Sarcoidosis

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Sarcoidosis is an idiopathic granulomatous disease. Although often considered a pulmonary disease, it can affect virtually any organ with diverse and protean manifestations. However, most patients present with typical symptoms that are recognizable at the first clinical encounter. Although the cause is incompletely understood, the pathogenesis of sarcoidosis involves antigen exposure in a genetically susceptible host resulting in typical granulomatous inflammation with a prominent Th1-cell–mediated immune response, which either resolves or progresses to organ fibrosis. The identity of the antigen or antigens and the exact genetics of predisposition remain areas of intense research. The clinical course of sarcoidosis ranges from an incidental finding to a devastating, life-threatening disease. No clinical parameters allow an accurate prediction of the clinical course of sarcoidosis, although certain manifestations, such as lung fibrosis, cutaneous disease, and neurologic disease, suggest chronicity. It is benign in most cases; however, mortality seems to be increasing in the United States and England, particularly in women. Most deaths are related to pulmonary or cardiac disease.

### Risk Factors and Clinical Features

**Who is at risk?**

The incidence of sarcoidosis varies significantly among ethnic groups (1). In the United States, African American patients have an estimated 2.4% lifetime risk for sarcoidosis compared with 0.85% of white Americans. Although the age-adjusted incidence of sarcoidosis in the United States is 10–35 per 100,000, a recent prospective cohort study found a yearly incidence of 71 per 100,000 in African American women (2). Sarcoidosis is more common among persons of Scandinavian, Irish, German, and West Indian descent and is relatively rare in Japan, Spain, and Portugal. Familial clustering of sarcoidosis is reported in 5%–19% of patients, depending on ethnic background (3). Inheritance patterns are polygenic, complex, and non-Mendelian. In virtually all studies, more than 80% of cases of sarcoidosis present in patients between the ages of 20 and 40 years and is marginally more common in women than in men.

**Is there a role for screening?**

Despite clear at-risk populations, there is no role for screening for sarcoidosis. This reflects the variable prognosis and lack of evidence that an early diagnosis affects prognosis. Therefore, screening in family members of an index case is not recommended.

**What symptoms and clinical findings should prompt a clinician to consider sarcoidosis?**

Sarcoidosis can affect any organ system and present in virtually any manner. Typical presenting features, however, should prompt a high index of suspicion (see the Box). Specific organ involvement differs among study populations, but the lung or thoracic lymph nodes are involved in up to 90% of patients (4).

A common presentation is with the Lofgren syndrome (fever, bihilar lymphadenopathy [BHL], ankle swelling, and erythema nodosum [EN]). Sarcoidosis is the most common cause of EN in at-risk populations and is more common in sarcoidosis occurring in Europeans and Puerto Ricans than in African Americans and Japanese. The presence of all features of the Lofgren syndrome has a 95% diagnostic specificity for sarcoidosis, allowing a clinical diagnosis to be made without biopsy. Among patients with this syndrome, EN is more common in women, and marked periarticular inflammation of the ankles without EN is more common in men (5). Thus, EN is not required for diagnosis of the Lofgren syndrome. Recent
sarcoidosis is diagnosed in only 5% of patients, it accounts for a significant proportion of death due to sarcoidosis, particularly in Japanese patients. Autopsy studies in patients with sarcoidosis found cardiac granulomas in up to 25% of cases; however, cardiac involvement is probably often underdiagnosed. Any cardiac symptoms, but particularly syncope and palpitations (which may reflect conduction abnormalities or arrhythmias), should raise suspicion of cardiac disease in a patient with sarcoidosis (10).

Other patients may present with symptoms of congestive heart failure. Idiopathic cardiac disease, in particular atrioventricular block, in a patient younger than 55 years should raise consideration of isolated cardiac sarcoidosis (11).

Neurosarcoidosis is described in 5% of patients. Manifestations are diverse and can involve virtually any neurologic compartment. Most typical are cranial neuropathies, in particular VII nerve palsy, neuroendocrine disease related to hypothalamic–pituitary involvement, parenchymal brain disease, and peripheral (often small-fiber) neuropathy characterized by often-symmetrical sensory peripheral neuropathic symptoms.

Ocular disease occurs in about 20% of patients and is the presenting sign in at least 5% of patients with neuropathy. In a recent prospective study, uveitis was due to sarcoidosis in 7% of patients referred to an ophthalmologist (12). Uveitis can be subtle but usually presents with painful red eyes and is more common in African Americans and women. Other ocular manifestations are also common, in particular retinal vasculitis, and may coexist with uveitis. Untreated or inappropriately treated ocular sarcoidosis can result in chronic sequelae, including glaucoma and blindness.

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How is sarcoidosis diagnosed? Do all suspected cases require biopsy?

The diagnosis of sarcoidosis is one of exclusion (1). Multiple entities, including infections, can present with pathology and organ involvement identical to those seen in sarcoidosis (Table 1). Consensus recommendations are that a diagnosis of sarcoidosis generally requires demonstration of typical noncaseating granulomata on biopsy in the appropriate clinical setting and exclusion of other causes of granulomatous inflammation (Table 1). In addition, one may only be confident of the diagnosis at 3–6 months of follow-up when the clinical picture continues to evolve in a manner typical of sarcoidosis—close follow-up over the first year is essential to diagnose sarcoidosis.

