Sarcoidosis
Sterling G. West

Key Points
- Sarcoidosis is a systemic inflammatory disorder of unknown cause characterized by noncaseating, granulomatous inflammation that can affect virtually any organ.
- Acute and chronic forms of inflammatory arthritis particularly involve the ankles and knees.
- Cystic bone lesions may produce dactylitis or rarely involve the skull, vertebrae, ribs, or pelvis.
- Muscle involvement is usually asymptomatic but may cause acute or chronic myopathies or nodular masses.
- Nonmusculoskeletal features are common and include bilateral hilar adenopathy, pulmonary infiltrates, uveitis, cardiac and neurologic involvement, and skin lesions such as erythema nodosum and lupus pernio.

HISTORY
Sarcoidosis derives from the Greek sarco, meaning “flesh,” eidos, meaning “like,” and sis, meaning “condition.” In 1877, Jonathan Hutchinson published the first case seen at King’s College Hospital in London. Later, Caesar Boeck advanced the description of sarcoidosis by emphasizing the granulomatous inflammation characteristic of this disease. He was the first to use the term sarboïd (sarcoid) because he thought the lesions resembled scarcoma but were benign. In 1953, Sven Löfgren published the acute sarcoidosis syndrome of bilateral hilar adenopathy and erythema nodosum, frequently associated with arthritis, fever, and uveitis. Over the past century, sarcoidosis has become recognized as a multisystem granulomatous disorder with protein manifestations that may affect any organ.1,2

EPIDEMIOLOGY
Sarcoidosis occurs worldwide.4 It has been reported in all races and ethnic groups but with marked variations. Prevalence estimates using mass chest radiographic screening range from 0.2 in 100,000 (Portugal) to 64 in 100,000 (Sweden). In the United States, the age-adjusted annual incidence rates are three times higher for blacks (35.5 in 100,000) than for whites (10.9 in 100,000) and for U.S. whites of 0.85%. In most series, sarcoidosis affects women slightly more than men (1.5 to 2:1 sex ratio). People of all ages can be affected, but it particularly occurs in young adults 20 to 40 years of age (>70% of cases) with possibly a second peak in women after age 50 years. Disease onset occurs approximately 10 years earlier in black than white patients.

Clinical evidence indicates that the presentation and severity of sarcoidosis vary according to race and ethnicity. Whites are more likely to have erythema nodosum, have less extrapulmonary involvement, and have lower age-adjusted mortality than other racial groups. The Japanese have more cardiac and ocular involvement, and blacks have the most severe disease with higher mortality rates.

CLINICAL FEATURES
Sarcoidosis is a systemic inflammatory disorder. The clinical manifestations are diverse, ranging from an abnormal chest radiograph found incidentally in an otherwise asymptomatic individual (5% of cases) to severe multorgan involvement.2,3 Although sarcoidosis most commonly involves the lung, up to 30% of patients present with extrapulmonary sarcoid as their initial manifestation. Because there is no specific test for sarcoidosis, the diagnosis is established when well-recognized clinical and radiographic findings are supported by histologic evidence of widespread noncaseating epithelioid granulomas in more than one organ system. Other granulomatous diseases must be excluded. The presenting manifestations and cumulative organ involvement in patients with sarcoidosis are shown in Table 175.1. The ACCESS (A Case Control Etiologic Study of Sarcoidosis) trial evaluating 736 patients with sarcoidosis confirmed that during the course of their follow-up, 95% of patients had thoracic involvement, 50% had extrathoracic involvement, and only 2% had isolated extrathoracic sarcoidosis. Notably, there were significant differences in clinical findings and prognosis among groups on the basis of race, sex, and age.5

RESPIRATORY TRACT INVOLVEMENT
Respiratory tract involvement is the most common visceral manifestation (90%–95% of cases), and any part from the upper respiratory tract to lungs can be involved.3,7 The clinical spectrum ranges from asymptomatic hilar adenopathy (20%–50%) to parenchymal lung disease with granulomatous infiltration or fibrosis. Pleural effusions are rare (<5% of cases). Endobronchial involvement is found on biopsy in 50% and may lead to airway stenosis (10%) and wheezing, which may be confused with asthma. Symptoms of lung disease include dry cough (30%), dyspnea (28%), and chest pain (13%). Hemoptysis is rare and occurs primarily in patients with fibrosis and cavitation filled with aspergillomas. Lung cracksles are heard in only 20%, and clubbing is rare. Pulmonary hypertension occurs in 5% to 15% of all patients and in 50% of patients with dyspnea.

Chest radiographs show abnormal findings in more than 90% of patients and are classified using the modified Scadding staging system:■ Stage 0, normal chest radiograph (5%–10% of patients at presentation)■ Stage I, bilateral hilar adenopathy (45%–65%) (Fig. 175.1)■ Stage II, adenopathy with nonfibrotic pulmonary infiltrates (30%–40%)■ Stage III, nonfibrotic pulmonary infiltrates only (10%–15%)■ Stage IV, end-stage pulmonary fibrosis (5%)Notably, the stages are not chronologic and do not indicate disease chronicity or correlate well with changes in pulmonary function. Hilar adenopathy is noted in 50% to 85% of patients; in the majority of patients, hilar node enlargement is bilateral. Parenchymal changes occur in 25% to 60% of cases, have a mid-to-upper-zone predominance, and typically are located in perilymphatic areas and along the bronchovascular bundles. High-resolution computed tomography (HRCT) is more sensitive than chest radiography and may show mediastinal node involvement or unexpected parenchymal disease (or both) in patients with normal chest radiographic findings. Up to 20% with stage I and 40% to 70% with stage II and III disease on chest radiographs have abnormal pulmonary function tests (PFTs) at presentation. PFTs typically show a restrictive pattern, with a reduction in vital capacity, residual volume, and total lung capacity.1,7 The loss of diffusing capacity is the most common abnormality. Bronchial hyperreactivity can be seen. Fixed obstructive airway disease also occurs in 50% of patients caused by obstruction of large and small airways from endobronchial granulomas or bronchiolitis and is a poor prognostic sign, suggesting extensive and progressive disease.

