Coccidioidomycosis occurs in arid and semi-arid regions of the New World from the western United States to Argentina. Highly endemic areas are present in the southwest United States. *Coccidioides* species live in the soil and produce pulmonary infection via airborne arthroconidia. The skin may be involved by dissemination of the infection, or by reactive eruptions, such as a generalized exanthem or erythema nodosum. Interstitial granulomatous dermatitis and Sweet’s syndrome have recently been recognized as additional reactive signs of the infection. Coccidioidomycosis is a “great imitator” with protean manifestations. Cutaneous findings may be helpful clues in the diagnosis of this increasingly important disease. (J Am Acad Dermatol 2006;55:929-42.)

**Learning objective:** At the conclusion of this learning activity, participants should be familiar with the pathogenesis, clinical manifestations, risk factors, diagnosis, and treatment of coccidioidomycosis.

Cutaneous findings played an important role in the first reported case of coccidioidomycosis more than a century ago. In 1892, Posada described an Argentine soldier who had verrucous facial lesions, which clinically resembled mycosis fungoides. Distinctive organisms were visualized microscopically in the skin. Although initially believed to be a protozoan, *Coccidiodes immitis* was identified as a fungus in 1900. At that time, the disease was considered to be frequently fatal. The broad clinical spectrum of coccidioidomycosis was not appreciated until the 1930s, when *C immitis* was recognized as the cause of “valley fever” in the San Joaquin Valley of California. This common syndrome was a relatively mild, self-limited respiratory illness associated with erythema nodosum. Throughout the 20th century, as the desert southwest transformed into a popular destination for tourism and migration, coccidioidomycosis became an increasingly important and common disease. In recent decades, *Coccidioides* species have emerged as significant opportunistic pathogens in HIV patients and in organ transplant recipients in endemic areas. In the current era, there is growing concern that certain new biologic therapies may predispose patients to an increased risk of severe coccidioidomycosis. The 21st century also brings the recognition of *Coccidioides* species as potential agents of bioterrorism.

**Coccioidoides immitis*/posadasii*

*Coccidioides* species are dimorphic fungi with saprophytic and parasitic phases (Fig 1). Humans, dogs, horses, and other animals may serve as hosts. The organisms’ life cycle explains several interesting characteristics of the disease. Coccidioidomycosis is infectious, but not contagious. Nearly all infections are acquired from the environment by the inhalation of airborne arthroconidia from the soil. In laboratory cultures, the organisms grow as the extremely infectious mycelial form, which may be hazardous to laboratory workers.

The organisms are considered to be potential agents of bioterrorism. Because they are highly infectious and sporulate easily in culture, *Coccidioides* species are the only fungi on the Select Agent list of the Department of Health and Human Services. Federal regulations restrict the possession, use, and transfer of select biological agents. According to a recent review, however, terrorists would likely encounter significant difficulties in attempting to employ the organisms as effective weapons.

The genus *Coccidioides* demonstrates genomic diversity. DNA polymorphisms distinguish the California strains of *Coccidioides* from the non-California strains. A separate species name (*C posadasii*) has recently been proposed for the non-California clade, while the original species name (*C immitis*) is reserved for the Californian clade. At the current time, the designation of two

---

**From the Departments of Dermatology and Pathology, Mayo Clinic.**

**Funding sources:** None.

**Conflict of interest:** None identified.

**Reprint requests:** David J. Dicaudo, MD, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259. E-mail: dicaudo.david@mayo.edu.

© 2006 by the American Academy of Dermatology, Inc.

doi:10.1016/j.jaad.2006.04.039
species is controversial. Some researchers recognize only a single species, *C. immitis*, and consider the non-California clade to be a variety (*C. immitis var posadasii*). The clinical manifestations of coccidiodomycosis are generally similar regardless of geographic location.

**IMMUNE RESPONSE**

In coccidiodomycosis, cell-mediated immunity is important in establishing an effective response to the infection. The clinical course may be greatly influenced by whether the immune response is directed predominantly towards a TH1 pattern or towards a TH2 pattern. Interferon-gamma, a TH1-associated cytokine, activates macrophages, which are subsequently able to inhibit or kill the organisms. In contrast, TH2-associated cytokines promote the production of antibodies and down-regulate TH1 functions. The antibodies do not appear to confer protection against the organisms.