Not all patients with suspected sarcoidosis require biopsy confirmation, and the risks and benefits of the procedure should be carefully considered. For example, in patients with classical Lofgren syndrome, the Heerfordt syndrome, or asymptomatic BHL, a clinical diagnosis may be reasonable given the high likelihood of self-limited disease and lack of benefit of biopsy to justify the risk (1). Erythema nodosum is a marker of acute disease and is diagnosed on the basis of its characteristic appearance; biopsy will show panniculitis and not granulomas and thus biopsy is not recommended. A

### Table 1. Organ Involvement in Sarcoidosis*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cases</th>
<th>At-Risk Group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/thoracic lymph nodes</td>
<td>95%</td>
<td>All studies</td>
<td>Most common finding in sarcoidosis</td>
</tr>
<tr>
<td>Skin (exclusive of erythema nodosum)</td>
<td>15%</td>
<td>African Americans/Women</td>
<td>Marker of chronic disease</td>
</tr>
<tr>
<td>Peripheral lymph nodes</td>
<td>15%</td>
<td>Not reported</td>
<td>Small, mobile, nontender; cervical (posterior triangle), inguinal, axillary</td>
</tr>
<tr>
<td>Eye</td>
<td>12%</td>
<td>African Americans/women</td>
<td>All patients merit ophthalmology review</td>
</tr>
<tr>
<td>Liver</td>
<td>11%</td>
<td>African Americans</td>
<td>Found on biopsy in 50%–80%; palpable &lt;20%; isolated elevated alanine transaminase levels usually not clinically significant</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>8%</td>
<td>Europeans, Puerto Ricans, women</td>
<td>Marker of acute disease</td>
</tr>
<tr>
<td>Spleen</td>
<td>7%</td>
<td>Not reported</td>
<td>Small, occasional pressure symptoms and cytopenia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5%</td>
<td>Not reported</td>
<td>VII nerve palsy; panhypopituitary–hypothalamic</td>
</tr>
<tr>
<td>Parotid/salivary</td>
<td>4%</td>
<td>Not reported</td>
<td>The Heerford syndrome; good prognosis</td>
</tr>
<tr>
<td>Calcium</td>
<td>4%</td>
<td>Whites, men</td>
<td>Vitamin D–dependent; urinary calcium levels elevated in 30% of cases</td>
</tr>
<tr>
<td>Ear, nose, throat</td>
<td>3%</td>
<td>Not reported</td>
<td>Marker of chronic disease</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2%</td>
<td>Japan</td>
<td>Subclinical; at risk for sudden death</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;1%</td>
<td>Not reported</td>
<td>Nephrolithiasis, interstitial nephritis</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>&lt;1%</td>
<td>Not reported</td>
<td>Bone cysts, excluding the Lofgren syndrome</td>
</tr>
</tbody>
</table>

*Data from reference 4.
Complication rates are very low. To rule out tuberculosis (14, 15), features can be sent to the laboratory for mediastinal lymph node biopsy using transbronchial needle aspiration with endobronchial ultrasound-guided biopsy of mediastinal lymph nodes. If these are not present, biopsy of intrathoracic lymph nodes or the lung is usually recommended (1).

Until recently, most pulmonologists favored transbronchial lung and endobronchial biopsy obtained via bronchoscopy, because this approach has a diagnostic yield of up to 90% in the setting of radiographic pulmonary infiltrates. In the absence of pulmonary infiltrates, however, the yield falls to 40% with a 10% risk for pneumothorax (13). Mediastinoscopy-guided biopsy of mediastinal lymph nodes has a diagnostic yield approaching 100% but is associated with higher morbidity, the risks of general anesthesia, and scarring. Recent studies support an approach to mediastinal and hilar lymph node biopsy using transbronchial needle aspiration with endobronchial ultrasonography (EBUS-TBNA), with a reported diagnostic sensitivity of 79%–94% for sarcoidosis, and cultures can be sent to the laboratory to rule out tuberculosis (14, 15). Complication rates are very low. In a prospective study of 62 patients with suspected stage I and II sarcoidosis, the yield and complications of EBUS-TBNA was compared with transbronchial lung biopsy (TBLB). Fifty-four patients were diagnosed with sarcoidosis. The diagnostic yield of EBUS-TBNA was 94% (stage I, 97%; stage II, 88%) and for TBLB was 37% (stage I, 31%, stage II, 50%). The difference was statistically significant (P < 0.001). One case of pneumothorax and 3 cases of moderate bleeding resulted from TBLB, and 1 case of severe cough resulted from EBUS-TBNA (14).

Other tests have been used to establish a diagnosis of sarcoidosis but are less specific. Bronchoalveolar lavage will often demonstrate lymphocytosis with an elevated CD4–CD8 ratio; a ratio greater than 3.5 is sometimes used as supportive evidence of sarcoidosis (16). However, fewer than half of patients with sarcoidosis have this degree of CD4 lymphocytosis in lavage samples (17).

Serum angiotensin-converting enzyme levels are elevated in 60% of patients with acute sarcoidosis and in 10% of patients with chronic disease (18). Although levels greater than 2 times the upper limit of normal are rarely seen in other diseases and are not seen in cancer or lymphoma, serum levels of these enzymes in isolation are neither specific nor sensitive for sarcoidosis and have no role in monitoring disease activity (1, 19).

A tuberculin skin test should be considered as part of the workup for newly diagnosed sarcoidosis. Because almost all patients with active sarcoidosis are anergic to purified protein derivative, a positive test suggests a diagnosis other than sarcoidosis (20).

Consensus recommendations include measurement of total immunoglobulin levels to assess for common variable immunodeficiency, because up to 10% of patients with this deficiency develop a sarcoid-like illness (1, 21). Common variable immunodeficiency should also be considered in any patient with sarcoidosis who presents with recurrent sinopulmonary infection.

In observational studies, gallium scans have a specific but insensitive pattern of lacrimal and parotid uptake (“panda sign”) and right paratracheal and hilar uptake (“lambda sign”) in sarcoidosis (22). Although this distinct finding has diagnostic potential, gallium scans are not recommended for routine use. A recent systematic review suggested that fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning is superior to gallium scanning in diagnosing sarcoidosis and may have a role in monitoring disease activity or finding sites for possible biopsy in atypical presentations (e.g., neurosarcoidosis) (23). Sarcoidosis is FDG-PET–avid and thus can mimic carcinoma or infection on scanning. Given the relative lack of specificity and cost of this investigation, it is unlikely to be recommended routinely in sarcoidosis.