The characteristic bronchoalveolar lavage (BAL) fluid cell differential shows greater than 30% to 60% lymphocytes. There is a normal percentage of eosinophils and neutrophils and an absence of plasma cells. A CD4/CD8 T-cell ratio greater than 3.5 (94% specific, 52% sensitive) is supportive of a diagnosis of sarcoidosis. The CD4+ T cells are activated with an effector memory phenotype (CD45RO). Notably, the number of cells exhibiting cytotoxic activity (CD8+ T cells, natural killer [NK] cells, and NK T cells) increases progressively between Scadding stages I and IV. The diagnostic yield of an adequate transbronchial biopsy is 40% with normal and more than 90% with abnormal chest radiographic findings. Endoscopic (bronchial, esophageal) ultrasound-guided fine needle aspiration of hilar/mediastinal adenopathic lesions has a diagnostic yield of 80% to 93%.

Patients with good prognostic signs (Scadding stages 0 and I, Löfgren syndrome, asymptomatic stages II and III disease) should be observed for 3 to 6 months before starting therapy. During the first 2 to 3 years, repeat chest radiographs and PFTs should be performed every 3 to 6 months in patients with symptoms or radiographic abnormalities to monitor for progression. For the 10% to 30% of patients who develop symptomatic and progressive stages II and III lung disease (a decrease in total lung capacity of ≥10%, a
Acute anterior uveitis is the most common presentation, manifested by blurred slit-lamp and funduscopic eye examination with repeat examinations annually occurring at any time during the disease course. Because the disease may be clinical manifestation. It can be the initial manifestation (5% of cases) or Eye involvement occurs in up to 25% of patients and can be the major OPHTHALMOLOGIC INVOLVEMENT in the allograft has been observed in 50%.

More than 70% of patients respond favorably, but relapses occur in 25% to 50% after tapering or discontinuation of corticosteroids, so patients need to be monitored closely. Some patients need 10 to 20 mg/day or every other day indefinitely to prevent relapses. Steroid-sparing agents include methotrexate (15 mg/wk), mycophenolate mofetil (1–1.5 mg/kg/day), azathioprine (2 mg/kg/day), or anti–tumor necrosis factor (anti-TNF) biologics (infliximab 3–5 mg/kg every 1–2 months intravenously) or rituximab (two doses of 1000 mg given 2 weeks apart). Pulmonary hypertension may respond to sildenafil, bosentan, or epoprostenol. In patients in whom therapy fails and who develop end-stage pulmonary fibrotic disease, lung transplantation offers a potential cure, although asymptomatic recurrence of sarcoidosis in the allograft has been observed in 50%.

**OPHTHALMOLOGIC INVOLVEMENT**

Eye involvement occurs in up to 25% of patients and can be the major clinical manifestation. It can be the initial manifestation (5% of cases) or occur at any time during the disease course. Because the disease may be asymptomatic (33%), all patients with sarcoidosis should have a baseline slit-lamp and funduscopic eye examination with repeat examinations annually or with development of symptoms. Any area of the eye may be involved. Acute anterior uveitis is the most common presentation, manifested by blurred vision, eye redness, photophobia, pain, and “mutton fat” keratic precipitates on slit-lamp examination. Involvement is usually bilateral, which distinguishes it from the unilateral uveitis seen in human leukocyte antigen B27 (HLA-B27)–associated spondyloarthritis. Other ophthalmologic manifestations include interstitial keratitis, posterior uveitis or venulitis, pars planitis (“snowballs” or “string of pearls” on slit-lamp examination), scleral plaques, lacrimal gland enlargement (15%–28%) with dry eyes, optic neuropathy, corneal or conjunctival nodules, and extraocular muscle involvement. Approximately 20% of patients with uveitis experience some visual loss. Eye manifestations are treated with topical, injectable, and systemic corticosteroids. Topical corticosteroids and cycloplegics are usually sufficient for anterior uveitis, although granulomatous involvement of ocular structures and posterior segment inflammation require oral corticosteroid or periocular steroid injections. Azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, leflunomide, infliximab, adalimumab, and rituximab have all been effective for treatment of corticosteroid-refractory disease.

**CUTANEOUS INVOLVEMENT**

Skin involvement occurs in up to 30% of cases and can be divided into specific and nonspecific categories. Specific lesions demonstrate granulomatous inflammation on biopsy. The most common specific skin manifestation is hyperpigmented (red-brown or yellow-brown) maculopapular lesions (2–5 mm) commonly located on the face, nape of the neck, upper back, and at sites of skin trauma (scars, tattoos, skin piercings). Other specific lesions include skin plaques and annular lesions, which are associated with chronic disease and a poor prognosis when they occur on the head and neck. Subcutaneous Darier-Roussy sarcoidosis presents as nodules deep in the dermis and subcutaneous tissue and can remit spontaneously. Lupus pernio has a predilection for black and Puerto Rican women and is the most characteristic specific skin manifestation of sarcoidosis (Fig. 175.2). Lesions are indurated and violaceous, occurring primarily on the nose, cheeks, ears, lips, and fingers. They tend to be slowly progressive and can be disfiguring. Lupus pernio has a significant association with chronic upper respiratory tract involvement, pulmonary fibrosis, and bony lesions of the phalanges. Conversely, nonspecific skin lesions are inflammatory but do not demonstrate granulomas on histologic examination. Erythema nodosum is the most common nonspecific skin manifestation, occurring in 10% of patients with sarcoidosis. It is seen more commonly in young white women and usually is associated with an acute presentation and benign course. A variety of atypical lesions also may be seen. In general, chronic sarcoid skin lesions do not ulcerate, itch, or cause pain. Topical corticosteroids and monthly intralesional injections of triamcinolone are often effective therapy for small sarcoid papules or plaques. Larger, disfiguring skin lesions require systemic...
corticosteroid therapy, antimalarials (chloroquine and hydroxychloroquine; overall response rate of 35%), methotrexate, and/or infliximab. Thalidomide, pentoxifylline, apremilast, minocycline, psoralsen and ultraviolet A phototherapy, and retinoids have been anecdotally successful in a few patients with refractory sarcoid skin lesions.13,14

