Lofgren's syndrome. This syndrome, which is also associated with hilar adenopathy, fever and pain in the ankles and other joints, typically resolves completely in a few months. It can be usually treated with only nonsteroidal drugs for painful skin lesions and joint pain; however, occasionally corticosteroids are required.

We suggest an approach to the various forms of cutaneous sarcoidosis. For *lupus pernio*, a large retrospective study reported that anti-TNF therapy was significantly better than cytotoxic or antimalarial therapy, and it could be considered as second-line therapy for this particular form of skin sarcoidosis. However, anti-TNF therapy is associated with more toxicity and the risk/benefit ratio must be considered in treating this chronic cutaneous condition.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.

+Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.

++Anti-TNF therapy includes infliximab and adalimumab.

CUTANEOUS CHART

LIVER DISEASE

Estimates of liver involvement in sarcoidosis vary from 11- 80 percent of cases, with lower rates based on symptomatic disease and higher rates reported in studies performing random liver biopsies. Women and African Americans are affected more frequently. Most individuals with liver disease present asymptotically with evidence of hepatomegaly, increased liver function test or CT scan abnormalities. Non-specific symptoms, including abdominal pain, fevers and weight loss are common in sarcoidosis liver disease, although patients may present with pruritus, jaundice and chronic cholestasis. Cirrhosis, portal hypertension, Budd-Chiari syndrome and variceal bleeding occur rarely. In cases of known sarcoidosis a probable diagnosis of liver disease may be established based on increased alkaline phosphatase, or transaminases, or CT findings of characteristic nodules, consisting of low attenuation lesions of varied but usually small size. Occasionally a liver biopsy may be obtained, although this is not necessary to confirm liver sarcoidosis. Radiographic findings are not specific for hepatic sarcoidosis; ultrasound may be obtained to assess portal hypertension and to exclude other causes of liver disease. In general, a diagnosis of hepatic sarcoidosis must be confirmed and other causes of liver disease must be excluded.

There is limited data on which to base treatment recommendations for sarcoidosis liver disease. As there are no controlled trials, much of the following is based on clinical experience and retrospective case studies.