**What imaging studies should be ordered in the evaluation of a patient with sarcoidosis?**

A chest x-ray is the only routine imaging recommended for suspected sarcoidosis because 90% of patients have intrathoracic disease, most often including hilar and mediastinal lymphadenopathy (in 75%) and pulmonary infiltrates (in 50%), typically with an upper lobe and nodular predominance (4) (Figure 2). The original Scadding staging system based entirely on chest x-ray findings correlates with prognosis in sarcoidosis (Table 2). Although there is little evidence that sarcoidosis progresses from stage to stage over time, it is clear that lung disease is more likely to resolve in earlier-stage disease (1).

Although thoracic computed-tomography (CT) and high-resolution CT are frequently ordered,
the findings are almost always evident on plain chest x-rays alone (24). Therefore, high-resolution CT is more useful in atypical cases and to differentiate sarcoidosis from other conditions (e.g., idiopathic pulmonary fibrosis). Current consensus statements from the American Thoracic Society, European Respiratory Society, and World Association of Sarcoidosis do not recommend routine use of CT scans (1).

Monitoring disease activity, progression, and response to treatment is difficult in sarcoidosis. Despite some evidence to support the utility of CT and PET scans, consensus statements do not recommend these methods for routine monitoring of patients with sarcoidosis.

Are pulmonary function tests useful in evaluating patients with sarcoidosis?

Results of pulmonary function tests are often normal, even in the setting of parenchymal lung disease in sarcoidosis (4). The most common abnormalities are a restrictive ventilatory defect with reduced FVC, reduced DLCO, or both. Airflow obstruction with FEV1/FVC < 70% is seen in approximately 16% of patients. Serial spirometry and measurement of DLCO can be useful in following response to therapy and disease progression.

What additional investigations should be ordered in a patient with suspected sarcoidosis?

Laboratory tests should be ordered for evaluation of involvement of other organs (see the Box) (1). In an observational study, anemia and leukopenia were seen in over 20% of patients with sarcoidosis (25). Liver involvement may be indicated by elevated alkaline phosphatase levels (most common), transaminase levels, or both; hyperbilirubinemia is a more ominous sign but is seen much less frequently (26). Hypercalcemia is seen in up to 10% and hypercalcuria in up to 30% of patients (27).

Cardiac involvement should be considered in patients with sarcoidosis. An electrocardiogram (EKG) is indicated in all patients, and if there are unexplained findings—in particular conduction abnormalities—further assessment is required. Because involvement is often patchy and limited, endomyocardial biopsy has poor sensitivity and significant risk. No one test definitely diagnoses cardiac sarcoidosis (28). Lack of consensus among experts in diagnosis and management is supported by a recent U.S. study (29). Concerns about cardiac disease should be referred to a cardiologist with an interest in sarcoidosis.

Unexplained neurologic symptoms or seizures should prompt evaluation for neuromyelitis optica. Biopsy is helpful but pursued in fewer than 20% of patients due to risk and low yield and because neurologic signs in a patient with sarcoidosis are probably neurosarcoid. In the setting of compatible neurologic symptoms, assessment should attempt to identify extraneural disease that may be amenable to biopsy before high-risk biopsy for neurologic disease is considered (30). A neurologist should be consulted to consider other potential diagnoses; the safety of biopsy; and other neurodiagnostic tests, such as lumbar puncture and gadolinium-enhanced MRI.

What other conditions should be considered in the differential diagnosis of sarcoidosis?

The differential diagnosis of sarcoidosis is broad and varies according to the population and the presenting clinical features (Table 1). While any systemic disease might be considered, the major considerations are infectious causes of granulomatous disease (e.g., tuberculosis and endemic fungal infections), lymphoma, and other types of cancer. Antineutrophil cytoplasmic antibody–associated vasculitis also can mimic sarcoidosis but is less common.

Asymptomatic symmetrical BHL is due to sarcoidosis in over 95% of cases. However, in populations at high risk for tuberculosis, mediastinal adenopathy (and less commonly hilar adenopathy) may also be due to tuberculosis, even in asymptomatic patients, and is often asymmetrical. Patients with cancer, including lymphoma, are virtually always symptomatic in the setting of mediastinal adenopathy. Similarly, although the Lofgren syndrome is characteristic of sarcoidosis, coccidiomycosis can present in an identical manner and should be suspected in endemic areas. Sarcoid-like parenchymal pulmonary infiltrates

<table>
<thead>
<tr>
<th>Table 2. The Scadding Staging System</th>
</tr>
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<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
</tr>
</tbody>
</table>

BHL = bihilar lymphadenopathy.

*Proportion of patients with spontaneous resolution of adenopathy and pulmonary infiltrates.
can be seen in tuberculosis, fungal infection, hypersensitivity pneumonia, and cancer. A high-resolution CT scan can be helpful in differentiating these diagnoses, but a biopsy is often required.

**When is consultation required?**

Because sarcoidosis is a diagnosis of exclusion, patients with suspected disease should be referred to a specialist, usually a pulmonologist, with experience in disease evaluation and diagnosis. Consultation with a cardiologist or neurologist with experience in sarcoidosis should be obtained in the setting of possible or confirmed cardiac or neurosarcoidosis to facilitate diagnosis and specific treatment. Newly diagnosed patients should be seen by an ophthalmologist. Uveitis and other ocular sarcoidosis can be asymptomatic, and if overlooked can result in glaucoma and blindness. Symptomatic eye disease is also best managed by an ophthalmologist with experience in sarcoidosis.

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**Figure 2.** Stages of sarcoidosis. 

A. Stage 1. The Lofgren syndrome. A 24-year-old man presented with 1 day of bilateral symmetrical ankle swelling and pain; he also noted dusky nodules on his shins. A chest x-ray revealed bilateral hilar and right paratracheal adenopathy. Note the convex shape of the enlarged hila (arrows). 

B. Stage 2 pulmonary sarcoidosis. A 38-year-old man with cough, showing bilateral perihilar nodular infiltrates and bilateral hilar fullness. 

C. The patient initially presented with stage 2 disease with nodular interstitial lung disease and hilar fullness as shown in the x-ray. He improved with prednisone therapy. Three months after stopping prednisone the presented with fatigue and dyspnea. The chest x-ray shows stage 3 sarcoidosis with recurrence of the infiltrates, although there is no adenopathy (D). 