CARDIAC INVOLVEMENT
Symptomatic cardiac involvement occurs in 5% of patients with sarcoidosis, but cardiac lesions are considerably more common at autopsy (20% [United States] to 67% [Japan]).11,13 It is more common in patients with severe disease, frequently coexists with neurosarcoidosis, and causes 50% of deaths from sarcoidosis. Sarcoidosis may affect any part of the heart except the valves. The most common manifestations include conduction disturbances of all types, ventricular arrhythmias, and infiltrative cardiomyopathy with congestive heart failure. Papillary muscle involvement causing valvular dysfunction, atrial arrhythmias, pericarditis, and cor pulmonale due to severe restrictive lung disease occur less commonly. Sudden death caused by heart block or ventricular arrhythmias is the most feared complication. Therefore, all patients with sarcoidosis should be asked about cardiac symptoms (chest pain, orthopnea, palpitations, syncope [near-syncope]) at each visit and should have a baseline electrocardiogram (ECG) that is repeated annually or with development of symptoms. ECG abnormalities occur in more than 50% of patients with cardiac involvement. Twenty-four-hour Holter monitoring and exercise ECG should be performed in all patients with arrhythmias, conduction disturbances, or palpitations. In those with conduction blocks or arrhythmias, electrophysiologic studies are needed as part of a risk assessment for sudden cardiac death. Two-dimensional and M-mode echocardiography is performed in all patients with cardiac symptoms or an abnormal ECG finding. In patients with cardiac sarcoidosis, it may show granulomatous inflammation in the myocardium (hyperechogenicity of the ventricular septum), left ventricular hypertrophy and dyskinesis, restrictive cardiomyopathy, valvular incompetence caused by papillary muscle dysfunction, and asymptomatic pericardial effusions (20% of patients). Cardiac magnetic resonance imaging (MRI) with gadolinium enhancement and fasting cardiac positron emission tomography (FDG-PET) are important modalities with high sensitivity (89%–100%) and specificity (78%) used in the assessment of patients with cardiac sarcoidosis suspected by screening tests.12 Because of less radiation exposure and cost, cardiac MRI is usually done instead of FDG-PET unless there is a contraindication to MRI (renal insufficiency, pacemaker). Endomyocardial biopsy is rarely necessary, and results are often negative (80%) because cardiac sarcoid lesions tend to be heterogeneous and may have a predilection for the left ventricular free wall. If needed, cardiac MRI can better identify sites for biopsy. Symptomatic cardiac sarcoidosis must be treated early and aggressively. Heart failure and sudden cardiac death caused by conduction block or ventricular arrhythmias account for 75% of deaths from cardiac sarcoidosis. Therefore, treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies. Treatment with high-dose prednisone (>60 mg/day) should be initiated in patients with ventricular arrhythmias or cardiomyopathy. Antiarrhythmic agents and medication used as adjunctive therapies.

NERVOUS SYSTEM INVOLVEMENT
Symptomatic involvement of the central or peripheral nervous system occurs in approximately 5% to 13% of patients, although signs of such involvement are three times more common at autopsy.13,14 Up to 33% of patients who develop neurosarcoidosis have neurologic manifestations either preceding the disease or at the time sarcoidosis is first diagnosed. Neurosarcoidosis has a predilection for the base of the brain and can occur without pulmonary or systemic features of sarcoidosis (10% of cases). Cranial nerve (CN) palsy, most frequently of the seventh or second CN (or both), is the most common presentation (50% of cases with up to 33% bilateral and 10% multiple CN). Heerfordt syndrome is the combination of fever, parotid enlargement, arthritis, uveitis, and facial palsy. It occurs most commonly in men and usually has a poor prognosis. Other features of neurosarcoidosis include leptomeningeval involvement (20%–40%), other cranial neuropathies, hypothalamic and pituitary lesions, localized mass lesion, myelopathy (<10%), seizures, and psychiatric and cognitive dysfunction, as well as other less common manifestations. Peripheral neuropathy documented by electromyography and nerve conduction studies occurs in 15% to 20% of patients with neurosarcoidosis. Chronic sensorimotor polyneuropathy is the most common presentation, although mononeuritis multiplex, pure sensory neuropathy, intercostal neuritis, small-fiber neuropathy (sensory, autonomic), and acute Guillain-Barré syndrome may occur.

MUSCULOSKELETAL INVOLVEMENT
Overall 4% to 38% of patients with sarcoidosis have at least one musculoskeletal manifestation, including arthritis or periarteritis, bony lesions, or muscle disease. Joints Arthralgias are considerably more common (70%) than arthritis (≤25%). Arthritic involvement is generally divided into acute and chronic types. The most common form of joint involvement is an acute polyarthropathy and periarteritis. This type of arthritis may be migratory, resembling rheumatic fever; in therapy, it may mimic in cardiac sarcoidosis. Uncontrolled reports have suggested that antimarial agents, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide (oral and monthly pulse), cyclosporine, infliximab, rituximab, and cranial irradiation may be effective.14 Intravenous gammaglobulin and neuroleptic medications are effective for small fiber neuropathy. Surgical intervention is necessary for hydrocephalus and mass lesions that are expanding or causing increased intracranial pressure. Bone marrow aspiration and bone biopsy are occasionally indicated to rule out synchronous malignancy. Ultimately, the reaction of sarcoidosis, most patients are maintained on low-dose prednisone and an immunosuppressive medrock for life.