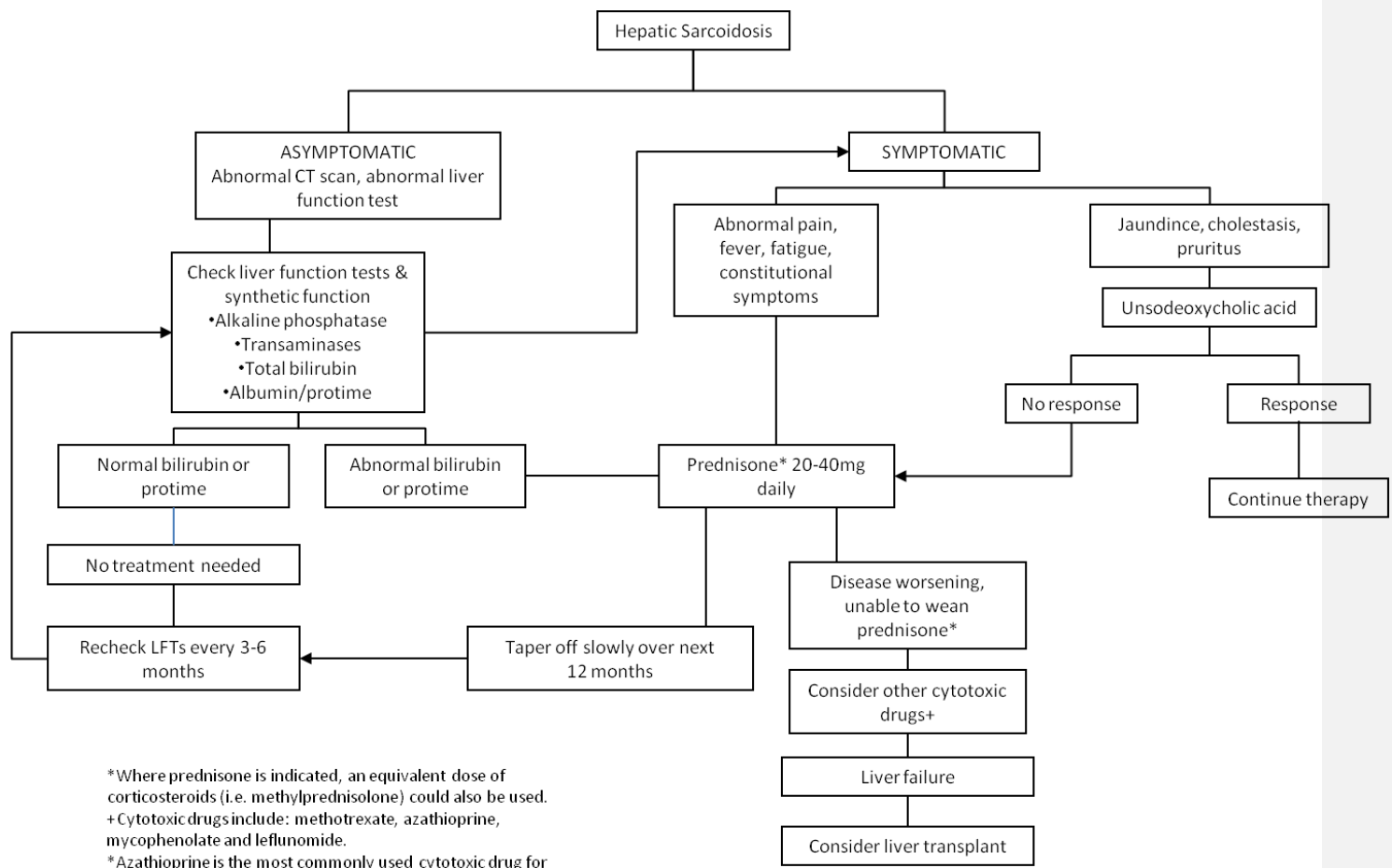
The majority of patients with sarcoidosis liver disease do not require therapy. This includes patients with asymptomatic disease and mildly elevated liver function tests, no evidence of cholestasis (normal bilirubin) and normal liver synthetic function (e.g., protime, PT), or with hepatomegaly noted on physical exam and/or radiographic abnormality. These individuals - including those with liver function tests more than three times the upper limit of normal, even without symptoms - should be followed using liver-function tests to determine if they develop evidence of cholestasis or abnormal prothrombin time (PT), which would be considered reasons for starting systemic therapy. Liver-function test abnormalities may resolve spontaneously over time or with treatment aimed at other organ involvement (e.g., lung disease).

Granulomatous hepatitis is usually treated in individuals with symptomatic liver disease, such as those with abdominal pain or jaundice with evidence of cholestasis, or if there are significant abnormalities in liver function, or even frank cirrhosis, demonstrated with increased PT. If liver-function tests are more than 10 times normal, therapy may be considered and these patients should be followed closely.

Corticosteroids are usually the first line therapy. If the liver is the only treatment target, oral budesonide can be considered, since it is metabolized in the liver and therefore systemic corticosteroid toxicity may be markedly reduced. When an inadequate response to corticosteroids is noted, cytotoxic agents are often used. Most experience has been with azathioprine for hepatic sarcoidosis. Methotrexate and leflunomide are more likely to be hepatotoxic; however, azathioprine can also be hepatotoxic, so one would still have

to closely monitor LFTs. Ursodeoxycholic acid at 10 mg/kg/day may be used to manage symptoms of cholestasis, including jaundice and pruritus. Unfortunately, cirrhosis may occur despite therapy, and even result in the need for liver transplantation.

Splenomegaly is common in sarcoidosis, more so than hepatomegaly, but does not usually require treatment and may resolve spontaneously. Although there are limited data upon which to make recommendations for treatment, clinical indications for treatment include hypersplenism with cytopenia, or splenic infarction. Usually corticosteroids are effective treatment. Splenectomy is not usually performed.