E. Stage 4 sarcoidosis. A 58-year-old man with a 30-year history of sarcoidosis, showing upper lobe fibrosis and cyst formation. Note the metallic densities in the upper-left lung, representing previous coil embolization for hemoptysis associated with aspergillosis.

**Diagnosis...** Sarcoi'dosis is a diagnosis of exclusion. Even with typical biopsy findings, close follow-up over 6 months is required to be definitely confident of the correct diagnosis. All patients should have a chest x-ray and carefully selected tests aimed at detecting extrapulmonary involvement. Essential differential diagnostic considerations include cancer and infection, particularly lymphoma and tuberculosis. In the Lofgren syndrome and asymptomatic BHL, a clinical diagnosis is reasonable assuming the presentation is typical, no systemic immunosuppression is required or prescribed, and the subsequent clinical course is one of improvement and disease resolution. If biopsy is required, the most accessible and least invasive site should be chosen. If there are no peripheral lymph nodes or skin lesion, EBUS-TBNA, which can access intrathoracic lymph nodes, has less risk and similar yield to transbronchial biopsy and may be useful if local expertise is available.

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**CLINICAL BOTTOM LINE**

Treatment

Which patients with pulmonary sarcoidosis require treatment?

There are no evidence-based guidelines on timing or indications for starting therapy for pulmonary sarcoidosis. Many people with pulmonary sarcoidosis and mild symptoms do not require treatment, because the disease will either resolve spontaneously or remain stable in most patients. As such, whenever possible, systemic treatment should be withheld for 3–6 months in newly diagnosed sarcoidosis to determine whether the disease will spontaneously resolve. In the acute setting, EN or ankle arthralgias seen in the Löfgren syndrome should be managed with nonsteroidal anti-inflammatory medications rather than systemic steroids. Dry cough, which is common, or wheezing can be managed initially with inhaled corticosteroids (1).

Persistent or severe pulmonary symptoms (cough or dyspnea) or worsening pulmonary function should be treated. Treatment with oral corticosteroids usually results in improvement in chest x-ray findings as well as cough and dyspnea (1).

Treatment of asymptomatic patients with progression of pulmonary disease on chest imaging is controversial (31). Some experts advocate treatment to reduce progression to fibrosis, but the evidence to support this view is lacking. In a prospective randomized, controlled study, systemic steroids were associated with only a 10% improvement in FVC at 5 years, despite the risks of exposure to systemic steroids (32). Initiation of systemic steroids has been associated with a higher risk for recurrence and long-term steroid dependence (33–36). A lack of benefit from steroid therapy may be due to the presence of irreversible fibrotic disease, noncompliance, inadequate dose or duration of therapy, or intrinsic corticosteroid resistance. Treatment of established fibrotic lung disease is not warranted because fibrosis is irreversible. Evidence of such disease can be obtained from a CT scan of the chest, although a role for PET scans in identifying treatable pulmonary disease has been suggested (37).

Ongoing monitoring of pulmonary symptoms, imaging, and function may allow clinicians to provide early therapy for patients with chronic progressive disease and to avoid potentially toxic therapy in patients whose condition is likely to resolve spontaneously.

Which patients with extrapulmonary sarcoidosis require treatment?

Extrapulmonary sarcoidosis should be treated on an individual basis. Generally, disease involving critical organ function should be treated promptly. For example, active uveitis, cranial nerve abnormalities, pituitary or hypothalamic dysfunction, meningitis, and seizures or other manifestations of central nervous system involvement require prompt treatment, as does cardiac dysfunction or dysrhythmias caused by granulomas. Symptomatic hypercalcemia or interstitial nephritis from sarcoidosis usually warrants therapy, as do disfiguring facial lesions (1).

What is the role of nonsystemic steroids?

Data on the efficacy of inhaled corticosteroids for the treatment of pulmonary parenchymal sarcoidosis conflict (38–41). Two meta-analyses found no compelling evidence to support their use (42, 43). Thus, the role of inhaled corticosteroids in pulmonary parenchymal sarcoidosis is uncertain, and routine use in this context is not recommended. Inhaled corticosteroids are an adjunct for treating bronchospasm or cough associated with sarcoidosis (41).
Mild ophthalmologic disease may respond to topical steroids alone and avoid potentially toxic systemic therapy. Topical treatment for anterior uveitis should only be done by an ophthalmologist, as posterior or recalcitrant anterior disease may require systemic therapy. Topical or intrascleral steroids are effective in reducing the size and prominence of skin lesions. Consensus recommendations caution that potent fluorinated steroids should not be used on the face because they may lead to thinning of the skin and increased appearance of blood vessels (1). Intrascleral steroids may be effective in the treatment of rhino-nasal sarcoidosis (44).

**What is the role of systemic steroids for the treatment of pulmonary sarcoidosis?**

No treatments for sarcoidosis have been approved by the U.S. Food and Drug Administration, although immunomodulatory therapy is generally used and is effective. Systemic corticosteroid therapy should be considered first-line therapy to treat symptomatic or progressive pulmonary sarcoidosis. Oral prednisone (0.5-1 mg/kg lean body weight) is the cornerstone of therapy (45). Consensus recommendations are to begin oral prednisone at 20–40 mg/d or the equivalent on alternate days. Patients should be evaluated for response after 1–3 months (46). Therapy should continue for at least 1 year, with periodic attempts at tapering to the lowest effective dose. If there is no response, an alternative agent (methotrexate) should be added.

Corticosteroids for long-term treatment of sarcoidosis is controversial. Although some argue that steroids suppress the granulomatous inflammation that may lead to fibrosis and end organ damage, others opine that granulomatous inflammation is caused by an ineffective inflammatory response and that immunosuppressive treatment may be harmful (35, 36). Short-term improvements in pulmonary symptoms, radiographic findings, and pulmonary function occur with steroid treatment; however, randomized trials have not shown substantial long-term benefit in pulmonary function or reduced disability for sarcoidosis with pulmonary involvement (42); thus, most practitioners minimize patient exposure to steroids.