In self-limited infections, patients typically have strong delayed hypersensitivity responses to coccidoidal antigens and have low antibody titers. Conversely, patients with disseminated infection typically manifest weak or absent delayed hypersensitivity responses and have high antibody titers.

An effective cell-mediated response provides resistance to re-infection. Following recovery from self-limited infections, patients typically have lifelong immunity. In addition to the T cell–mediated mechanisms of acquired immunity, natural killer (NK) cells may play a role in innate resistance to the organism. A recent review provides a detailed discussion of innate and adaptive mechanisms of immunity in coccidiodomycosis.

**EPIDEMIOLOGY**

**Incidence in endemic areas**

An estimated 100,000 cases of coccidiodomycosis occur annually in the United States. The geographic
distribution corresponds to regions with hot, dry summers, few winter freezes, low annual rainfall, and alkaline soil.\(^{43,44}\) Highly endemic areas include parts of Arizona and California (Fig 2).\(^{45}\) Major metropolitan areas with high incidence rates include Bakersfield, California; Phoenix, Arizona; and Tucson, Arizona. Confirmed cases are reportable in some states, including Arizona, California, and New Mexico.

Skin test surveys generally suggest a downward trend in the incidence of coccidioidomycosis in the Bakersfield area over the past 60 years.\(^{46}\) This phenomenon is attributed to irrigation and urbanization of the region. Nevertheless, the same area witnessed a remarkable resurgence in the number of cases in the early 1990s. Climatic and demographic factors may have been responsible.\(^{45}\) Similarly, in Arizona, the incidence increased by more than 100% between 1990 and 1995,\(^{47,48}\) and by an additional 180% between 1995 and 2001.\(^{49}\) The incidence in Arizona has continued to increase, from 43 cases per 100,000 people in 2001 to 63/100,000 in 2004.\(^{50}\)

**Climatic and environmental factors**

Local climatic factors, including precipitation and temperature, influence the variable yearly incidence of coccidioidomycosis.\(^{44,45,51-53}\) Seasonal variations in incidence also occur. In Arizona, the number of new infections peaks during the winter months.\(^{49}\) In the western United States, epidemics have been associated with environmental events, such as dust storms,\(^{54}\) earthquakes,\(^{55,56}\) and droughts.\(^{51}\) An increased risk of infection is seen in persons with exposure to dust and soil. Outbreaks have occurred with occupational exposure in archeological workers\(^{57-60}\) and in military personnel.\(^{53,61-66}\) In the medical community, awareness of coccidioidomycosis is important even in non-endemic areas. Travelers who are exposed to the organism may develop symptoms after they return home.\(^{57-72}\)

**HOST FACTORS**

Genetic factors and co-morbid conditions may influence the host response to coccidioidal infection. The incidence of primary pulmonary coccidioidomycosis appears to be similar among different ethnic groups. However, specific groups, such as Filipinos and African Americans, have a markedly increased risk of severe disease and dissemination.\(^{73,74}\) HIV-infected persons,\(^{6-15,75-82}\) organ transplant recipients,\(^{16,17,19-22,83-85}\) other immunocompromised patients,\(^{23,86-92}\) and pregnant women\(^{82,93-97}\) also have an increased risk of severe disease and dissemination.

Coccidioidomycosis is an AIDS-defining illness. Patients with CD4 counts less than \(0.250 \times 10^9/L\) have an increased risk of active coccidioidomycosis.\(^{8,10}\) In endemic areas, antiretroviral therapy appears to
have decreased the incidence of coccidioidomycosis in the HIV-infected population.9,13

By impairing cell-mediated immunity, immuno-suppressive medications, such as prednisone and cyclosporine, may predispose to severe primary infection or may permit re-activation of the latent infection. Similar concerns may apply to tumor necrosis factor (TNF)—alpha antagonists, which are approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn’s disease, and psoriasis. In a retrospective case series, coccidioidomycosis was documented in 13 patients receiving TNF-alpha antagonists (infliximab or etanercept) for inflammatory arthritis. Two of the patients, who were receiving both infliximab and methotrexate, died of disseminated coccidioidomycosis.25 In endemic areas, Crum et al24 recommend chest radiographs and serologies at baseline and every 3 to 4 months during treatment with TNF-alpha antagonists. Similar testing is recommended for patients who have previously resided in an endemic area.24 Further studies are needed to define the risk of severe coccidioidomycosis in patients receiving biologic therapies.