ISEASE AND ABNORMALITIES IN CALCIUM METABOLISM

RENAL DISEASE AND ABNORMALITIES IN CALCIUM METABOLISM

Sarcoidosis nephropathy manifests as interstitial nephritis more commonly than glomerular disease, although renal failure from either mechanism is uncommon. Granulomatous inflammation or other pathologic manifestations may be seen, including membranous nephropathy, minimal change disease, proliferative or crescentic glomerulonephritis, focal glomerulosclerosis and even IgA nephropathy. While there is limited data upon which to base therapeutic recommendations, corticosteroids are usually used with evidence of renal insufficiency starting at 40 mg daily, with a slow wean of therapy as used for other organ involvement. Usually there is evidence of improvement in renal function with treatment, although normalization of creatinine may not occur. Rarely renal transplantation is needed.

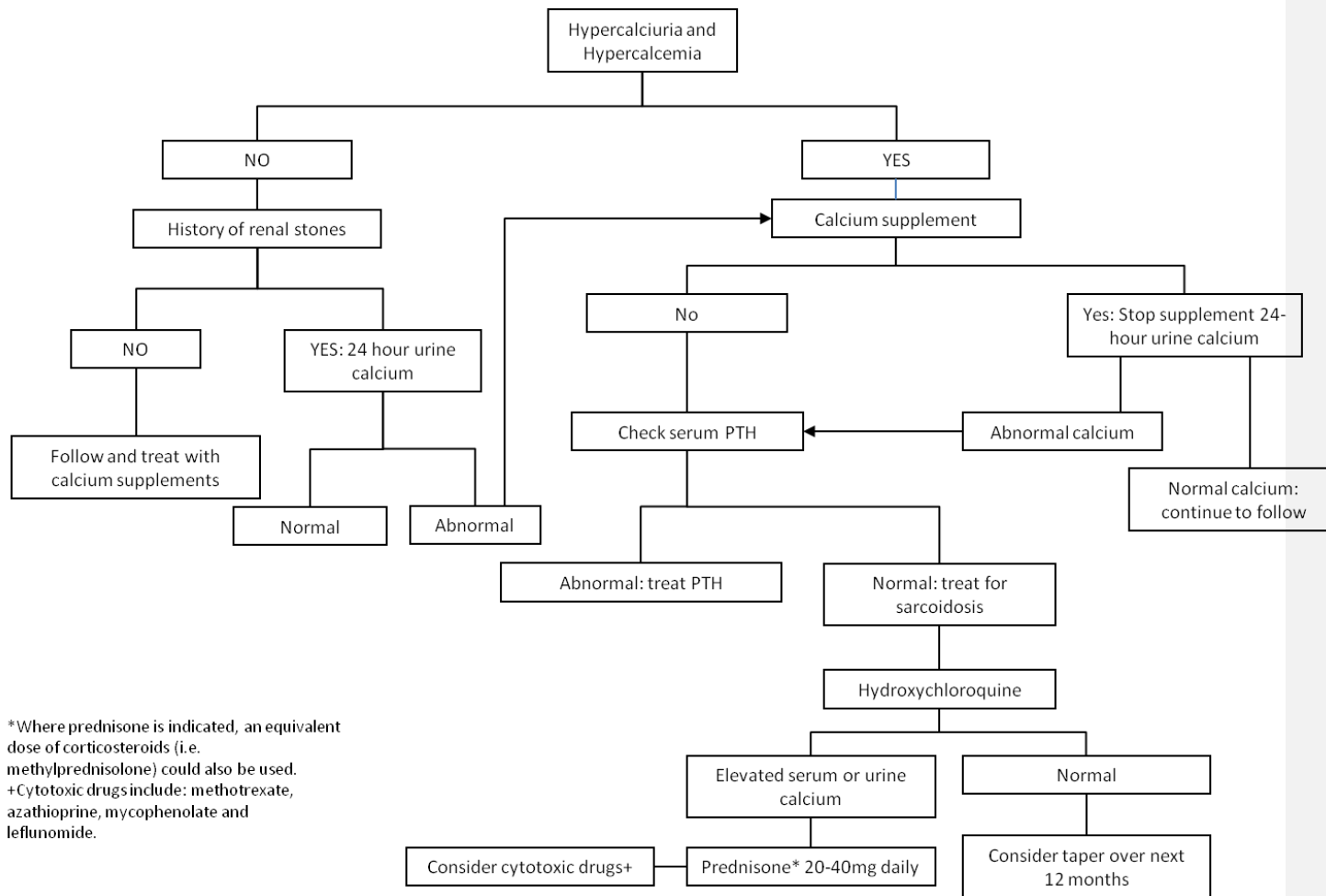
An increase in 1,25-(OH)₂- vitamin D₃ production from pulmonary macrophages and granulomas may lead to increased absorption of calcium. This can eventually result in hypercalcemia, seen in up to 5 percent of patients with sarcoidosis, and more commonly hypercalciuria.