A meta-analysis of 13 studies found that oral corticosteroids were associated with improved chest x-rays, symptoms, and functional status but not lung function (41). There was also no convincing evidence of a disease-modifying effect. Debate about the role of steroids and the long-term course of disease continues (31, 42, 43). Fifty-four patients were randomly assigned to either continuous prednisolone therapy to achieve maximal radiographic clearing or therapy required by symptoms or deteriorating lung function. After 5 years of follow-up, FEV1 and FVC were significantly better in the long-term treatment group vs. patients treated selectively. These differences were small (95.9% predicted and 86.9% predicted for FEV1, respectively; 99.8% and 90.8% predicted for FVC, respectively). Grade of dyspnea did not differ significantly between the groups (32). Thus, corticosteroids may attenuate loss of lung function, even in asymptomatic patients, although the benefit was small in this study.

**When should nonsteroidal pharmacologic treatment be considered for pulmonary sarcoidosis?**

When prednisone is ineffective or has unacceptable side effects (e.g., massive weight gain, problematic diabetic control, elevated intraocular pressure, avascular necrosis of the hip), alternatives have been used to replace or augment the effects of prednisone. None has been compared with prednisone or to each other in a large randomized, controlled trial, but there is consensus that methotrexate or another immunosuppressant (azathioprine, mycophenolate mofetil) should be tried (1, 45, 47).

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An empirical 6-month trial of a cytotoxic agent (methotrexate or azathioprine) should be considered in patients who do not respond to an adequate trial of prednisone (up to 40 mg daily for 3 months) or who cannot tolerate glucocorticoids (48). Of the cytotoxic agents, methotrexate has been most intensively studied, but even this drug should be prescribed on a long-term basis only in patients manifesting objective and unequivocal improvement. Folic acid should be used with long-term methotrexate to reduce the incidence of myelosuppression. Consider the use of chloroquine or hydroxychloroquine, particularly for cutaneous or mucosal disease or for control of hypercalcemia, or for those who develop severe hyperglycemia on corticosteroids (1).

Recently, tumor necrosis factor inhibition with infliximab has been used to treat progressive sarcoidosis in persons resistant to steroids and cytotoxic medications or who experience intolerable side effects (47). However, whether this treatment is effective remains unclear.

In a phase 2 randomized, placebo-controlled trial of 138 patients with pulmonary sarcoidosis, treatment with infliximab (n = 93) for 24 weeks resulted in a 2.5% increase in FVC compared with no change in the placebo group; more severely affected patients seemed to have a more robust response. In another randomized, placebo-controlled trial, treatment of 13 patients with infliximab was associated with a nonsignificant 15% increase in FVC compared with 8 in 6 receiving placebo (49).

More toxic agents, such as cytoxan, chlorambucil, and cyclosporine, should be reserved for patients with severe progressive sarcoidosis refractory to steroids and less toxic immunosuppressive agents. Although not systematically studied, the need for continued immunosuppressive therapy should be evaluated every 1 to 2 years (45).

How long should pharmacologic therapy be continued in patients with pulmonary sarcoidosis?

Initial therapy with prednisone is usually continued for 9–12 months, with periodic attempts to taper to the lowest effective dose (1). Patients started on corticosteroids for pulmonary disease frequently require treatment for more than 2 years (50–52). Repeated relapse may indicate the need for lifelong treatment (50, 53)

How should extrapulmonary sarcoidosis be treated?

Systemic therapy with either corticosteroids or steroid-sparing agents should be used in patients with cardiac or neurologic disease and in those with skin or eye disease that has not responded to topical therapy (1). For myocardial sarcoidosis, the recommended dose is 40–60 mg/d for 1–3 months, tapering slowly to 10–15 mg/d for maintenance for many months or years. Steroid-sparing agents, such as methotrexate or azathioprine, may be considered, although randomized trials are lacking (54). An EKG, Holter monitoring, and echocardiograms may be helpful in assessing response to therapy. A role for follow-up myocardial imaging with MRI or PET is not yet clear.

Initial therapy for facial nerve palsy or other neurologic disorders is prednisone 40–60 mg a day, tapering slowly over many months or years. Randomized trials are lacking, although small retrospective case series have suggested that the addition of a second cytotoxic agent (methotrexate, azathioprine or cyclophosphamide, mycophenolate mofetil) may improve response rates in neurosarcoidosis (55, 56).

Posterior uveitis, lacrimal, and orbital sarcoidosis warrant treatment with systemic corticosteroids, particularly as posterior segment disease is more apt to be associated with central nervous system...
involvement (57). Intravenous methylprednisolone may be helpful when vision is threatened or is changing rapidly, although here, too, data are limited (31).

Hypercalciuria and hypercalcemia often respond to low-dose prednisone (20 mg/d tapering to lowest effective dose) or hydroxychloroquine (1).

**Which patients require life-long therapy?**

After tapering of oral corticosteroids, relapse occurs in up to 80% of patients, most often within 2 years (1). Although there are no randomized trials guiding practice, consensus suggests that patients with repeated relapse after prednisone tapering be treated life-long with low-dose prednisone (e.g., 10 mg/d or every other day) to help prevent relapse (31). Evidence for a similar effect using low-dose cytotoxic agents is lacking.

**What other pharmacologic therapies are available?**

Antimicrobial therapy may be required to treat the bronchiectasis resulting from chronic sarcoidosis. Antifungal therapy should be considered in patients with hemoptysis associated with aspergillosis, although surgical resection or embolization of the bronchial arteries may be required. Vitamin D, calcium supplementation, nasal calcitriol, and bisphosphonates may be required to prevent or reverse osteoporosis related to steroid therapy. If calcium and vitamin D are given to prevent glucocorticoid-induced bone loss, levels of serum calcium, urine calcium, and creatinine should be measured to monitor for hypercalcemia and hypercalciuria; levels of both 25-OH and 1,25-diOH vitamin D should also be followed (58).