CLINICAL FEATURES

Approximately 60% of individuals with primary coccidioidomycosis are asymptomatic.3 Most of the remaining 40% experience mild to moderate influenza-like symptoms, including cough, fever, arthralgias, myalgias, and fatigue. In most patients, symptoms resolve or significantly improve within 2 to 3 weeks. Protective immunity follows recovery from the infection.40,98 Coccidioidomycosis occasionally produces prolonged morbidity or death. In a recent series of 223 patients, 2 died of respiratory failure. An additional 8 suffered chronic morbidity from disseminated involvement of the bones or meninges.74

The lungs are nearly always the primary focus of infection. Pulmonary manifestations may include pneumonia, pleural effusion, hilar lymphadenopathy, and lung nodules.43 Severe pulmonary involvement may occur, especially in immunocompromised patients. Rarely, a chronic progressive pneumonia may continue for years and produce pulmonary cavities and fibrosis.

Disseminated infection occurs in approximately 1% of patients.3 Almost all patients with disseminated infection experience systemic symptoms, such as fever, cough, and night sweats.74 In rare cases of disseminated infection, there may be no clinical or radiographic evidence of a preceding respiratory illness.28 Dissemination may occur acutely with the primary pulmonary infection, or may be chronic and relapsing. Like Mycobacterium tuberculosis,

C inimitis/posadasii may be contained, rather than destroyed, by the immune response.99 In some cases, viable organisms may persist indefinitely within the tissues. If the host subsequently becomes immunocompromised, the quiescent infection may reactivate and disseminate.

Common sites of disseminated coccidioidomycosis include the skin, meninges, bones, and joints. Coccidioidal meningitis is potentially lethal.106 Early manifestations of meningitis include headache, nausea, vomiting, and altered mental status. Nuchal rigidity and cranial neuropathies may occur. Dissemination to the bones and joints produces osteomyelitis and synovitis.101,102 Like tuberculosis and syphilis, coccidioidomycosis is a “great imitator” with protean manifestations.103,104

CUTANEOUS MANIFESTATIONS

Cutaneous manifestations may be categorized as organism-specific or reactive.105 Organism-specific lesions contain the organisms, which may be identified in skin biopsy specimens by histopathologic examination or by culture. Organism-specific lesions result from hematogenous dissemination to the skin or, much more rarely, from a primary cutaneous infection. Reactive eruptions, which contain no viable organisms, include erythema nodosum, an acute generalized exanthem, erythema multiforme, Sweet’s syndrome, and reactive interstitial granulomatous dermatitis.

Erythema nodosum

Erythema nodosum (EN) is generally considered to be the most characteristic reactive cutaneous manifestation of coccidioidomycosis.106 One to three weeks after the onset of the illness,107 patients develop painful subcutaneous red nodules, typically on the lower extremities. The diagnosis of EN is frequently based upon the clinical features. If an excisional biopsy is performed, the characteristic histopathologic pattern is a septal granulomatous panniculitis. Other well-recognized causes of EN include sarcoidosis, streptococcal infection, other infections, inflammatory bowel disease, pregnancy, and oral contraceptives.108,109

Both ethnicity and gender appear to influence the incidence of EN in coccidioidomycosis.64,107 In a large study of military personnel from the early 1940s, EN developed in 50% of white women and in 18% of white men with the diagnosis of coccidioidomycosis.5 EN appears to be rare in African American men with the infection.3,64,107

EN may reflect the presence of a vigorous cell-mediated immune response, which may confer a protective advantage against the organism.95 In
patients with EN, the onset of the eruption tends to coincide with the acquisition of delayed hypersensitivity, as determined by coccidioidal skin testing. In a report of 61 pregnant women with coccidioidomycosis, EN was associated with a favorable outcome. Of the 30 pregnant women with EN, none developed disseminated disease, and only one experienced chronic infection. Of the 31 pregnant women without EN, 11 developed disseminated disease, 11 experienced chronic infection, and one died.

