Sarcoidosis

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues; etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ. Pulmonary symptoms range from none to exertional dyspnea and, rarely, lung or other organ failure. Diagnosis usually is first suspected because of pulmonary involvement and is confirmed by chest x-ray, biopsy, and exclusion of other causes of granulomatous inflammation. First-line treatment is corticosteroids. Prognosis is excellent for limited disease but poor for more advanced disease.

Sarcoidosis most commonly affects people aged 20 to 40 but occasionally affects children and older adults. Worldwide, prevalence is greatest in black Americans and ethnic northern Europeans, especially Scandinavians. Disease presentation varies widely by racial and ethnic background, with black Americans and Puerto Ricans having more frequent extrathoracic manifestations. Sarcoidosis is more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Löfgren syndrome: Löfgren syndrome manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It often causes fever, malaise, and uveitis, and sometimes parotitis. It is more common among Scandinavian and Irish women.

Löfgren syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Blau syndrome: Blau syndrome is sarcoidosis inherited in a autosomal dominant fashion that manifests in children. In Blau syndrome, children present before the age of 4 yr with arthritis, rash, and uveitis. Blau syndrome is often self-limited Symptoms usually are relieved with NSAIDs.

Etiology

Sarcoidosis is thought to be due to an inflammatory response to an environmental antigen in a genetically susceptible person. Proposed triggers include

- *Propionibacterium acnes* and mycobacteria (potentially the *Mycobacterium tuberculosis* catalase-peroxidase [mKatG] protein)
- Mold or mildew and certain unidentified substances present in workplaces with musty odors and pesticides

Tobacco use is inversely correlated with sarcoidosis.

Evidence supporting genetic susceptibility includes the following:

- Higher rate of disease concordance in monozygotic than dizygotic twins
- Increased prevalence of sarcoidosis (about 3.6 to 9.6%) among 1st- or

2nd-degree relatives of patients who have sarcoidosis

- Fivefold increase in relative risk of developing sarcoidosis in siblings of patients who have sarcoidosis
- Identification of several possible HLA and non-HLA genes associated with sarcoidosis

Pathophysiology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T cells and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition, shared exposures, or, less likely, person-to-person transmission.

The inflammatory process leads to formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that differentiate into epithelioid and multinucleated giant cells and are surrounded by lymphocytes, plasma cells, fibroblasts, and collagen. Granulomas occur most commonly in the lungs and lymph nodes but can involve any organ and cause significant dysfunction. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Hypercalcemia may occur because vitamin D analogs are produced by activated macrophages. Hypercalciuria may be present, even in patients with normal serum Ca levels. Nephrolithiasis and nephrocalcinosis may occur, sometimes leading to chronic kidney disease.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Accordingly, frequent reassessment for new symptoms in different organs is needed. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90% of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise, weakness, anorexia, weight loss, and low-grade fever are also common. Sarcoidosis can manifest as fever of unknown origin. Systemic involvement causes various symptoms (Table 1: Systemic Involvement in Sarcoidosis), which vary by race, sex, and age. Blacks are more likely than whites to have involvement of the eyes, liver, bone marrow, peripheral lymph nodes, and skin; erythema nodosum is an exception. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

Children with sarcoidosis may present with Blau syndrome (arthritis, rash, uveitis), or manifestations similar to those of adults. Sarcoidosis may be confused with juvenile idiopathic arthritis (juvenile RA) in this age group.

Table 1

Systemic Involvement in Sarcoidosis

System	Estimated Frequency	Comments
Pulmonary	> 90%	Causes granulomas to form in alveolar septa and bronchiolar and bronchial walls, causing diffuse pulmonary disease; pulmonary arteries and veins also involved

		Often asymptomatic Spontaneously resolves in many patients but can cause progressive pulmonary dysfunction, leading to limitations in physical function, respiratory failure, and death in a few
Pulmonary lymphatic	90%	Hilar or mediastinal involvement incidentally detected by chest x-ray in most patients; nontender peripheral or cervical lymphadenopathy in others
Muscle	50–80%	Asymptomatic disease with or without enzyme elevations in most patients Sometimes insidious or acute myopathy with muscle weakness
Hepatic	40–75%	Usually asymptomatic Manifests with mild elevations in liver function test results, hypolucent lesions on CT scans with radiopaque dye Rarely, clinically significant cholestasis or cirrhosis Unclear distinction between sarcoidosis and granulomatous hepatitis when sarcoidosis affects the liver only
Joint	25–50%	Ankle, knee, wrist, and elbow arthritis (most common) May cause chronic arthritis with Jaccoud deformities or dactylitis