Other pharmacologic therapies include nonsteroidal anti-inflammatory drugs to relieve musculoskeletal symptoms and pain associated with EN. Ketoconazole, 600–800 mg/d, may be considered for use in hypercalcemia (44). Therapy for pulmonary hypertension may improve functional status but has not been systematically studied and requires expert evaluation (59).

**What nonpharmacologic interventions should be considered?**

Patients with advanced lung disease are often physically deconditioned and have psychological complications of lung disease. Although not specifically studied in sarcoidosis, consider enrolling the patient in a rehabilitation program that includes exercise training, education on sarcoidosis lung disease, and psychosocial support. Education may also enhance adherence with therapy and improve emotional stability (60).

Treatment of hypoxemia at rest or with exercise as indicated by testing may be beneficial. Although not specifically studied in patients with sarcoidosis, it is assumed that the same hypoxemia level that applies to patients with COPD (i.e., a PaO₂ less than 55 mm Hg or SpO₂ less than 88% at rest or with exercise) is an indicator for oxygen therapy in patients with sarcoidosis. Vaccination for pneumococcal pneumonia and influenza are recommended, as with other lung diseases.

Sudden death in cardiac sarcoidosis may be related to cardiac arrhythmia. As a result, a pacemaker or implantable defibrillator may be required for treatment of dysrhythmia or heart block, although no large series have documented improved survival in patients with sarcoidosis who have implantable devices (54).

**Which patients should be referred for organ transplantation?**

Transplantation should be considered for patients with severe functional impairment, severe end organ damage including hypoxemic respiratory or heart failure, and those who experience progressive deterioration.
despite appropriate medical therapy (61, 62). The ideal time to refer a patient for lung transplantation remains relatively imprecise. Referral should occur before the patient’s condition has deteriorated to the point at which survival would be less than the anticipated time on a waiting list.

Pulmonary and cardiac complications are the primary cause of death in patients with sarcoidosis (63). In a prospective study of 479 patients followed over a 7-year period, those with total vital lung capacity greater than 1.5 L were unlikely to die of respiratory failure, whereas those with a vital capacity less than 1 L despite therapy had a 30% mortality rate (64). Patients with advanced sarcoidosis awaiting lung transplantation have a high mortality rate, with approximately 50% dying before transplantation. At 1 transplant center, 23 of 43 sarcoid patients died while waiting for a transplant; elevated right atrial pressure was the strongest predictor of death, although the effect of pretransplantation treatment of pulmonary hypertension on survival has not been assessed (65, 66).

How should patients with sarcoidosis be monitored?

Consensus recommendations include intensive longitudinal clinical surveillance of patients with sarcoidosis for at least 5 years after presentation, and as needed thereafter (Table 3) (1). Physicians should regularly review symptoms and repeat physical examinations, targeting signs and symptoms that frequently occur in sarcoidosis (e.g., those that affect the pulmonary system, eyes, and skin) and consider repeated chest x-ray and spirometry.

### Table 3. Follow-up for Patients With Sarcoidosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Issue</th>
<th>How?</th>
<th>How Often?</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>Organ involvement</td>
<td>Detailed review of systems and examination</td>
<td>Initially every 3–6 months, and then yearly in follow-up if stable; more often as indicated</td>
<td>Detection of organ system involvement (pulmonary, ocular, dermatologic, cardiac, neurologic)</td>
</tr>
<tr>
<td></td>
<td>Eye examination by ophthalmologist</td>
<td>Pulmonary function tests</td>
<td>Detection and recommended by specialist</td>
<td>Detection and treatment of ocular involve-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spirometry every 6–12 months; more frequently if patient is symptomatic from lung disease</td>
<td>ment, which may be asymptomatic</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>Response to therapy; prognosis</td>
<td>Chest x-ray</td>
<td>If clinical deterioration occurs to assess progression of disease or to identify superimposed infection or cancer</td>
<td>Repeated oximetry is helpful in adjusting oxygen therapy; prescribe supplemental oxygen to keep SpO₂ above 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRCT</td>
<td>Only as needed</td>
<td>Spirometry is the simplest way to follow; obtain lung volumes, DLCO, and oximetry (rest and exercise SpO₂) as indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver function tests, CBC, calcium, creatinine, vitamin D</td>
<td>Initial evaluation, at least yearly for first 5 years, then as needed</td>
<td>Significant changes include ≥10% change in FVC or DLCO and decreased oxygen saturation to &lt;90% at rest or with exercise</td>
</tr>
<tr>
<td></td>
<td>EKG; Holter monitor</td>
<td></td>
<td>Initially, then yearly or as indicated by symptoms or examination</td>
<td>Detection of arrhythmia or heart block, especially in patients with cardiac symptoms (palpitations, syncope)</td>
</tr>
</tbody>
</table>

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ABG = arterial blood gas; CBC = complete blood count; EKG = electrocardiogram; HRCT = high-resolution computed tomography; LFTs = liver function tests; WBC = white blood cell.
In patients with neurologic disease, symptoms and examinations should be regularly assessed, with imaging reviewed at strategic intervals as recommended by specialty care. In cardiac sarcoidosis, periodic review of echocardiograms and EKGs should augment history and physical examination. Intervals for review of cardiac imaging (MRI or PET) have not been established, nor have intervals for follow-up MRI scanning in neurosarcoidosis.

Patients with no symptoms may be seen every 3 months for the first year and then at least every 6 months thereafter. Patients who require systemic therapy should be seen more frequently. Patients should be monitored for at least 5 years after therapy is discontinued because of the high rate of relapse in patients who require therapy. Patients with persistent abnormalities on chest x-rays or quiescent neurologic, cardiac, or ocular sarcoidosis should be monitored on an annual basis. Long-term follow-up with appropriate specialists in patients with progressive pulmonary disease or those with extrapulmonary involvement is suggested.