Acute exanthem

An acute generalized exanthem or “toxic erythema” (Fig 3) frequently begins early in the course of coccidioidomycosis, typically within 48 hours of the patient’s first symptoms. In some cases, the cutaneous eruption may be the chief complaint and may precede the development of detectable antibodies in the serum. The cutaneous lesions have been clinically described as macular, papular, urticarial, morbilliform, or target-like. The clinical appearance may be mistaken for severe, generalized allergic contact dermatitis or erythema multiforme (EM). Pruritus is severe in some cases. An oral enanthem may be associated. The exanthem may persist up to several weeks, and occasionally is followed by desquamation of the palms.

Skin biopsies demonstrate a non-specific pattern of spongiotic dermatitis and/or interface dermatitis with a mild perivascular inflammatory infiltrate including lymphocytes, neutrophils, eosinophils, and karyorrhectic debris. In contrast to EM, necrotic keratinocytes are rare.

Erythema multiforme

For more than six decades, EM has been reported to be associated with coccidioidomycosis. The clinical spectrum of EM appears to overlap with those of the acute exanthem and Sweet’s syndrome. Like the acute exanthem, EM is reported to occur early in the course of coccidioidomycosis, often within 48 hours of the first symptoms. Target-like lesions, oral involvement, pruritus, and palmar desquamation have been reported to occur in both conditions. Thus, the acute exanthem may clinically mimic EM, although the two entities differ histopathologically. Similarly, Sweet’s syndrome (see below) may have annular or target-like features which clinically resemble EM, although the histopathologic findings are extremely different.

In a comprehensive review of EM, Huff et al did not consider coccidioidomycosis to be among the well-documented causes. While EM-like eruptions are described in numerous different infectious diseases, the association is well documented only in recurrent herpes simplex infection and in very few other specific infections. In published cases of coccidioidomycosis, the diagnosis of EM has almost always been based solely upon the clinical features. To the best of this author’s knowledge, the only published histologic description would not fulfill currently accepted criteria for EM. Necrotic
keratinocytes, which are the most characteristic histologic feature, were lacking in the description.

It is unclear whether true EM occurs in coccidioidomycosis, or whether the EM-like eruptions actually represent the acute exanthem or Sweet’s syndrome. Regardless of whether or not the eruptions are truly EM, EM-like eruptions are important clues to the diagnosis of coccidioidomycosis.

Sweet’s syndrome

Sweet’s syndrome (acute febrile neutrophilic dermatosis) is a distinctive, reactive, immunologically-induced eruption, which may be associated with a variety of underlying systemic diseases. Well-demarcated, boggy, tender red papules and plaques develop abruptly in association with fever and peripheral blood leukocytosis. The lesions may sometimes have vesicular or pustular features. Skin biopsies reveal a diffuse, dense dermal inflammatory infiltrate with numerous neutrophils and leukocytoclastic debris, but no microorganisms are detected in the skin. Common associations include nonspecific upper respiratory infections, hematologic malignancies, inflammatory bowel diseases, and connective tissue diseases.

Only three patients have been reported with Sweet’s syndrome associated with acute pulmonary coccidioidomycosis. Yet, the association is likely more common than has been recognized. Since the publication of 2 cases with my coworkers in 2004, I have encountered 5 additional similar patients. Skin lesions resolve as the patient recovers from the underlying pulmonary infection. In most clinical situations, systemic corticosteroids are the mainstay of therapy for Sweet’s syndrome. In cases associated with coccidioidomycosis, however, recognition of the pulmonary infection is important so that treatment with systemic corticosteroids is avoided.

Interstitial granulomatous dermatitis

Granulomatous dermatitis may be seen not only in a variety of cutaneous infections, but also in immunologically-induced eruptions. Granulomatous tissue reactions, which resemble granuloma annulare or necrobiosis lipoidica, may occur as a reactive manifestation of diverse systemic diseases, such as connective tissue diseases, systemic vasculitis, lymphoma, infectious diseases, and inflammatory bowel disease.

A single case series described 5 patients who presented with interstitial granulomatous dermatitis in association with acute pulmonary coccidioidomycosis. Edematous or indurated cutaneous papules, nodules, and plaques develop abruptly at the onset of the illness (Fig 5). Skin biopsies reveal interstitial dermal inflammation with macrophages, often accompanied by eosinophils, neutrophils, and leukocytoclastic debris. Fungal stains and cultures reveal no organisms within the skin biopsy specimens. In the published series, cutaneous lesions resolved...
over 1 week to 2 months, as the patients recovered from their respiratory symptoms.