Chronic sarcoid arthritis without involvement of adjacent bone is most likely to occur in black patients (Fig. 175.4).13,14 This type of joint involvement
Sarcoidosis

contrast to acute sarcoid arthritis, synovial biopsy specimens in chronic sarcoid arthropathy characteristically show granulomatous inflammation. Tenosynovitis of the wrist, ankle, patella, or Achilles tendons can also occur (5%–13% of cases). For chronic synovitis, low-dose corticosteroids (prednisone 10–15 mg/day) may be helpful if NSAIDs and colchicine fail. Chloroquine, hydroxychloroquine (400 mg/day), azathioprine, leflunomide, methotrexate, infliximab, adalimumab, rituximab, and arthroscopic synovectomy have been used successfully in patients with severe musculoskeletal manifestations refractory to corticosteroids.3,16-19

Bone

The frequency of bone involvement on plain radiographs ranges from 3% to 13%. Bone changes may be present at disease onset but are more frequently seen in patients with chronic and established disease. More than 50% of patients with bone lesions are asymptomatic. Women are affected more than men (2:1), and blacks are affected more than other racial groups. Bone lesions occur frequently in patients with lupus pernio or other granulomatous skin lesions and predict a poor prognosis with excessive mortality. There is a predilection for the phalanges of the hands and feet. Other bones can be involved, particularly the nasal bones in patients with lupus pernio and the calcaneus, which causes heel pain mimicking spondyloarthritis. The skull, vertebrae, ribs, sternum, maxilla, and distal ends of long bones may be affected. Sclerotic lesions of the axial skeleton occur mainly in middle-aged black patients and may mimic metastatic disease.

Bone lesions of the phalanges can be lytic, permeative, or destructive and tend to be bilateral in distribution. Lytic lesions appear as rounded, “punched-out” bone defects on radiographs and are most frequently located at the ends of the proximal and middle phalanges (Fig. 175.5). Permeative lesions reflect granulomatous involvement of cortex and trabeculae of the phalangeal shafts, resulting in a reticular, lace-like appearance on radiographs. This may result in the phalangeal shafts becoming tubular. In advanced cases, sclerosis or fractures may develop or joints may be affected owing to subchondral bony involvement and collapse. Notably, sarcoid bone lesions are not associated radiographically with periostitis and rarely with sequestra, which helps to separate sarcoidosis from chronic osteomyelitis. Technetium-99m diphosphonate bone scanning, MRI, and FDG-PET have shown that up to 33% of sarcoid patients have unsuspected bone or bone marrow involvement that is not detected by plain radiographs.

It is not known why sarcoidosis has a predilection for the phalanges. Pathologically, granulomatous infiltration into the marrow results in rarefaction of the trabeculae. In the cortical bone, there is irregular resorption, with enlargement of haversian canals containing granulomas. Occasionally, granulomatous inflammation can extend into surrounding tissues, causing infiltration of tendon sheaths. MRI can distinguish soft tissue involvement from bony lesions. Granulomatous involvement of tendon sheaths can result in sarcoid dactylitis, with swelling over the affected digits associated with pain and stiffness. The overlying skin can be erythematous, and when the terminal phalanges are involved, the nails may become thickened and dystrophic. Clubbing involving one or more digits has been described. Osteosarcoidosis responds poorly to therapy.17-19 Corticosteroids decrease swelling but do not completely normalize bony
Sarcoidosis can rarely (40%–60%) cause granulomatous ulcers or masses in the gastrointestinal tract from the esophagus to the rectum. Pancreric and peritoneal sarcoidosis are also rare. Granulomatous interstitial nephritis, glomerulonephritis, and amyloidosis may also rarely (<1%) occur. All areas of the male and female genitourinary tract have been reported to be involved in small case series. Sarcoidosis has been rarely associated with vasculitis, and all sizes of blood vessels can be involved. Black and Asian children are more likely to have large-vessel involvement that can resemble Takayasu arteritis.

Overproduction of 1,25-dihydroxyvitamin D can lead to increased intestinal absorption of calcium, causing hypercalcemia (10%–15%), hypercalcicuria (40%–60%), nephrocalcinosis, nephrolithiasis (10%), and renal insufficiency. The risk of nephrolithiasis is 20% higher than in the general population. Hypercalcemia (>11 mg/dL), elevated serum creatinine concentration, and nephrolithiasis are indications for corticosteroid therapy at dosages of 20 to 40 mg/day of prednisone. Both hypercalcemia and hypercalciuria usually respond rapidly within 7 to 10 days. Antimalarials and ketokonazole (600–800 mg/day) act more slowly but produce a more sustained lowering of calcium level after cessation of therapy. Consumption of a low-calcium diet, avoidance of vitamin D supplements, and limiting exposure to sunlight are helpful adjunctive measures. Patients should keep well hydrated to help prevent nephrolithiasis.

**CHILDHOOD SARCOIDOSIS**

Children of both sexes develop sarcoidosis less commonly than adults. The clinical manifestations in older children (ages 8–15 years) are similar to those in adults. Blacks have more severe disease. However, in children younger than 5 years, the characteristic presentation includes mild constitutional symptoms, including painless, boggy, and effusive large-joint polyarthritis and tenosynovitis; skin lesions; uveitis; and lymphadenopathy and splenomegaly without typical lung disease. This presentation must be differentiated from the rare autosomal dominant familial granulomatous disorder Blau syndrome, which is caused by a genetic mutation of the NOD2/CARD15 protein. Children with sarcoidosis usually have a spontaneous resolution of disease, but some experience residual complications. Corticosteroids with or without methotrexate are the treatment of choice for children with severely symptomatic or progressive disease.

**SARCOIDOSIS ASSOCIATIONS**

A variety of autoimmune disorders have been reported to occur in association with sarcoidosis in case reports. Sarcoidosis has also been associated with common variable immunodeficiency and 5q myelodysplasia and appears as part of the immune reconstitution syndrome in patients with human immunodeficiency virus (HIV) receiving highly active antiretroviral therapy. It also has been reported to occur before or simultaneously with various malignancies or after chemotherapy. Medication-induced sarcoidosis has been described after treatment with interferon-α (IFN-α), interleukin-2 (IL-2), anti-TNF therapy, and IFN-γ. Notably, each of these therapies promotes a T helper type 1 (Th1) response.