**When should patients with sarcoidosis be hospitalized?**

Patients with sarcoidosis generally require admission in the setting of severe or life-threatening disease. This may include respiratory failure, which is usually seen in advanced fibrotic lung disease, cardiac failure or dysrhythmia, symptomatic hypercalcemia, new or progressive neurologic disease, acute vision loss, or acute renal failure. Neurologic symptoms pertaining to the hypothalamic–pituitary axis, such as diabetes insipidus or hypothermia, require urgent assessment. In a patient with known sarcoidosis, onset of cardiac symptoms—syncope in particular—requires urgent hospital referral to rule out cardiac sarcoidosis and to assess for risk for sudden cardiac death due to granuloma formation in the conducting cardiac channels or arrhythmia.

**Treatment side effects also merit consideration for hospitalization.** Corticosteroids can induce hyperglycemia and cause acute osteonecrosis, usually manifesting as severe pain in the hip joint. Osteoporotic fractures are also a risk. Methotrexate and other immunosuppressive drugs are associated with cytopenia and risk for neutropenia and opportunistic infection. Anti–tumor necrosis factor therapy significantly increases the risk for tuberculosis. Thus, fever or infectious symptoms in a patient receiving immunosuppressive treatment may require urgent referral.

**What is the prognosis of patients with sarcoidosis?**

Definitive data to assess prognosis are lacking, and guidance regarding the likely outcome is based largely on expert consensus (1). At least a third of patients never require systemic therapy. After 2–5 years, the disease will have resolved in 50% or more of patients; 25% will have fibrosis in 1 or more areas that may cause symptoms but remains stable without progression. Only 25% of patients have chronic progressive disease. Some predictors of a good prognosis include the presence of EN, stage 1 chest radiographic findings, and an asymptomatic presentation. Predictors of chronic disease or a poor prognosis include the presence of lupus pernio; cardiac, neurologic, or bone involvement; or kidney stones (1).

Approximately 5% of patients with sarcoidosis will die of the disease, most commonly due to pulmonary or cardiac impairment (63). Death from sarcoidosis seems to be increasing in the United States (68)—African American women are particularly affected. The reason for this, despite increased recognition and treatment of the complications of pulmonary and cardiac sarcoidosis, is not known.

**CLINICAL BOTTOM LINE**

Not all patients require treatment for pulmonary sarcoidosis. Observe new cases if possible for 3–6 months before therapy because spontaneous remission can occur. Mild skin or eye disease may be treated with topical corticosteroids. Symptomatic neurologic, cardiac, or eye sarcoidosis or symptomatic hypercalcemia should be treated promptly. When systemic therapy for pulmonary sarcoidosis is warranted, prednisone is first-line therapy. Initial therapy should last for 9–12 months followed by tapering and eventually discontinuing the prednisone. Higher doses (40–60 mg/d or high-dose intravenous) are often used for cardiac or neurologic sarcoidosis, but controlled trials are lacking. High doses of prednisone and “burst” steroids for short periods should be avoided. When disease is resistant to prednisone or unacceptable toxicity is encountered, alternative agents can be used. Oral methotrexate is preferred as the most common alternative. Concurrent use of folic acid may reduce the incidence of methotrexate side effects. If disease progresses or side effects occur, consider infliximab.


What education do patients with sarcoidosis require?
In addition to prognostic information, patients should be educated about organ involvement in sarcoidosis other than lung (e.g., skin, eye) and the symptoms to be alert for. Education on the risks and side effects of treatment should be provided, as well as measures to counteract toxicity of medications.

In the Clinic

Patient Education

What do professional organizations recommend for the care of patients with sarcoidosis?
A consensus statement from the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders was last issued in 1999 and provides guidance regarding evaluation, treatment, and monitoring of patients with sarcoidosis (1). An updated version of these recommendations is pending.

Practice Improvement

Are there performance measures for the care of patients with sarcoidosis?
There are no specific Centers for Medicare & Medicaid Services performance measures with regard to care of patients with sarcoidosis. There are several pulmonary-related measures that may be relevant, such as vaccination rates against influenza and pneumococcus. (https://www.cms.gov/PQRS/Downloads/2010_PQRI_MeasuresList_111309.pdf).

In the Clinic Tool Kit

Sarcoidosis

PIER Module
http://pier.acponline.org/physicians/diseases/d459/d459.html
Access the PIER module on sarcoidosis from the American College of Physicians. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Information
http://pier.acponline.org/physicians/diseases/d459/d459-pi.html
Patient information that appears on the next page for duplication and distribution to patients.

www.nlm.nih.gov/medlineplus/sarcoidosis.html

Resources related to sarcoidosis from the National Institutes of Health’s MedlinePLUS, including an interactive tutorial in English and Spanish.

www.ninds.nih.gov/disorders/neurosarcoidosis/neurosarcoidosis.htm
Information on neurosarcoidosis from the National Institute of Neurological Disorders and Stroke.

Clinical Guidelines
www.ishlt.org/publications/guidelines.asp
Guidelines for the selection of lung transplant candidates from the International Society for Heart and Lung Transplantation, updated in 2006.

www.bmj.com/content/339/bmj.i3206?view=long&pmid=19717499

Diagnostic Tests and Criteria
http://radiopaedia.org/articles/chest-radiograph-classification-of-pulmonary-sarcoidosis
Staging system for sarcoidosis based on chest x-ray at presentation.
http://pier.acponline.org/physicians/diseases/d459/tables/d459-1lab.html
List of laboratory and other studies for sarcoidosis, from PIER.
THINGS YOU SHOULD KNOW ABOUT SARCOIDOSIS

What is sarcoidosis?
• A disease causing small patches of inflamed cells (granulomas) to form, usually in the lungs but sometimes in other parts of the body.
• The cause is unknown.

Who gets it?
• Risk for sarcoidosis may be higher if a close family member has it.
• It tends to affect young adults between 20 and 40 years of age.
• African Americans and northern European whites are at higher risk.
• Sarcoidosis is not contagious.

What are the signs and symptoms?
• Fatigue, weight loss, and unexplained fever.
• Dry cough, mild chest pain, and shortness of breath.
• Red, sore eyes.
• Scaly rash or red bumps on skin.
• Sore, swollen muscles and abnormal heart rhythms.
• Changes in memory or mental sharpness.