Since publication of the 5 cases with my coworker in 2001, I have encountered similar biopsy findings in 3 additional patients with serologically confirmed coccidioidomycosis. Further observation has revealed that the neutrophilic component of the infiltrate may vary greatly. Neutrophil-rich cases may lie on a continuum with Sweet’s syndrome. In other cases, the dermis may contain only a sparse collection of interstitial macrophages with rare neutrophils. Nevertheless, the histopathologic pattern is often distinctive and may raise suspicion for coccidioidomycosis, even in the absence of clinical history.

Interstitial granulomatous dermatitis and Sweet’s syndrome may clinically and histopathologically resemble a disseminated infection. Skin biopsy specimens should be evaluated by culture and by histopathologic examination, in order to distinguish these two reactive eruptions from a disseminated infection.

Disseminated infection

The skin is the most common site of disseminated coccidioidomycosis.\textsuperscript{33,129} When dissemination occurs, it usually begins within several weeks or months after the primary infection,\textsuperscript{3} but occasionally it may be the initial manifestation.\textsuperscript{130} Almost all disseminated cases arise from a primary pulmonary infection, which spreads hematogenously to the skin.

A variety of cutaneous lesions may occur, including papules, nodules, verrucous plaques, abscesses, pustules, and sinus tracts.\textsuperscript{129,131} Skin lesions may be solitary or multiple and may ulcerate (Fig 6). Even after resolution of other symptoms, disseminated skin lesions may rarely become chronic (Figs 7 and 8). The diverse presentations include unusual cases that clinically resemble tumor-stage mycosis fungoides,\textsuperscript{1,74} or lepromatous leprosy.\textsuperscript{132}

In disseminated coccidioidomycosis, skin biopsies reveal granulomatous and/or suppurative inflammation in the dermis or subcutaneous adipose tissue. The inflammatory infiltrate often includes numerous eosinophils.\textsuperscript{131} The overlying epidermis may show pseudocarcinomatous hyperplasia with or without ulceration. Organisms are identified by histopathologic examination and by cultures of skin biopsy specimens, although either method may sometimes yield falsely negative results.\textsuperscript{131} If the organism is identified in the skin, other possible sites of dissemination should be investigated.\textsuperscript{33,130,155}

Primary cutaneous infection

Only approximately 20 cases of primary cutaneous coccidioidomycosis have been reported in the literature.\textsuperscript{134-142} A comprehensive review of the subject has recently been published.\textsuperscript{141} Traumatic inoculation of the organism results from direct contact with a source in the environment or in the laboratory. Primary cutaneous infections have been reported in agricultural workers,\textsuperscript{136} laboratory workers,\textsuperscript{137,139,142} an embalmer,\textsuperscript{140} and in persons suffering splinter injuries or lacerations.\textsuperscript{134,135,138}

Primary cutaneous coccidioidomycosis typically manifests as an ulcerated nodule on an extremity, although other sites may also be affected (Fig 9). In a pattern resembling sporotrichosis, secondary nodules sometimes arise in a linear distribution along the lymphatic pathways of an extremity.\textsuperscript{135} Fever and regional lymphadenopathy may be associated, and the affected lymph nodes may ulcerate. Though primary cutaneous infections sometimes resolve spontaneously, at least one patient experienced a severe clinical course with meningeal dissemination.\textsuperscript{135}

In some cases, a primary pulmonary infection may disseminate to a single focus in the skin and may mimic a primary cutaneous infection. If the patient’s
pulmonary symptoms are minimal or absent, it may be difficult to distinguish a disseminated infection from a primary cutaneous infection. The histopathologic features in the skin are similar in both instances. Organisms may be detected by histopathology or by culture in both situations. Even a history of localized trauma to the affected area does not completely rule out the possibility of a disseminated infection. In some cases, disseminated organisms in the bloodstream may specifically localize to the site of an injury (blunt trauma, laceration, or surgical wound). This phenomenon, termed *locus minoris resistentiae*, is well documented in disseminated coccidioidomycosis.143

Several clues may support the possibility of a primary cutaneous infection. Regional lymphadenopathy, a relatively low complement fixation titer, and a history of a trauma-induced break in the skin are all typical of primary cutaneous infection. Nevertheless, these findings are not entirely specific. In some cases of isolated cutaneous coccidioidomycosis, it may not be possible to distinguish primary cutaneous infection from a disseminated infection.