**INVESTIGATIONS**

The diagnosis of sarcoidosis is made by a combination of clinical, radiologic, and laboratory findings and confirmed by characteristic histologic findings. Patients with a classic presentation such as Löfgren syndrome may not need to undergo tissue biopsy. However, in all doubtful cases and in cases in which immunosuppressive treatment is likely to be needed, histologic confirmation of disease in one organ is essential. The requirement that more than one organ be involved to confirm the diagnosis of sarcoidosis does not require a second organ to be sampled. Clinical criteria for organ involvement without a biopsy have been published. After the diagnosis is established, the American Thoracic Society recommends the comprehensive baseline evaluation presented in Box 175.1.

**LABORATORY TESTS**

Laboratory evaluation of patients with sarcoidosis shows many abnormalities. Most patients have anemia of chronic disease and lymphopenia. Some (≤25%)
may have eosinophilia. Leukocyte and platelet counts are normal (95%) unless there is significant bone marrow involvement (<5%), hypersplenism, or another associated autoimmune disease. Chemistry panels are performed to rule out diabetes insipidus caused by pituitary involvement or renal insufficiency caused by nephrocalcinosis. Hypercalciuria occurs three times more commonly than hypercalcemia and places the patient at risk of nephrolithiasis and renal insufficiency. Liver-associated enzyme levels are abnormal in up to one third of patients, with elevations in alkaline phosphatase and γ-glutamyl transferase occurring more often than elevations in aminotransferase levels.

Serologic abnormalities, including elevated ESR, increased C-reactive protein level, and hypergammaglobulinemia (30%–80%), are common during active sarcoidosis. Low-titer rheumatoid factor is seen in up to 40% of patients, depending on the method used, and is more likely in those with chronic lung disease. A positive antinuclear antibody test result with a speckled pattern of immunofluorescence in low titer is seen in up to one third of patients. Antiphospholipid antibodies have been reported, particularly in patients with extrathoracic organ involvement. Tuberculin and energy skin testing show that many patients with active disease are anergic.

Angiotensin-converting enzyme (ACE) levels are elevated in 40% to 90% of patients with sarcoidosis. Of note, ACE inhibitors can suppress the serum ACE level so patients should be tested when off these medications. ACE elevations correlate with active pulmonary disease and normalize with successful therapy. Elevated ACE levels are not specific for sarcoidosis and may be caused by other diseases, such as hyperthyroidism, Gaucher disease, diabetes mellitus, leprosy, α1-antitrypsin deficiency, Kaposi sarcoma in HIV-infected patients, primary biliary cirrhosis, silicosis, hypersensitivity pneumonitis, cirrhosis, histoplasmosis, coccidioidomycosis, tuberculosis, beryllium disease, and asbestosis. Additionally, ACE levels are influenced by ACE gene polymorphisms (DD allele). Serum lysozyme levels may also be elevated in active sarcoidosis. Lysozyme is produced by monocytes and may be elevated when serum ACE levels are normal. It has a sensitivity of 69% to 79% but is nonspecific because it can be elevated in other diseases. Therefore, an elevated ACE or lysozyme level may be supportive but is not diagnostic of sarcoidosis.

**IMAGING**

The chest radiographic staging system has been described earlier (see section on respiratory tract involvement). The HRCT scan is more sensitive and correlates with histologic and PFT abnormalities more closely than the plain chest radiograph. Plain bone radiographs and technetium-99m diphosphonate scanning can detect bone lesions. MRI with gadolinium enhancement can be used to detect brain involvement, myocardial disease, muscle disease, and bone involvement. FDG-PET is a sensitive test for detecting sarcoid involvement of multiple tissues and showing organs that are candidates for diagnostic biopsy. Gallium-67 citrate scans are not specific and are no longer routinely used for the diagnosis of sarcoidosis.

**BIOPSY**

Tissue biopsy is the gold standard for confirming a clinical and radiographic diagnosis of sarcoidosis. Tissue biopsy should be performed in any patient who has an atypical presentation or for whom therapy is being considered to exclude infection or malignant disease. Transbronchial, lymph node, and skin biopsies are the most common, but a specimen can be obtained from any clinically involved organ. The diagnostic yield is shown in Table 175.2.

The characteristic histologic finding is that of well-circumscribed, compact, noncaseating granulomas of the epithelioid type rimmed by hyaline collagen (Fig. 175.6). However, the presence of noncaseating granulomas is not diagnostic of sarcoidosis until other granulomatous diseases are excluded (see section on differential diagnosis). Notably, a few patients with sarcoidosis (20%) may have granulomas with some minor necrosis on biopsy. Use of the Kveim-Siltzbach skin test is no longer recommended.

**ADDITIONAL TESTS**

Three tests that should be done as a baseline assessment in all patients are (1) an ECG, (2) an ophthalmologic examination with a slit lamp to rule out asymptomatic abnormalities, and (3) a 24-hour urine collection for calcium to rule out hypercalciuria. Fluorescein angiography is helpful to document posterior uveitis. PFTs, BAL fluid cell analysis, Holter monitoring, and echocardiography are described in the sections discussing respiratory tract and cardiac involvement, respectively.

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**Table 175.2**

<table>
<thead>
<tr>
<th>Site</th>
<th>Diagnostic yield (%)</th>
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<tbody>
<tr>
<td>Transbronchial</td>
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<tr>
<td>Normal CXR</td>
<td>40</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>&gt;90</td>
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<tr>
<td>Endobronchial</td>
<td></td>
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<tr>
<td>Normal mucosa</td>
<td>40–60</td>
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<tr>
<td>Abnormal mucosa</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
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<tr>
<td>Enlarged peripheral</td>
<td>&gt;90</td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>79</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
</tr>
<tr>
<td>Minor salivary</td>
<td>36</td>
</tr>
<tr>
<td>Parotid</td>
<td>93</td>
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<td>50–80</td>
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<tr>
<td>Liver</td>
<td>50–80</td>
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<tr>
<td>Endomyocardial</td>
<td>20</td>
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CXR, chest radiography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial fine needle aspiration.
DIFFERENTIAL DIAGNOSIS

Several diseases can result in clinical presentations and granulomas on biopsy specimens that resemble those of sarcoidosis. Acute histoplasmosis can simulate Löfgren syndrome and must be excluded by serologic studies and cultures. Acute arthritis with erythema nodosum, but without hilar adenopathy, can occur in inflammatory bowel disease, coccidioidomycosis, histoplasmosis, psittacosis, and reactions to various medications. The pattern of arthritis in these patients is also similar to that seen in sarcoidosis.