Nephrocalcinosis may result from persistent hypercalciuria and/or hypercalcemia, and can cause renal insufficiency. As in the other organs discussed above, data on which to base treatment recommendations are limited. However, in isolated hypercalciuria, treatment may begin with a reduction in calcium intake, increased fluids and avoidance of sun. Occasionally, hydroxychloroquine may be effective at 200- 400 mg daily for more significant hypercalciuria.

Mild hypercalcemia may also be treated with a reduction in dietary calcium and increased fluid intake. For more significant hypercalcemia (e.g. Ca >11 mg/dl) or nephrolithiasis, corticosteroid therapy is usually implemented at 20-40 mg daily. Reduction in hypercalcemia usually occurs fairly quickly with steroid implementation, and some will attempt to taper the corticosteroids more quickly after 1-2 months.

Occasionally other agents, including hydroxychloroquine, are needed for more refractory disease. Vitamin D supplementation should be avoided in those with hypercalciuria and hypercalcemia. Ketoconazole has no direct effect on sarcoidosis granulomas, but it inhibits vitamin D metabolism and can be used as an adjunct for treating hypercalcemia and hypercalciuria.

In sarcoidosis patients, vitamin D-1,25 may be elevated with normal or even low levels of vitamin D- 25. In that setting, further supplementation with vitamin D can lead to hypercalcemia and/or hypercalciuria. For sarcoidosis patients, screening for vitamin D deficiency should be done by measurement of vitamin D-1,25.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.
 +Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.

QUALITY OF LIFE ISSUES

The clinical course of sarcoidosis is highly variable, and virtually every organ can be involved. In addition to organ-specific symptoms such as coughing, dyspnea on exertion, chest pain, and wheezing, many patients experience non-specific symptoms such as fatigue, psychologic distress, and pain issues that are disabling, particularly when they become chronic and have a great impact on the quality of life (QOL).

