Coccidioidomycosis

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KEYWORDS

• Coccidioidomycosis • Coccidioides • Epidemiology • Treatment • Meningitis
• Primary infection

KEY POINTS

- The incidence and geographic range of coccidioidomycosis continues to expand.
- Coccidioidomycosis is responsible for up to 25% of all community-acquired pneumonia within the endemic region.
- Pulmonary nodules secondary to prior coccidioidal infection represent a significant problem within the endemic region and are not easily distinguishable from malignancy.
- Disseminated coccidioidal infection requires long courses of antifungal therapy increasing toxicity concerns.

INTRODUCTION

Coccidioidomycosis is a fungal disease caused by *Coccidioides immitis* and *C posadasii*. These dimorphic saprophytic fungi lay latent as a mycelial form in dry desert soil developing into arthroconidia. The organism seems to survive well in areas with lower amounts of rainfall (12–50 cm per year), few winter freezes, and alkaline soils. Initial human infection occurs primarily by inhalation of aerosolized spores and in rare cases through direct cutaneous inoculation.[1,2] The inoculum needed for infection can be quite small, even a few arthroconidia.[3] Following inhalation, arthroconidia undergo morphologic change and turn into spherules (large structures containing endospores).[4] This structure can rupture, leading to the spread of endospores hematogenously or through the lymphatics into virtually any organ, which in turn may develop into a new spherule. Human disease can range from asymptomatic to severe,

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disseminated disease, and death. Individual control of disease depends greatly on that host's immune response.

EPIDEMIOLOGY

The geographic range of *Coccidioides* has been derived from clinical cases, soil testing, and from skin testing performed in 1957 throughout the Southwestern United States.[5,6] The exact ecologic niche remains to be determined. Endemic areas where disease is prevalent include Arizona, California, New Mexico, Nevada, Utah, Washington, Texas, Mexico, and some areas in Guatemala, Honduras, Venezuela, Brazil, Argentina, and Paraguay.[7,8] In the United States, the annual incidence of coccidioidomycosis is variable but overall is increasing, from a rate of 5.3 per 100,000 in 1998 to a rate of 42.6 in 2011.[9] Of these cases reported to the Centers for Disease Control and Prevention, 66% were from Arizona and 31% from California. Despite the increased incidence, from an analysis of death certificates, the age-adjusted mortality rate from 1990 to 2008 has remained stable at approximately 0.59 per million person years.[10] There were 1451 coccidioidomycosis-related deaths in California compared with 1010 in Arizona despite its higher annual reported case rate.

The incidence of coccidioidomycosis in California and Arizona can vary greatly by geographic region and may be seasonal in pattern. In a yearly summary by the California Department of Health, the overall incidence of coccidioidal infection in the state increased from 4.3 to 11.6 per 100,000 population between 2001 and 2010.[11] In Kern County, however, the rate reported in 2011 was much higher, 241 per 100,000 population.[12] Similar increases have been observed in Arizona.[13,14] The reasons for the overall increase are not fully clear and have been attributed to changing environmental conditions, human activities in endemic areas, changing surveillance methods and definitions, increased numbers of immunosuppressed individuals, and even improved awareness and diagnostic testing rates.[15] In endemic regions, the people most affected are construction and farm workers, military personnel, archaeologists, excavators, inmates, and officers in correctional facilities.

Epidemics in endemic regions have occurred after dust storms, earthquakes, and earth excavation where dispersion of arthroconidia is facilitated.[2,13] In Washington State, 3 cases were recently reported, an area not previously considered endemic; follow-up soil testing showed the presence of *Coccidioides immitis*, suggesting the geographic range of this organism is larger than previously thought.[16,17] After coccidioidomycosis became a reportable condition, the case rate even in nonendemic regions (eg, recent report in Missouri) increased substantially; but many cases were among people who never previously traveled to an endemic region and were diagnosed serologically rather than by culture, polymerase chain reaction (PCR), or histopathologically.[18] Clinical cases of coccidioidomycosis in patients from nonendemic regions are often reported; but frequently a link is established, however brief the transit, to an endemic region.[19] There is even a case report of coccidioidomycosis in Hong Kong in a patient who is thought to have contracted the disease by sweeping shipping containers from the United States with no other link to the endemic region.[20]

DIAGNOSTIC TESTING

Currently, diagnosis can be established using immunologic assays, culture, or histopathology of tissues involved.[21] In mammalian tissues, coccidioidomycosis exists nearly exclusively as a characteristic spherule with endospores (**Fig. 1**). Spherules are approximately 60 to 100 μm in diameter and can contain hundreds of variable-sized daughter endospores, each capable of propagating infection. Rarely, hyphae