In patients with more insidious presentations other diseases need to be considered, depending on the organ involved. In patients with pulmonary disease chronic berylliosis should be excluded by lack of a clinical history of exposure to beryllium or by an abnormal beryllium lymphocyte proliferation test. Hyperesensitivity pneumonitis is ruled out by lack of a history of occupational and environmental exposure and results of serologic tests for precipitins. Reactions to drugs (methotrexate, IFN-α, IFN-γ, anti-TNF agents, IL-2) and other inorganic agents, such as metals (titanium, aluminum, zirconium), silica, and talc, are excluded by good history taking. Fungal serologic studies or stains or cultures for organisms rule out fungal and mycobacterial disease. Granulomatosis with polyangiitis is excluded by the absence of a positive result on the ANCA test and the absence of vasculitis on biopsy. Patients with eosinophilic granulomatosis with polyangiitis have a history of asthma and prominent eosinophilia. Tissue biopsy results exclude lymphoma and eosinophilic granuloma. In patients with cutaneous granulomatous lesions treponemal infections, leprosy, tularemia, and leishmaniasis should be excluded by serologic studies, cultures, or both. Granuloma annulare and granulomatous rosacea are ruled out clinically by lack of systemic involvement. Lupus vulgaris caused by mycobacterial infection may mimic cutaneous lesions of sarcoidosis. Primary biliary cirrhosis can cause liver granulomas but is associated with antimitochondrial antibodies. Fungal or mycobacterial infections and brucellosis should be considered in patients with monoarticular, axial, or peripheral arthritis. Fungal and mycobacterial infections, leprosy, brucellosis, syphilis, granulomatosis with polyangiitis, eosinophilic granuloma, multiple myeloma, and lymphoma can cause bony lesions similar to those caused by sarcoidosis. Toxoplasmosis can mimic acute and chronic sarcoid myopathy, and various neoplasms and infections need to be excluded in patients with a muscle mass. Finally, granulomas in a single organ (e.g., idiopathic granulomatous hepatitis, giant cell myocarditis, or panuveitis) without evidence of other organ involvement should not be diagnosed as sarcoidosis.

ETIOLOGY

The cause of sarcoidosis is unknown. Multiple environmental agents and several genetic associations have been reported.

ENVIRONMENTAL RISK FACTORS

Because the lung is most commonly involved, exposure to an airborne antigen is postulated. The ACCESS trial reported an increased risk of sarcoidosis in people with exposure to (1) water sources that serve as reservoirs for aero-solized microbial antigens (agriculture and water-damaged areas rich in molds), (2) metal industry (heavy metals and metalworking fluids), (3) inorganic particulate matter (silicates), and (4) insecticides. Notably, chronic beryllium disease causes lesions in the lung (but not in other organs) that are histologically identical to those in sarcoidosis. Likewise, heavy dust exposure in first-responders from the World Trade Center disaster was associated with a granulomatous pulmonary disease similar to sarcoidosis. Interestingly, multiple studies have shown that cigarette smoking decreases the probability of developing sarcoidosis. It is postulated that the acrolein (breakdown product of cyclophosphamide) in cigarette smoke is cytotoxic to lymphocytes trying to enter the lungs.

Infectious agents have been associated with sarcoidosis. Mycobacterial and proionobacterial nucleic acid have been recovered from sarcoid granulomas. Recently, Mycobacterium tuberculosis DNA targeting 16S rDNA has been found in sarcoid biopsy specimens (38%). Additionally, peripheral blood and lung T-cell responses as well as circulating immunoglobulin G against mKatG are increased in half of sarcoid patients. Japanese investigators have isolated Propionibacterium acnes DNA in more than 70% of sarcoidosis tissue samples. They suggest this organism resides in the lung in a latent or cell wall–deficient form and in some patients can incite hyperplastic inflammation. However, the inability of any of these agents to cause sarcoidosis in animal models, the diversity of tissues involved in sarcoidosis that are not typically infected by some of these organisms, the lack of response to antibiotics but improvement with immunosuppressive agents, and the failure of the prevalence of sarcoidosis to decrease in countries where bacillus Calmette-Guérin vaccination is used are all evidence against a single infectious agent causing sarcoidosis.

SERUM AMYLOID A AGGREGATION

Recent studies have reported that the amyloid precursor protein, serum amyloid A (SAA), is increased and localized to sarcoid granulomas. This accumulation of SAA was much higher in sarcoidosis compared with other diseases causing granulomatous inflammation. SAA was also shown to enhance cytokine expression in BAL cells from patients with sarcoidosis compared with control participants. The investigators hypothesized that sarcoidosis could be triggered by an environmental or nonviable microbial antigen that was poorly cleared or degraded. The persisting antigen would stimulate SAA production initially as part of the innate and later as part of the polarized Th1 response. SAA could then maintain the granulomatous process by its accumulation and aggregation within granulomas. Misfolded fragments of SAA and the persisting antigen could further amplify the ongoing Th1 cytokine production at local sites of inflammation, thereby promoting the granulomatous inflammation. Cure of the disease would require the clearance of both SAA and the sequestered antigen.