Fatigue

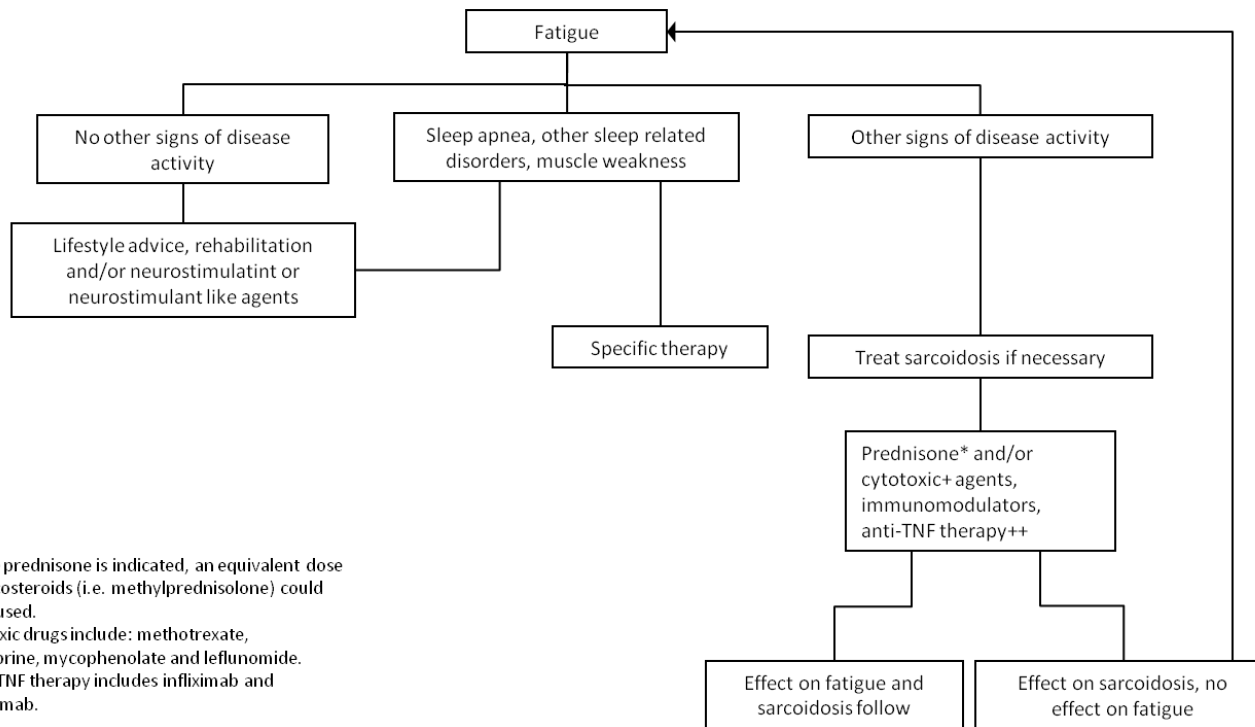
Despite adequate treatment for other manifestations of sarcoidosis, a substantial number of sarcoidosis patients suffer from persistent fatigue. Fatigue appears to be the most frequently reported symptom in sarcoidosis patients. Recent studies suggest that fatigue may persist after all other manifestations of sarcoidosis have resolved.

Fatigue may be debilitating, may become chronic and lead to substantial curtailment of professional, recreational, social, and/or educational activities and, as a consequence, reduced QOL. When features of disease activity - for example, radiological abnormalities and lung function impairment - are resolved during treatment, fatigue and pain may persist. Therefore, objective test results such as chest radiographs, lung-function tests and laboratory parameters do not always reflect the well-being of the patient. Other factors that need to be considered are small fiber neuropathy, autonomic dysfunction, depression, and steroid myopathy. Hypogonadism, hypothyroidism and sleep apnea syndrome can also lead to fatigue.

Reduced respiratory muscle strength and endurance time were demonstrated in sarcoidosis patients with normal lung function test results at rest, especially in those suffering from fatigue. Moreover, fatigue was related to dyspnea, sleeping disorders and to the 6-minute walk distance during an exercise test. Fatigue appeared to be associated with specific types of pain, such as muscle pain, chest pain, arthralgia, abdominal pain and headache.

Little data are available regarding specific treatment for fatigue associated with sarcoidosis. In small double- blinded, placebo-controlled crossover studies, the neurostimulant dexamethylphenidate hydrochloride (d-MPH) and neurostimulant like agent r-modafinil were both associated with a significant reduction in sarcoidosis-associated fatigue. Anti-TNF treatment for other sarcoidosis-related problems also appeared beneficial for fatigue. Other studies suggest that prednisone usage can be associated with patient fatigue.

Unfortunately, these studies were not designed to ascertain if conditions of weight gain, diabetes, depression, inactivity, steroids represent cause or effect for fatigue. It is possible that sleep disturbance or altered mood states are the drivers of fatigue in the sarcoidosis population.. Besides medication, cognitive-behavioral therapy and exercise programs may also be considered in severe or chronic disease or in the development of co-morbid treatment strategy.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.

+Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.

++Anti-TNF therapy includes infliximab and adalimumab.

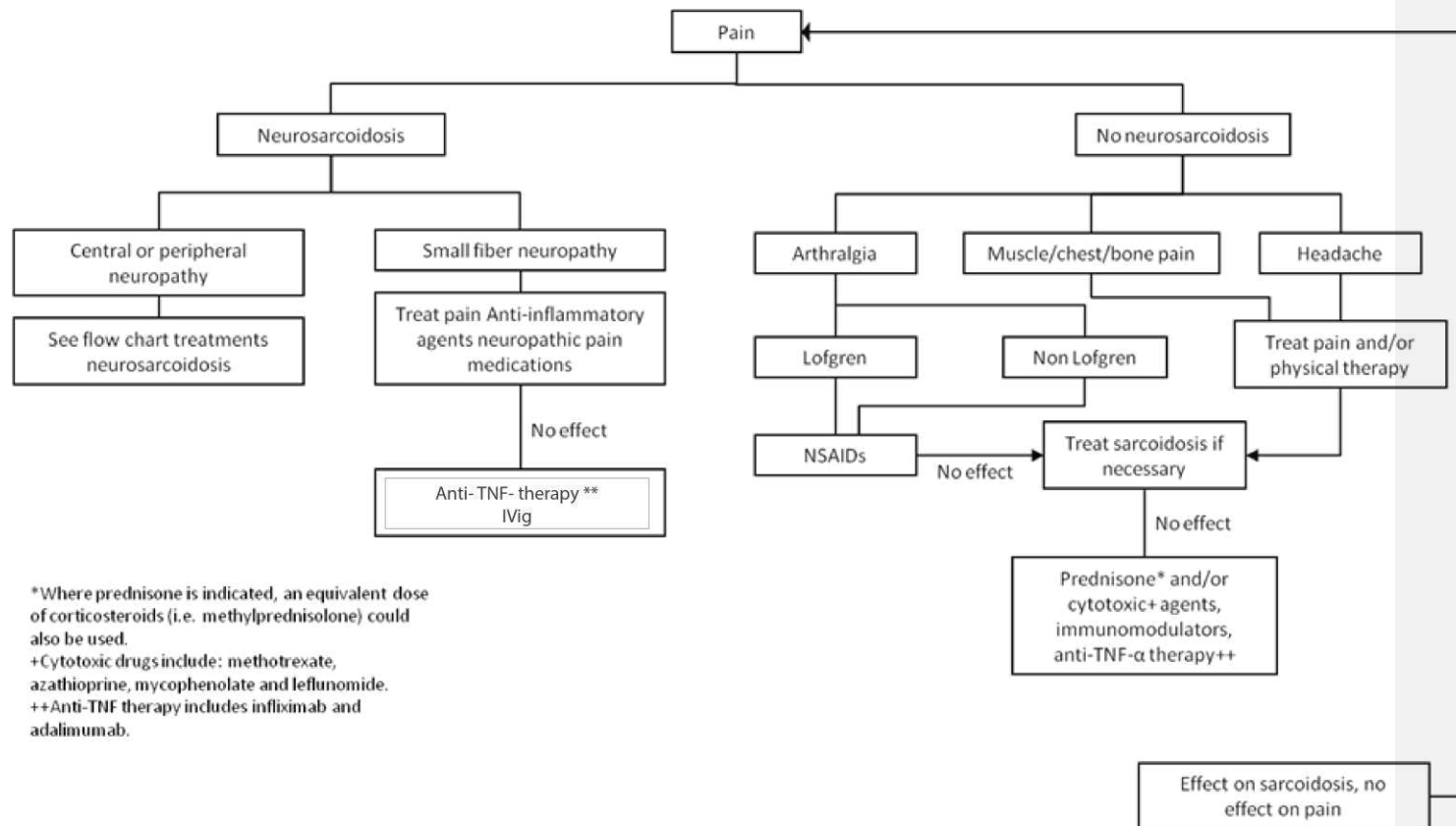
Pain, Small Fiber Neuropathy and Cognitive Dysfunction

Chronic pain is a particular problem for sarcoidosis patients. A stepwise approach to management is shown.