		Löfgren syndrome (triad of acute polyarthritis, erythema nodosum, and hilar adenopathy)
Hematologic	< 5–30%	Lymphocytopenia Anemia of chronic disease Anemia due to granulomatous infiltration of bone marrow, sometimes causing pancytopenia Splenic sequestration causing thrombocytopenia Leukopenia
Dermatologic	25%	Erythema nodosum: • Red, indurated, tender nodules on anterior legs • More common among Europeans, Puerto Ricans, and Mexicans • Usually remits in 1–2 mo • Surrounding joints often arthritic (Löfgren syndrome) • May be good prognostic sign Biopsy of erythema nodosum lesions is unnecessary because granulomas characteristic of sarcoidosis are absent Common skin lesions: Plaques, macules and papules, subcutaneous nodules, hypopigmentation and hyperpigmentation Lupus pernio: • Violaceous plaques on the nose, cheeks, lips, and ears • More common among black Americans and Puerto Ricans • Often associated with lung fibrosis Poor prognostic sign

Ocular	25%	Uveitis (most common), causing blurred vision, photophobia, and tearing Can cause blindness Spontaneously resolves in most patients May manifest with conjunctivitis, iridocyclitis, chorioretinitis, dacryocystitis, lacrimal gland infiltration causing dry eyes, optic neuritis, glaucoma, or cataracts Ocular involvement more common among black Americans and people of Japanese descent Annual screening indicated for early disease detection
Psychiatric	10%	Depression (common), but uncertain whether it is a primary manifestation of sarcoidosis or a response to the prolonged course of disease and frequent recurrences
Renal	10%	Asymptomatic hypercalciuria (most common) Interstitial nephritis Chronic renal failure caused by nephrolithiasis and nephrocalcinosis and requiring renal replacement (dialysis or transplantation) in some patients
Splenic	10%	Usually asymptomatic

		Manifests with left upper quadrant pain and thrombocytopenia or as an incidental finding on x-ray or CT
Neurologic	< 10%	Cranial neuropathy, especially the 7th nerve (causing facial nerve palsy) or 8th nerve (causing hearing loss) Optic and peripheral neuropathy (common) May affect any cranial nerve CNS involvement, with nodular lesions or diffuse meningeal inflammation typically in the cerebellum and brain stem Hypothalamic diabetes insipidus, polyphagia and obesity, and thermoregulatory and libidinal changes
Nasal sinus	< 10%	Acute and chronic granulomatous inflammation of sinus mucosa with symptoms indistinguishable from common allergic and infectious sinusitis Diagnosis confirmed by biopsy More common in patients with lupus pernio
Cardiac	5%	Conduction blocks and arrhythmias (most common), sometimes causing sudden death Heart failure due to restrictive cardiomyopathy (primary) or pulmonary hypertension (secondary)

		Transient papillary muscle dysfunction and pericarditis (rare) More common among Japanese, in whom cardiomyopathy is the most frequent cause of sarcoidosis-related death
Bone	5%	Osteolytic or cystic lesions Osteopenia
Oral	< 5%	Asymptomatic parotid swelling (most common) Parotitis with xerostomia Heerfordt syndrome (uveoparotid fever), characterized by uveitis, bilateral parotid swelling, facial palsy, and chronic fever Oral lupus pernio, which may disfigure the hard palate and may involve the cheek, tongue, and gums
Gastric or intestinal	Rare	Rarely gastric granulomas Rarely intestinal involvement Mesenteric lymphadenopathy that may cause abdominal pain
Endocrine	Rare	Hypothalamic and pituitary stalk infiltration, possibly causing panhypopituitarism May cause thyroid infiltration without dysfunction Secondary hypoparathyroidism due to

		hypercalcemia
Pleural	Rare	Causes lymphocytic exudative effusions, usually bilateral
Reproductive	Rare	Case reports of endometrial, ovarian, epididymal, and testicular involvement No effect on fertility May subside during pregnancy and relapse postpartum

Diagnosis

- Chest imaging
- Biopsy
- Exclusion of other granulomatous disorders

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. These changes are the most common abnormality. Therefore, if sarcoidosis is suspected, a chest x-ray should be the first test if it has not already been done. The x-ray appearance tends to roughly predict the likelihood of spontaneous remission (Table 2: Chest X-ray Staging of Sarcoidosis) in patients with only pulmonary involvement. However, staging sarcoidosis by chest x-ray can be misleading; for example, extrapulmonary sarcoidosis, such as cardiac or neurologic sarcoidosis, can portend a serious prognosis in the absence of pulmonary involvement. Also, chest x-rays findings predict pulmonary function poorly, so that chest x-ray appearance may not accurately indicate the severity of pulmonary sarcoidosis.