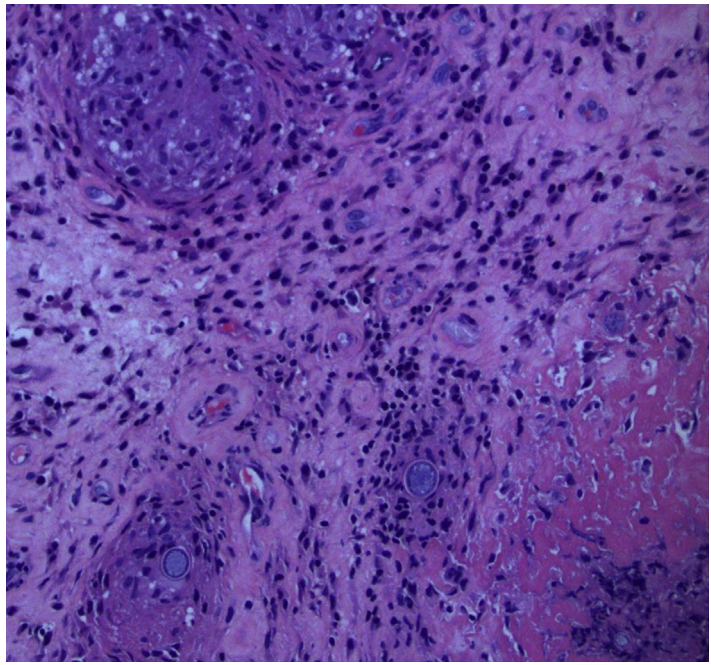

Fig. 1. *Coccidioides* spherules with associated granuloma obtained from a hip fluid collection (hematoxylin-eosin, magnification ×40).

and other atypical forms have been identified in tissues, such as lung cavities or bone.[22–25] In addition to histopathology, culture of the fungus isolated from a clinical specimen (ie, bronchoalveolar lavage, cerebrospinal fluid [CSF] culture, tissue culture) confirms the diagnosis.[21] Nucleic acid amplification is still being evaluated and developed for use in clinical diagnosis, with several centers using novel primers.[26–30] Its potential ability to effectively detect organism in culture-negative samples would be welcome but is as yet unproven. Skin testing to identify the presence of cellular immunity to *Coccidioides* species is also being redeveloped after a multi-decade absence; the reader is referred to the excellent review by Wack and colleagues.[31] Its use is anticipated in both clinical and epidemiologic scenarios and for screening of at-risk populations.

Currently, most clinical infections are diagnosed serologically in the setting of a compatible clinical syndrome. Immunodiffusion (ID) for the detection of immunoglobulin G–(IgG) and IgM-specific antibodies is a preferred test for detection of exposure to *C immitis*, with high specificity. Complement fixation (CF) tests for IgG-specific antibody are most useful in immunocompetent patients, both for diagnosis and long-term disease assessment.[32] The CF titer can be useful in monitoring disease activity and may revert to negative with long-term disease control. CF titers greater than 1:16 increase the possibility of disseminated disease. Very early in a patient's infection, serologic results may be negative. Most frequently performed on blood samples, serology may also be performed on CSF and other samples, such as joint or pleural fluid. Serologic assays are less reliable in immunocompromised patients with 20% to 50% of patients testing negative with these methods. In forms of disease with a more benign clinical course, such as patients with isolated pulmonary nodules confirmed by culture or histopathology, serologic testing may often be negative.

Other assays, such as latex agglutination and enzyme-linked immunosorbent assay, have been used in the endemic region as well, though with mixed results and often with a high false-positive rate.[33,34] *Coccidioides* galactomannan antigen testing and serum (1→3)-β-D-glucan are available in some reference laboratories and undergoing further evaluation for their role in patient diagnosis or management.[35] Identification may also be possible through the use of commercially available ribosomal RNA probes.[36]

CLINICAL MANIFESTATIONS AND MANAGEMENT

Coccidioidomycosis is a highly variable illness. On inhalation of the spores, 60% of people may develop an asymptomatic infection or a mild respiratory illness and the rest will develop the disease in a variable manner.[37] Disseminated infection or progressive pulmonary infection occurs in 1% to 3% of people infected with *Coccidioides* spp. Dissemination is often an early clinical event; the most common extrapulmonary (EP) sites include skin, lymph nodes, bones, joints, and the most severe being the central nervous system.