A number of hitherto unexplained symptoms such as fatigue and pain and cognitive dysfunction may - at least partly - be attributable to small fiber neuropathy. However, the relationship between all these features is unclear, and their concomitant occurrence does not demonstrate causality.

It has been observed that sarcoidosis patients with symptoms displayed more depressive symptoms and scored lower on health status compared with patients without current symptoms. Moreover, patients suffering from sarcoidosis often report cognitive complaints, such as memory loss and concentration problems. Cognitive failures are a substantial problem in sarcoidosis patients, even after adjustment for differences in age and sex distribution. No substantial relationship has been found with clinical characteristics, such as disease duration, and severity. In some studies, fatigue, depression and symptoms related to autonomic dysfunction were associated with the occurrence of cognitive dysfunction. These findings emphasize the need for further research to integrate knowledge about coping, cognitive performance, fatigue and depressive symptoms in sarcoidosis into clinical management

Standard anti-inflammatory therapies are usually ineffective for this condition. Neuropathic drugs such as gabapentin may be useful for symptomatic pain relief. For refractory cases, anecdotal reports suggest the effectiveness of intermittent intravenous immunoglobulin (IVIg) therapy and/or anti-TNF agents in selected cases.



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.
 +Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.
 ++Anti-TNF therapy includes infliximab and adalimumab.

Treatment Protocol – Authors

Robert Baughman, MD
University of Cincinnati

Dan Culver, DO
Cleveland Clinic

Wonder Drake, MD
Vanderbilt University

Marc Judson, MD
Albany Medical College

Lisa Maier, MD
National Jewish Health

Dave Moller, MD
Johns Hopkins University

Adam Morgenthau, MD
Icahn School of Medicine at Mt. Sinai

Milton Rossman, MD
Professor of Medicine
University of Pennsylvania

Barney Stern, MD
Professor of Neurology
University of Maryland

Disclosures.

Only prednisone and ACTHAR gel have FDA approval for treatment of sarcoidosis. All other drugs discussed in this document are not FDA approved for treatment of sarcoidosis.

Dr. Baughman has received research grants for treatment of sarcoidosis by the following sources: Actelion, Bayer, Forest Pharmaceuticals, Celgene, Janssen, Glaxo, Genentech, Questcor, and the National Heart, Lung, and Blood Institute.

Dr. Baughman has been a consultant regarding treatment of sarcoidosis for Celgene, Janssen, Questcor, Mitsubishi.

Dr. Culver has received support to cover solely study-related expenses related to the treatment of sarcoidosis from the following sources: Actelion, Janssen, Glaxo Smith Kline, Pfizer, Celgene, Araim, and the NHLBI.

Dr Culver has received consulting fees from: Celgene, Questcor, Mitsubishi Tanabe.

Dr Drake has no potential conflicts of interest related to sarcoidosis to report.

Dr Judson has received support to cover solely study-related expenses related to the treatment of sarcoidosis from the following sources: Questcor, Janssen, and Forest Pharmaceuticals.

Dr Judson has received consulting fees from: Janssen, Celgene, Novartis, Questcor, Mitsubishi Tanabe.

Dr Maier has received support to cover solely study-related expenses related to the treatment of sarcoidosis from the following sources: Janssen, and the NHLBI.

Dr Moller has received grants or research support from: Life and Breath Foundation, NHLBI, and support of the sarcoidosis clinic from the Euwood Foundation

Dr Morgenthau has received support to cover solely study-related expenses related to the treatment of sarcoidosis from the following sources: Auvon Pharmaceuticals.

Dr Stern has no potential conflicts of interest related to sarcoidosis to report.

| Dr. Rossman has received support to cover solely study-related expenses related to the treatment of sarcoidosis from the following sources: Pfizer, and the NHLBI.

Dr. Rossman has reviewed study grants for Questcor.