A normal chest x-ray (stage 0)

does not exclude the diagnosis, particularly when cardiac or neurologic involvement is suspected. A high-resolution CT is more sensitive for detecting hilar and mediastinal lymphadenopathy and parenchymal abnormalities. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls; beading of the interlobular septa; ground-glass opacification; parenchymal nodules, cysts, or cavities; and traction bronchiectasis.

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease (see Table 3: Differential Diagnosis of Sarcoidosis). Löfgren syndrome does not require confirmation by biopsy.

Table 2

Chest X-ray Staging of Sarcoidosis

Stage	Definition	Incidence of Spontaneous Remission
0	Normal chest x-ray	—
I	Bilateral hilar, paratracheal, and mediastinal lymphadenopathy without parenchymal infiltrates	60–80%
II	Bilateral hilar and mediastinal adenopathy with interstitial infiltrates (usually in upper lung fields)	50–65%
III	Diffuse interstitial infiltrates without hilar adenopathy	< 30%
IV	Diffuse fibrosis, often associated with fibrotic-appearing conglomerate	0%

masses, traction bronchiectasis, and traction cysts

The diagnostic evaluation, therefore, requires the following:

- Selection of a biopsy site
- Exclusion of other causes of granulomatous disease
- Assessment of the severity and extent of disease to determine whether therapy is indicated

Table 3

Differential Diagnosis of Sarcoidosis

Type	Specific Disorder
Mycobacterial infection	Atypical mycobacteria
	TB
Fungal infection	Aspergillosis
	Blastomycosis
	Coccidioidomycosis
	Cryptococcal infection
	Histoplasmosis
Other infections	Brucellosis
	Cat-scratch disease (lymph nodes only)
	Mycoplasmal infection
	Pneumocystis jirovecii infection
	Syphilis
Rheumatologic disorders	Juvenile idiopathic arthritis (juvenile RA)
	Kikuchi-Fujimoto disease (lymph nodes

	only)
	Necrotizing sarcoid granulomatosis
	RA
	Sjögren syndrome
	Granulomatosis with polyangiitis (Wegener granulomatosis)
Hematologic cancer	Castleman disease (a lymphoproliferative disorder associated with infection by HIV or human herpesvirus 8)
	Hodgkin lymphoma
	Non-Hodgkin lymphoma
	Splenic lymphoma
Hypersensitivity	Metals encountered in occupational settings: Aluminum, beryllium, titanium, zirconium
	Organic antigens causing hypersensitivity pneumonitis: Actinomycetes, atypical mycobacterial antigens, fungi, mushroom spores, other bioaerosols
	Inorganic antigens causing hypersensitivity pneumonitis: Isocyanate, pyrethrins
	Drug reaction
Other	Inflammatory bowel disease
	Foreign body aspiration or inoculation

Granulomatous hepatitis

Granulomatous lesion of unknown significance

Lymphoid interstitial pneumonia

Sites for biopsy: Appropriate biopsy sites may be obvious from physical examination and initial assessment; peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal or hilar lymph node has a reported diagnostic yield of about 90%. It is usually the diagnostic procedure of choice in patients with intrathoracic involvement. Bronchoscopic transbronchial biopsy can be tried when EBUS-TBNA is nondiagnostic; if the bronchoscopic transbronchial biopsy is nondiagnostic, it can be tried a second time. If EBUS-TBNA and bronchoscopic transbronchial biopsies are nondiagnostic or if bronchoscopy cannot be tolerated, mediastinoscopy can be done to biopsy mediastinal or hilar lymph nodes, or video-assisted thoracoscopic (VAT) lung biopsy or open-lung biopsy can be done to obtain lung tissue. If sarcoidosis is strongly suspected but a biopsy site is not evident based on examination or imaging findings, PET scanning can help identify sites such as heart and brain.