**DIAGNOSIS**

**Serology**

Both qualitative and quantitative serologic tests are useful in the diagnosis of coccidioidomycosis. Enzyme immunoassay, latex particle agglutination, and immunodiffusion may be used as qualitative techniques, which yield positive results early in the course of the infection. Enzyme immunoassay provides rapid qualitative assessment of both IgM and IgG coccidioidal antibodies.144 While this test is highly sensitive, false positive reactions do sometimes occur.98,145 Positive reactions may require confirmation by another more specific technique. IgM antibodies occur mostly during early primary infection, although occasionally they may persist in chronic infections.98,145

IgG complement-fixing antibodies may appear within 2 to 3 weeks of the onset of symptoms, and are assessed quantitatively in the serum and other body fluids by quantitative immunodiffusion or complement fixation techniques.98 These techniques yield highly specific results.145 Even low titers of complement-fixing antibodies (1:2) are likely to signify a true infection. Complement-fixing antibodies usually disappear as the infection resolves but may persist in chronic infections. The titer generally correlates with the severity of the disease. Patients with disseminated infections typically have high titers (1:16, 1:32, or 1:64, depending upon the individual laboratory).98 However, some patients with limited dissemination to the skin may have lower titers, such as 1:4 or 1:8.98 Quantitative serologies are also useful in monitoring response to therapy.

False negative serologic results do sometimes occur, particularly early in the course of infection. Some cutaneous manifestations, such as the acute exanthem, occur within the first 48 hours of the illness, and may precede the development of detectable antibodies. If clinically indicated, serologic testing may be repeated once or twice over the following 2 months, in order to document seroconversion.146 Persistently false negative serologies may occur in a small percentage of HIV-infected patients, other immunosuppressed patients, and even occasionally in immunocompetent individuals.98

**Culture and microscopy**

The organism may be detected by culture of tissue specimens on most mycologic or bacteriologic media.146 Growth is rapid, occurring in as early as 2 days to more than 5 days.15 The colonies are typically white and cottony, but the morphology and color are variable.146 The microscopic appearance also
is nonspecific in cultured specimens. Arthroconidia are typically barrel-shaped. The cultured organism is specifically identified by DNA probes or by detection of specific coccidioidal exoantigens. When specimens are submitted for culture, the laboratory should be appropriately notified because of the potential danger to laboratory workers.

Direct microscopic visualization provides another means of identification. In tissue specimens and in cytologic smears, the spherules may be visualized with fungal stains or with a routine hematoxylin-eosin stain (Fig 10). The thick-walled spherules are usually distinguishable from other parasitic fungi by their relatively large size (10 to 80 microns). Characteristic endospores are frequently seen within the spherules.

Molecular techniques

Molecular techniques, such as in situ hybridization (ISH) and polymerase chain reaction (PCR), may assist in the identification of *C. immitis/posadasii* in paraffin-embedded tissue. ISH is less sensitive but more specific than standard histochemical stains, such as methenamine silver stain. In cases where the visualized organisms are not morphologically distinctive, ISH may provide specific confirmation in histologic sections. This technique may be particularly useful in distinguishing small, immature spherules of *C. immitis/posadasii* from Blastomyces dermatitidis and Cryptococcus neoformans. It should be noted that the spherules generally must be visible with standard histochemical stains, in order for ISH to be helpful. In addition to ISH techniques, PCR assays have recently been described for identification of *C. posadasii* DNA in paraffin-embedded specimens.

Skin testing

Delayed hypersensitivity skin tests for coccidioidal antigens are useful in population studies, which evaluate overall trends in the incidence of coccidioidomycosis. However, skin testing is of limited usefulness in the diagnosis of an acute infection. A positive skin test does not distinguish current infection from prior infection. In addition, anergy may develop during active infection in some cases. Individuals with reactive skin tests often show waning in reactivity after approximately 12 to 15 years. Currently, the delayed hypersensitivity skin tests for coccidioidal antigens are not generally available for clinical use in the United States.