Although coccidioidomycosis manifests primarily as a respiratory illness, in certain groups the chance of dissemination or development of a chronic infection remains high. Individuals with human immunodeficiency virus (HIV)/AIDS and recipients of immune-modulating drugs or immunosuppressive drugs or high-dose corticosteroids are at high risk for dissemination and chronic infection.[38] Diabetes mellitus is a significant risk factor for severe pulmonary infection as well as chronic structural lung disease or cardiopulmonary disease. Dissemination is more common in women in the third trimester of pregnancy or immediately post-partum.[39,40] There is also a several-fold higher relative risk of dissemination in individuals of African American and Filipino decent.[37] Accordingly, mortality rates are observed to be higher in persons greater than 65 years of age, men, Native Americans, and Hispanics as well as those with conditions such as vasculitis, rheumatoid arthritis, systemic lupus erythematosus, HIV infection, tuberculosis, diabetes mellitus, chronic obstructive pulmonary disease, and non-Hodgkin lymphoma.[10] Treatment and/or monitoring of such groups should be approached carefully and with diligence.

Management entails careful periodic assessment. Limited pulmonary infections may not require treatment, whereas other patients may require short-course, prolonged, or lifetime antifungal therapy, which is determined by comorbidities, risk of dissemination, and persistent systemic signs and symptoms, such as fever, night sweats, weight loss of more than 10%, fatigue, radiographic findings of extensive infiltrates involving multiple lobes or effusion, and CF of 1:16 or higher.[38]

Primary Pulmonary Infection

In endemic regions, primary coccidioidal pneumonia may account for approximately 25% of all community-acquired pneumonia.[41] It occurs 1 to 3 weeks after the exposure to arthroconidia. The presence of erythema nodosum or erythema multiforme is considered a favorable prognostic sign and is due to robust immune response rather than dissemination.[42] Radiographic findings are usually consistent with segmental or lobar consolidations and may have hilar or mediastinal adenopathy.[15] Before the advent of advanced imaging, mediastinal adenopathy was thought to be a risk factor for disseminated disease; however, more recent evidence has not demonstrated such an association.[43] Pleural effusion has been estimated to occur in 5% to 15% of primary pulmonary coccidioidomycosis.[30,44] In a recent series, pleural effusions were diagnosed more often in those with primary pulmonary infection than those with

disseminated disease ($P<.001$).[44] Pleural effusions are exudative, often with a lymphocytic predominance, and may have eosinophilia. Empyema occurred in a quarter of pleural effusions, and resolution required thoracotomy in one series.[44] However, in a recent series of pediatric cases, McCarty and colleagues[45] found that of 13 patients with pleural effusion and 4 with empyema, none required decortication and only 2 were in need of chest tube drainage.

Whether to treat or to observe acute pneumonia is an unresolved matter because of the lack of prospective randomized trials. Indeed, current guidelines depend heavily on expert opinion and clinical experience. It is estimated that approximately 95% of symptomatic primary coccidioidomycosis may resolve spontaneously.[38,46] Although many clinicians may elect to treat diagnosed primary coccidioidomycosis, the use of empirical antifungals for community-acquired pneumonia in endemic regions is unproven; in fact, very early administration may abrogate the development of IgG antibodies (although the clinical significance of this is unclear).[47] Factors that do influence the decision to treat are prolonged infection, radiographic findings, CF titers, immunosuppression, and comorbidities. If antifungal therapy is determined necessary, fluconazole or itraconazole are recommended for 3 to 6 months and possibly longer depending on the clinical response. Pregnant patients have significant risk for dissemination and can be treated with amphotericin B (AmB) or immediately postpartum with fluconazole.[38] Some experts suggest the use of azoles during the second and third trimester and an AmB-based regimen during the first trimester.[39]

Diffuse Pneumonia

Diffuse pneumonia is a more severe form of the disease that can happen in a setting of high inoculum exposure or with accompanying immunosuppression and is often seen in patients with the risk factors mentioned earlier (**Box 1**). Patients are ill appearing in mild to moderate respiratory distress often with fever. Radiographic finding are usually consistent with multilobar diffuse infiltrates and adenopathy. Serious complications, such as pleural effusions, empyema, and acute respiratory distress syndrome (ARDS), are often seen.[15] Even with antifungal therapy, clinical improvement in such disease may be slow and patients often require significant and prolonged supportive care.

Box 1
Risk factors for severe or disseminated coccidioidomycosis

Filipino or African ethnicity

HIV/AIDS

Immunosuppressive medications
- Prednisone
- TNF-α inhibitors
- Chemotherapy
- Organ transplantation (tacrolimus, and so forth)

Diabetes mellitus

Pregnancy

Cardiopulmonary disease

CF titer of 1:16 or greater

Abbreviation: TNF, tumor necrosis factor.

ARDS as a consequence of coccidioidal infection carries a very high mortality rate. AmB is frequently used until clinical improvement occurs, followed by an azole for at least 1 year or longer. In selected individuals with ongoing immunosuppression or irreversible conditions, long-term maintenance therapy with an azole is suggested. The role of adjunctive corticosteroid therapy in coccidioidomycosis-associated ARDS has not been defined, and considerable debate exists between different clinicians.