Exclusion of other diagnoses: Exclusion of other diagnoses is critical, especially when symptoms and x-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation (see Table 3: Differential Diagnosis of Sarcoidosis). Biopsy tissue should be cultured for fungi and mycobacteria. Exposure history to occupational (silicates, beryllium), environmental (moldy hay, birds, and other antigenic triggers of hypersensitivity pneumonitis), and infectious (TB,

coccidioidomycosis, histoplasmosis) antigens should be explored. PPD skin testing should be done early in the assessment along with anergy controls.

Disease severity assessment: Severity is assessed with

- Pulmonary function tests
- Exercise pulse oximetry

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DL_{CO}) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured at rest but may show effort desaturation in patients with more extensive lung involvement. ABG analysis at rest and during exercise is more sensitive than pulse oximetry.

Recommended routine screening tests for extrapulmonary disease include

- ECG
- Slit-lamp ophthalmologic examination
- Routine blood tests to evaluate renal and hepatic function
- Serum Ca levels and 24 h urinary Ca excretion

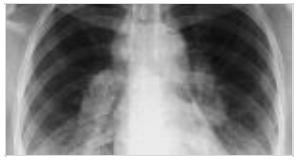
Echocardiography, cardiac MRI with gadolinium contrast, neuroimaging, bone scans, and electromyography may be appropriate in patients with cardiac, neurologic, or rheumatologic symptoms. PET scanning appears to be the most sensitive test for detecting bone and other extrapulmonary sarcoidosis. Abdominal CT with radiopaque dye is not routinely

recommended but can provide evidence of hepatic or splenic involvement (eg, enlargement, hypolucent lesions).

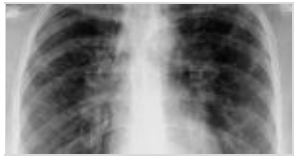
Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum Ca should be measured to detect hypercalcemia. BUN, creatinine, and liver function test results may be elevated in renal and hepatic sarcoidosis. Total protein may be elevated because of hypergammaglobulinemia. Elevated ESR is common but nonspecific. Measurement of Ca in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum Ca levels. Elevated serum ACE levels also suggest sarcoidosis but are nonspecific and may be elevated in patients with various other conditions (eg, hyperthyroidism, Gaucher disease, silicosis, mycobacterial disease, fungal infections, hypersensitivity pneumonitis, lymphoma). However, ACE levels may be useful for monitoring adherence with corticosteroid treatment. ACE levels plummet with even low-dose corticosteroids.

Bronchoalveolar lavage (BAL) is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes > 10%), a CD4+/CD8+ratio of > 3.5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

Sarcoidosis—Stage I



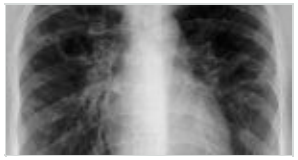
Sarcoidosis—Stage II



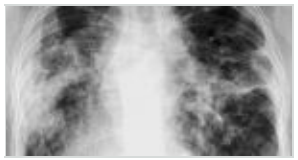
Whole-body gallium scanning has been largely

replaced by PET scanning. If gallium scanning is available, it may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal, parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

Sarcoidosis—Stage III



Sarcoidosis—Stage IV



Prognosis

Although spontaneous remission is common, disease manifestations and severity are highly variable, and many patients require corticosteroids at some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90% of patients who have spontaneous remission, remission occurs within the first 2 yr after diagnosis; < 10% of these patients have relapses after 2 yr. Patients who do not experience remission within 2 yr are likely to have chronic disease.

Sarcoidosis is thought to be chronic in up to 30% of patients, and 10 to 20% experience permanent sequelae. The disease is fatal in 1 to 5% of patients, typically due to respiratory failure caused by pulmonary fibrosis, and less often due to pulmonary hemorrhage caused by aspergilloma. However, in Japan, infiltrative cardiomyopathy causing arrhythmias and heart failure is the most common cause of death.

Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks. Remission occurs in 89% of whites and 76% of blacks with no extrathoracic disease and in 70% of whites and 46% of blacks with

extrathoracic disease.