Imaging studies

In acute symptomatic pulmonary coccidioidomycosis, chest radiographs demonstrate parenchymal abnormalities in almost 75% of cases. Segmental pneumonia is the most common pattern. Other common findings include single or multiple pulmonary nodules, hilar or mediastinal lymphadenopathy, and pleural effusions. The findings are not specific and may mimic bacterial pneumonia, tuberculosis, or a malignancy. Approximately 5% of patients will develop chronic abnormalities, such as pulmonary cavities or persistent nodules. In disseminated infections, chest radiographs may reveal a reticulonodular or diffuse milky pattern.

In complicated or disseminated infections, other imaging modalities may be indicated in addition to standard chest radiographs. Computed tomography of the lungs and central nervous system may be helpful in individual cases. Scintigraphy provides a useful screening tool when disseminated skeletal involvement is suspected. With plain radiographs, skeletal lesions usually have a lytic, “punched out” appearance. Nearly any bone can be affected, but the axial skeleton is most frequently involved. Computed tomography and magnetic resonance imaging may be useful in evaluating involvement of the soft tissues and spine.

**TREATMENT**

The therapeutic approach to coccidioidomycosis is based predominantly upon three factors: (1) the severity of the pulmonary infection, (2) the presence or absence of dissemination, and (3) the individual patient’s risk factors. Treatment guidelines have recently been published and are also currently available online at the Infectious Diseases Society of America Web site (http://www.IDSociety.org) under the heading of Practice Guidelines.

In immunocompetent patients with primary uncomplicated pulmonary infection, antifungal therapy is controversial. Prospective controlled trials have not been performed. There is no evidence that treatment of the primary infection mitigates the severity of the illness or prevents complications. For most patients with a mild respiratory illness, many authorities believe that antifungal therapy is not necessary. Patients should be periodically evaluated clinically and radiographically for one to two years, in order to document resolution of the infection. On the other hand, some experts advocate systemic antifungal therapy for all symptomatic patients. Either itraconazole 200 mg twice daily or fluconazole 400 mg/d may be given by mouth for approximately 3 to 6 months.

If risk factors for dissemination are present, antifungal therapy should be given. HIV patients, allograft recipients, and other immunosuppressed patients may be treated with systemic antifungal agents. Specific ethnic backgrounds, such as
Filipino or African American ancestry, may also be considered a risk factor for dissemination. Regardless of the patient’s ethnicity, antifungal therapy may be strongly considered for symptomatic pregnant patients (particularly during the third trimester) and in the post-partum period. During pregnancy, amphotericin B is the treatment of choice. In pregnant women, the azoles are contraindicated because of the risk of teratogenicity.

Prophylactic therapy may have a role in the care of some immunosuppressed patients, who have a high risk of developing coccidioidomycosis. Targeted azole chemoprophylaxis may be considered for specific groups of organ transplant recipients and HIV patients. Antifungal therapy is indicated in patients with disseminated infection or severe pulmonary infection. Treatment recommendations for severe infections are included in the recently published comprehensive guidelines and are beyond the scope of this review. After initial treatment of disseminated infection, lifelong therapy with azoles may be required in some cases. Azoles are fungicidal, rather than fungistatic. Recurrences are common after discontinuing therapy. In the future, a variety of new antifungal medications may prove to be useful in the treatment of coccidioidomycosis. Efforts to develop a vaccine are in progress.

CONCLUSION

Coccidioidomycosis is a "great imitator" with protean clinical manifestations. Knowledge of the diverse cutaneous clues can be helpful in the diagnosis of this increasingly important disease.

The author is grateful for the assistance of Ms Aimee Volner in the Section of Illustration & Design at Mayo Clinic in Rochester, Minnesota. Ms Volner designed the adaptations of the diagrams in Figs 1 and 2. The author’s colleague Dr Joseph P. Fiore is thanked for contributing adaptations of the diagrams in Figs 1 and 2. The author’s colleague Dr Joseph P. Fiore is thanked for contributing adaptations of the diagrams in Figs 1 and 2.

REFERENCES

29. Possession, use, and transfer of select agents and toxins; interim final rule. Vol 42 C.F.R §73.4-73.5; 2002.