GENETIC RISK FACTORS

Genetic factors most certainly play a role in the racial and ethnic variations in prevalence, clinical presentations, and severity of sarcoidosis. Reports of familial clustering (5%–16% of patients) with two or more affected members are considered the strongest evidence for a genetic component to this disease. The ACCESS study showed that first-degree relatives of patients with sarcoidosis had a five times increased relative risk of developing sarcoidosis. In addition, the concordance rate is reported to be up to 10 times higher in monozygotic (80-fold) than in dizygotic (7-fold) twins compared with the general population. Overall, the absolute risk that a sibling or parent of a patient with sarcoidosis will develop sarcoidosis is approximately 1%. Despite this increased risk of sarcoidosis within families, affected sibling pairs show minimal concordance in clinical manifestations and outcomes. The intraracial heterogeneity of clinical manifestations and prognoses makes it unlikely that a single gene is responsible for sarcoidosis. HLA genes confer the most important genetic risk of susceptibility. Whereas HLA-DRB1*0301, HLA-DRB1*1101, HLA-DRB1*1201, and HLA-DRB1*1501 alleles have the strongest association with sarcoidosis risk, HLA-DRB1*0101 is protective against disease. The HLA-DRB1*0301/DQB1*0201 haplotype is highly associated with Löfgren syndrome and a benign course; HLA-DRB1*0401 is associated with developing uveitis; and the HLA-DRB1*1501/DQB1*0602 haplotype is associated with a severe, chronically progressive course. Non-HLA candidate genes associated with disease in specific ethnic groups of patients with sarcoidosis include specific alleles of cytokines (TNF-α, TGF-β), receptors (chemokine, Toll-like, IL-23R), bryophillin-like 2 (BTNL2), and annexin 11 (ANXA11) among others. Several of these gene variants associate with other inflammatory disorders as well as sarcoidosis.

In summary, because of the variability of clinical manifestations and outcomes of sarcoidosis across different ethnic groups, it is likely there is more than one environmental or infectious trigger and multiple genetic alleles that interact immunologically to cause the multiple presentations seen in this disease.

IMMUNOPATHOGENESIS

The noncaseating epithelioid granuloma is the histologic hallmark of sarcoidosis and is formed by a stepwise series of events (Fig. 175.7). Granuloma formation is a protective response to isolate poorly degraded antigens to prevent both dissemination and further local tissue damage. Candidate antigens in sarcoidosis include environmental substances, microbial remnants, and misfolded serum amyloid A.

STEP 1: LYMPHOCYTIC ALVEOLITIS

The initial event in sarcoidosis is thought to be the uptake of a triggering antigen through Toll-like receptors and processing by antigen-presenting cells (type II alveolar epithelial cells, alveolar macrophages, and dendritic cells) bearing HLA class II molecules in the lower respiratory tract. This antigen uptake activates alveolar macrophages by stimulating secretion of chemoattractant cytokines (IL-15, IL-10) and chemokines (MCP1/CCL2, MIP-1/CCL3-4, RANTES/CCL5, IL-8/CXCL8, IP-10/CXCL10) coupled with the cytokine-mediated (TNF-α, IL-1, IL-15) upregulation of endothelial cell
adhesion molecules (ICAMs). This is central to the marked accumulation of inflammatory cells and recruitment of lymphocytes (CD4+ T cells) from the peripheral blood into the lung alveoli. Studies indicate that an inflammatory T cells) from infiltration of CD4+ T lymphocytes and mononuclear phagocytes. Th17 cells may also contribute to the alveolitis. However, the recognition of antigen presented by antigen-presenting cells to CD4+ T cells is considered to be a critical event in the disease. In patients with established disease, there is a selective oligoclonal expansion of αβ T cells in the lung, which exhibits a restricted T-cell receptor repertoire (Vβ2, Vβ8, Vβ12, Vα2.3). This strongly suggests an antigen-specific immune response.

**STEP 2: GRANULOMA FORMATION**

The accumulation and activation of antigen-specific Th1 lymphocytes and the reciprocal suppression of the Th2 subset and inadequate regulatory T-cell (Treg) function are the initial events in the development of granulomatous inflammation. Alveolar macrophage/dendritic cell–derived IL-12 with the help of IL-18 and IL-27 are critical to the differentiation of naïve CD4+ T lymphocytes into Th1 cells. The polarized Th1 cells secrete the Th1 cytokines IL-2 and IFN-γ. IL-2 acts synergistically with IL-15 and TNF-α from macrophages to stimulate further T-lymphocyte proliferation and differentiation. Other Th1-lymphocyte cytokines stimulate macrophage recruitment, activation, and proliferation (granulocyte-macrophage colony-stimulating factor, MIP-1/ CCL2, MIP-1/CCL3–4). The macrophage-derived cytokines, IL-12 and IL-18, coupled with IL-2, are potent stimulators of further IFN-γ production; this amplifies the immune response through its effects on multiple target cells, including macrophages, which differentiate into secretory epithelioid cells at the center of the granuloma. Whereas both IL-1β and IFN-γ as well as several chemokines are important in the early recruitment stage of granuloma formation, TNF-α may be particularly important in the later maintenance of granuloma formation and perpetuation of inflammation.

The sarcoid granuloma is well circumscribed, round or oval, noncaseating, and made up of compact, radially arranged epithelioid cells with pale nuclei (see Fig. 175.6). Some of the epithelioid cells fuse to form giant cells, typically of the Langhans type, in which the nuclei are arranged in an arc or circular pattern around a central granular zone. Stellate asteroids (entrapped collagen) and blue Schaumann inclusion bodies (altered lysosomes in giant cells) are occasionally observed. The center of the granuloma is composed of macrophage-derived epithelioid cells and CD4+ Th1 lymphocytes, and the outer zone contains many CD4+ and CD8+ T lymphocytes, fibroblasts, and interdigitating antigen-presenting cells entwined in bands of collagen. Notably, sarcoid granulomas have a predilection for forming in the perilymphatic areas and bronchovascular bundles within the lungs.