Good prognostic signs include

- Löfgren syndrome (triad of acute polyarthritis, erythema nodosum, and hilar adenopathy)

Poor prognostic signs include

- Chronic uveitis
- Lupus pernio
- Chronic hypercalcemia
- Neurosarcoidosis
- Cardiac involvement
- Extensive pulmonary involvement

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

Treatment

- NSAIDs
- Corticosteroids
- Occasionally immunosuppressants

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing, annual slit-lamp

ophthalmologic examination). The frequency of follow-up testing is determined by the severity of disease. Patients who require treatment regardless of stage include those with the following:

- Worsening symptoms
- Limitation of activity
- Markedly abnormal or deteriorating lung function
- Worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension)
- Heart, nervous system, or eye involvement
- Renal or hepatic insufficiency or failure
- Moderate to severe hypercalcemia
- Disfiguring skin or joint disease

NSAIDS are used to treat musculoskeletal discomfort.

Disease-modifying treatment begins with corticosteroids. A standard protocol is prednisone 0.3 to 1 mg/kg po once/day depending on symptoms and severity of findings. Alternate-day regimens may be used: eg, prednisone 40 to 60 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in patients with heart involvement or ocular or neurologic disease. Response usually occurs within 2 to 4 wk, so symptoms and pulmonary function tests may be reassessed between 4 and 12 wk. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (eg, prednisone 10 to 15 mg/day) after evidence of response and are continued for a minimum of 6 to 12 mo if improvement occurs. The optimal duration of treatment is unknown. Premature taper can result in relapse. The drug is slowly stopped if

response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50% of the time, monitoring should be repeated, usually every 3 to 6 mo. Corticosteroid treatment should be resumed for recurrence of symptoms and signs, including dyspnea, arthralgia, fever, hepatic insufficiency, cardiac arrhythmia, CNS involvement, hypercalcemia, ocular disease uncontrolled by local drugs, and disfiguring skin lesions. Because ACE production is suppressed with low doses of corticosteroids, serial serum ACE levels may be useful in assessing adherence with corticosteroid treatment in patients who have elevated ACE levels.

Inhaled corticosteroids can relieve cough in patients with endobronchial involvement. Topical corticosteroids may be useful in dermatologic, nasal sinus, and ocular disease.

About 10% of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate 10 to 15 mg/wk. Initially, methotrexate and corticosteroids are both given; over 8 wk, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 mo. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 wk initially and then every 4 to 6 wk once a stable dose is achieved. Folate (1 mg po once/day) is recommended for patients treated with methotrexate.

Prophylaxis against *Pneumocystis jirovecii* pneumonia should be considered if patients are taking corticosteroids or immunosuppressants.

Other drugs reported to be effective in small numbers of patients who are

corticosteroid-resistant or who experience complicating adverse effects include azathioprine, cyclophosphamide, chlorambucil, chloroquine or hydroxychloroquine, thalidomide, pentoxifylline, and infliximab. Immunosuppressants are often more effective in refractory cases; relapse is common after cessation. Infliximab, a TNF inhibitor, can be effective for treatment of chronic corticosteroid-dependent pulmonary sarcoidosis, refractory lupus pernio, and neurosarcoidosis. It is given intravenously 3 to 5 mg/kg once, again 2 wk later, then once/mo.

Hydroxychloroquine 200 mg po bid can be as effective as corticosteroids for treating hypercalcemia, disfiguring skin sarcoidosis, or enlarged uncomfortable or disfiguring peripheral lymph nodes.

Patients who have heart block or ventricular arrhythmias due to cardiac involvement should have an implantable cardiac defibrillator and pacemaker placed as well as drug therapy.

No available drugs have consistently prevented pulmonary fibrosis.

Organ transplantation is an option for patients with end-stage pulmonary, cardiac, or liver involvement, although disease may recur in the transplanted organ.

Key Points

- Systemic and extrapulmonary involvement are common with sarcoidosis, but > 90% of adult patients have pulmonary involvement.
- Obtain a chest imaging study but confirm the diagnosis by biopsy, usually endobronchial ultrasound-guided transbronchial needle aspiration of a mediastinal or hilar lymph node.

- Assess pulmonary severity with pulmonary function testing and exercise pulse oximetry.
- Test for extrapulmonary involvement with ECG, slit-lamp examination, renal and hepatic function tests, and serum and urinary Ca testing.
- Treat patients with systemic corticosteroids when indicated (eg, severe symptoms, hypercalcemia, progressive decline in organ function, cardiac or neurologic involvement).
- Treat with immunosuppressants if patients cannot tolerate moderate doses of corticosteroids, sarcoidosis is resistant to corticosteroids, or if corticosteroids are required long term.

Last full review/revision March 2014 by Michael C. Iannuzzi, MD; Birendra P. Sah, MD
Content last modified March 2014