How is it diagnosed?
• Your doctor will perform a careful physical examination and ask questions about your symptoms and family medical history.
• A chest x-ray may show scarring or granulomas in the lungs.
• Breathing tests may show restricted breathing capacity.
• Tests may include blood or urine testing, computed tomography (CT scan), electrocardiogram (EKG), an eye examination, and skin biopsy or tissue sampling.

How is it treated?
• Sarcoidosis often occurs for only a short time and heals without treatment.
• Corticosteroids, such as prednisone, are commonly prescribed if treatment is needed.
• A pulmonary rehabilitation program can help reduce symptoms.
• If sarcoidosis is severe, you may need to be hospitalized until your condition is stabilized.
• In rare cases, sarcoidosis damage is severe enough that lung transplantation or a pacemaker or implantable defibrillator is needed.

For More Information

www.lungusa.org/lung-disease/sarcoidosis/
Information on sarcoidosis from the American Lung Association.

www.stopsarcoidosis.org/
www.stopsarcoidosis.org/patientresources/doctor.htm
Information on sarcoidosis, including advice on talking to your doctor, from the Foundation for Sarcoidosis Research.

www.nhlbi.nih.gov/health/topics/topics/sarc/
www.nhlbi.nih.gov/health-spanish/health-topics/temas/sarc/
Patient handout titled “What is sarcoidosis?” from the National Heart, Lung, and Blood Institute, in English and Spanish.
1. A 28-year-old man is evaluated for an abnormal chest x-ray done for chronic intermittent nonproductive cough of 6 months' duration. The radiograph showed bilateral hilar lymphadenopathy and normal lung parenchyma. The patient has fatigue and intermittent mild central chest discomfort when he coughs. He has not had weight loss, fever, night sweats, or recent respiratory illness. Vital signs and cardiopulmonary examination are normal. There is no cervical or axillary lymphadenopathy and no skin findings. Laboratory studies show normal electrolytes and normal complete blood count with differential; serum calcium is 10.8 mg/dL (2.63 mmol/L). Chest CT scan with contrast shows bilateral hilar and mediastinal lymphadenopathy along with bilateral small lung nodules with a perihilar distribution. Which of the following is the most appropriate next diagnostic test for this patient?
A. Bone marrow biopsy
B. Bronchoscopy with mediastinal lymph node and lung biopsy
C. Mediastinoscopy
D. Serum Histoplasma antibody testing

2. A 57-year-old man with sarcoidosis is evaluated for a 4-week history of progressive dyspnea. He also has fatigue, ankle swelling, lower extremity aching, and lack of appetite. The sarcoidosis was diagnosed 7 years ago. The disease has slowly progressed despite therapy. He has no other medical disorders. His medications are methotrexate, 15 mg weekly; prednisone, 20 mg/d; folic acid; and trimethoprim-sulfamethoxazole.

On physical examination, he is afibrile; blood pressure is 104/86 mm Hg, pulse rate is 110/min, and respiration rate is 28/min. Oxygen saturation is 90% with the patient breathing oxygen, 3 L/min by nasal cannula. Cardiac examination reveals a loud P2, and fixed splitting of S2; jugular venous distention is present. The chest is clear to auscultation. There is pitting edema at both ankles to the mid-shin. Chest radiograph shows bilateral hilar lymphadenopathy and normal lung parenchyma. The patient has fatigue and intermittent mild central chest discomfort when he coughs. He has not had weight loss, fever, night sweats, or recent respiratory illness.

CME Questions

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A. Bone marrow biopsy
B. Bronchoscopy with mediastinal lymph node and lung biopsy
C. Mediastinoscopy
D. Serum Histoplasma antibody testing

3. A 45-year-old black woman is evaluated for a 2-month history of fatigue, nonproductive cough, decreased appetite, intermittent fever, right-upper-quadrant abdominal pain, and a 4.5-kg (10.0-lb) weight loss. On physical examination, temperature is 37.8°C (100.0°F), blood pressure is 104/68 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. BMI is 28. There are several erythematous 5- to 10-mm maculopapular lesions on the forehead. Cardiopulmonary examination is normal. Abdominal examination reveals hepatomegaly. There is bilateral inguinal lymphadenopathy. There is no edema. Results of laboratory tests are as follows: hemoglobin, 12.2 g/dL (122 g/L); albumin, 4.0 g/dL (40 g/L); phosphorus, 4.0 mg/dL (1.3 mmol/L); calcium, 11.2 mg/dL (2.8 mmol/L); serum creatinine, 2.0 mg/dL (176.8 µmol/L); protein-creatinine ratio, 0.914 mg/mg; urinalysis, 1+ protein; 20 leukocytes/hpf; occasional leukocyte casts; urine protein-creatinine ratio, 0.914 mg/mg.

Tuberculin skin testing is negative. Urine culture is negative. Chest radiograph shows bilateral hilar lymphadenopathy. On ultrasonography, the right kidney is 13.7 cm and the left kidney is 15.4 cm. There is no hydronephrosis, and no kidney calculi are seen. Which of the following is the most likely diagnosis?
A. Amyloidosis
B. Sarcoidosis
C. The Sjögren syndrome
D. Systemic lupus erythematosus

4. A 21-year-old man is evaluated for a 5-day history of pain and swelling in the right ankle. Seven days ago, he developed a nodule on the left leg. He has no history of trauma to either of these sites. He is otherwise asymptomatic. On physical examination, vital signs are normal. The right ankle is warm and swollen, and range of motion elicits pain. He also has a warm, firm, 2-cm erythematous nodule over the anterior left lower extremity that is tender to palpation and has been present for 7 days. The remainder of the physical examination is normal.

A plain x-ray of the right ankle is normal. Arthrocentesis of the right ankle is performed, and synovial fluid analysis reveals a leukocyte count of 3000/µL (80% lymphocytes, 12% macrophages). There are no crystals.

Which of the following is the most likely diagnosis?
A. Bacterial arthritis
B. Crystal-induced arthritis
C. Osteoarthritis
D. Sarcoidosis

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.