**STEP 3: GRANULOMA RESOLUTION**

The immunologic factors that determine the ultimate fate of sarcoid granulomas are poorly understood. Most granulomas resolve spontaneously or with therapy, but others are converted into a fibrotic scar. In the 25% of patients who develop progressive fibrosis there appears to be a shift from a Th1 to a Th2 cytokine (IL-4, IL-10, IL-13) predominance at the local tissue level. Alveolar macrophages, mast cells, and neutrophils contribute to this fibrotic process by releasing superoxide radicals and proteases that cause local tissue injury. This is reflected clinically by the association of progressive lung fibrosis and a worse prognosis with neutrophilia and cytotoxic T/NK cells in BAL fluid. Alveolar macrophages also secrete transforming growth factor-β (TGF-β) and CC motif ligand 18 (CCL18) among others. TGF-β induces local epithelial cells to transform into collagen matrix–producing fibroblasts. CCL18 attracts bone marrow–derived fibrocytes and Treg cells from the peripheral blood. The fibrocytes differentiate and contribute to the fibroblast pool. Treg cells produce IL-10 in conjunction with other cells producing IL-13. These Th2 cytokines contribute to the transformation of alveolar macrophages into macrophages of the M2 phenotype, which secrete fibroproliferative cytokines (platelet-derived growth factor). This adds to the profibrogenic cytokines (fibroblast growth factor 2, insulin-like growth factor 1, fibronectin) produced by fibroblasts, causing more proliferation and collagen matrix production. The collagen matrix produced stimulates alveolar macrophages to make more CCL18, which results in a positive feedback loop.

**NATURAL HISTORY AND PROGNOSIS**

The natural history of untreated sarcoidosis is difficult to predict in an individual patient. The ACCESS study showed that the extent of organ involvement in most cases is defined at presentation, with fewer than 25% of patients developing new organ involvement within 2 years of follow-up.
Therefore, during the first 2 to 3 years after disease onset, a complete review of systems, physical examination, certain tests (chest radiography, PFTs, calcium levels, any test that gives abnormal results initially) should be repeated every 3 to 6 months and others (eye examination, ECG) every 12 months, or sooner if symptoms develop. Because of cost and radiation exposure, the value of serial HRCT scans to follow pulmonary disease progression is debated. Most physicians recommend HRCT scans in patients with unexplained worsening of respiratory symptoms, hemoptysis, uncertain radiographic abnormalities, mycetomas, or pulmonary hypertension. Echocardiography, Holter monitoring, and MRI are ordered as indicated by symptoms or other tests.

Most patients (60%) undergo spontaneous remission within the first 3 years, with an additional 10% to 20% experiencing resolution with corticosteroid therapy. However, in 10% to 30%, the course is chronic. Of those having a chronic course, half will have progressive pulmonary disease, and half will display involvement of critical extrapulmonary organs, such as the eye, brain, and heart.

The probability of a spontaneous remission without treatment can be predicted by the patient’s clinical and radiologic presentation. Up to 80% of patients with hilar adenopathy alone (radiographic stage I disease) at presentation experience spontaneous remission. Patients with Löfgren syndrome and HLA-DRB1*0301 have the best overall prognosis with a 95% chance for full remission within 2 years compared with only 50% in those without this allele. Some 30% to 70% of patients with radiographic stage II disease experience remission, in contrast to 10% to 20% of those with stage III and 0% with stage IV disease. The mortality rate of patients with pulmonary fibrosis (radiographic stage IV with vital capacity of <1.5 L) is 23% to 40%. Although the overall prognosis for sarcoidosis is good, at least 50% of patients will have some degree of permanent organ dysfunction. In addition, there is a 5% mortality rate, with progressive pulmonary disease accounting for half and cardiac and neurologic disease causing the other half of all deaths from sarcoidosis. Of patients with cardiac or neurologic manifestations, up to 10% will die of organ failure. In Japan, patients die of cardiac complications, but in the United States, pulmonary disease causes most of the deaths.

In general, the more severe the involvement and the more organ systems involved at the time of diagnosis (three or more), the worse the prognosis. Extrapulmonary involvement (cardiac or neurologic involvement, lupus pernio, hypercalcemia, bone involvement) and pulmonary hypertension are poor prognostic signs, as are black race, disease onset after 40 years of age, and symptom duration of longer than 6 months.4,57

**MANAGEMENT**

Because the cause of sarcoidosis is unknown, therapy is empiric.43,45 Whenever patients with good prognostic signs should be observed for the first 3 to 6 months without immunosuppressive therapy because of the potential for spontaneous resolution. Notably, combination antimycobacterial antibiotic therapy has been reported to improve the chronic cutaneous manifestations of sarcoidosis. However, this improvement was attributed to the antinflammatory effects of the antibiotic regimen and not to the eradication of an unidentified infectious agent.47

In patients with progressive disease, corticosteroid therapy is recommended. The recommended dosages of corticosteroids and adjunctive therapies vary, depending on the organ system involved (see individual organ system sections for specific therapies). There have been few controlled, randomized trials to establish the appropriate dose and duration of any therapy for sarcoidosis. Despite a lack of well-controlled clinical trials proving that corticosteroids improve long-term outcome, oral corticosteroids are used as first-line treatment for symptomatic and progressive stages II and III lung disease, malignant hypercalcemia, nephrocalcinosis, and severe ocular, neurologic, cardiac, skin, and musculoskeletal involvement.4,58 In patients who have an inadequate response to or unable to taper their corticosteroids, steroid-sparing agents (antimalarials, dapsone, methotrexate, azathioprine, leflunomide, mycophenolate, cyclophosphamide, cyclosporine, tacrolimus, Acthar Gel) alone or in combination are used.4,59 Recently, the monoclonal anti-TNF-α agents, particularly infliximab and adalimumab, have been found to be effective for various disease manifestations refractory to standard immunosuppressive therapy.4,59,60 In case studies, rituximab has been used successfully for refractory disease.4,59,60 Solid organ transplantation can be lifesaving in patients for whom all medical therapies have failed.45

Patients must be monitored for adverse effects and prophyllactic measures used to prevent toxicities. Patients receiving high-dose corticosteroids should be given prophylaxis against Pneumocystis jiroveci. Osteopenia and osteoporosis caused by dysregulated calcium metabolism and medications used in therapy can occur in up to two thirds of patients.46 However, calcium and vitamin D supplements should either not be used or used with caution in all patients with sarcoidosis because of risk of hypercalcemia and hypercalciuria. All patients with sarcoidosis who are receiving corticosteroids or who are postmenopausal should have bone mineral density testing, and bisphosphonate therapy should be started in those at risk of fractures. Vaccinations should be given and kept current.53,54

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**REFERENCES**