Residual Nodule, Cavity, and Chronic Infiltrates

Approximately 5% of patient with resolution of primary pneumonic infiltrate can develop a pulmonary nodule or cavity. The initial identification of a coccidioidal infection could be a pulmonary nodule or cavity found incidentally on imaging studies. Nodules due to *Coccidioides* are often difficult to differentiate from malignancy, especially in persons who have not been diagnosed with coccidioidomycosis previously (**Fig. 2**). PET/computed tomography has been used but is not always able to differentiate malignancy from coccidioidal pulmonary nodules. In an endemic region of California with a lung nodule program, approximately one-third of nodules are attributable to *Coccidioides*. Certain factors may have increased association with a coccidioidal nodule rather than malignancy, including male sex, age less than 55 years, lack of underlying pulmonary disease, farm labor or construction occupations, a nodule less than 2 cm in size, and a nodule described as diffuse or smooth in appearance.[48] Immunologic assays may be less reliable in this setting; often a bronchoscopy or biopsy is required to establish the diagnoses via histopathology, culture, and possibly PCR. Asymptomatic nodules attributed to coccidioidomycosis do not require treatment. When such lesions are stable over time with repeated radiographic imaging over 2 years in combination with a benign clinical course, no intervention is necessary.[19] Any treatment decision should take into account patient risk factors, serologic studies, and characteristics of the lesion.

Coccidioidomycosis is also known to cause cavitary disease in the lung, ranging from asymptomatic to symptomatic and/or ruptured. Although cavities are characteristically described as thin-walled and solitary, the morphology can be variable. Asymptomatic cavities can often be monitored radiographically, and the use of azole therapy is unproven. Symptomatic cavities may cause local discomfort or hemoptysis, and bacterial superinfection is possible. For symptomatic cavities or in those with elevated CF titers, a course of oral antifungals may be considered in order to improve symptoms but may not result in cavity closure. A more serious complication is a rupture of a cavity into the pleural space causing hydropneumothorax. In such cases,

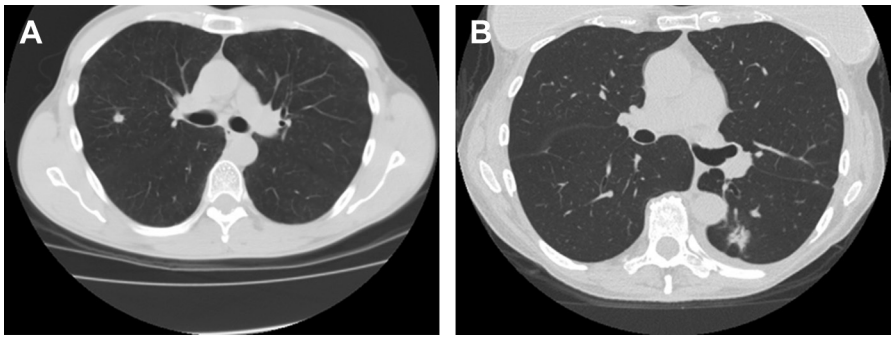

Fig. 2. Panel (*A*) coccidioidal nodule in a male, 40-pack-year smoker. Panel (*B*) adenocarcinoma of the lung in an asymptomatic, nonsmoking woman who recalls a respiratory infection 3 months prior. (*Courtesy of* Dr Michael Peterson, UCSF-Fresno, CA, USA.)

antifungal therapy along with surgical closure by lobectomy with decortication should be considered, especially in younger healthy patients. Initial antifungal therapy can include AmB or azole therapy.

A small percentage of patients may develop chronic fibrocavitary disease, which encompasses persistent ongoing symptoms of cough, fever, weight loss, and fatigue lasting for several months. Radiographic findings may show multifocal consolidations with cavitary lesions. Fluconazole or itraconazole are often prescribed for longer durations (a year or longer). If the response is suboptimal despite prolonged therapy, options include increased dosing or changing agents to AmB or an alternative azole. Newer azoles can be tried and have been used successfully.[49] Surgical options should be explored in those not responsive to therapy with persistent hemoptysis.

Extrapulmonary Disease

EP disease often develops through hematogenous or lymphatic spread and can involve one or multiple sites. Patients in certain risk groups or with impaired immunity as previously discussed are also at higher risk of dissemination. Depending on the anatomic site of infection, patients invariably require prolonged antifungals, with some needing concomitant surgical intervention for debridement and stabilization. Surgical treatment is especially important with vertebral column involvement with associated neurologic deficits. Surgical intervention can be essential where there is formation of abscesses, clinical evidence of worsening or incomplete disease control, persisting focal symptoms, and neurologic or physiologic compromise.[38,50] Dissemination to a wide range of tissues has been described. Common sites of dissemination include the meninges, skeleton, skin, and joints; but there are reports of involvement in glandular tissue, peritoneum, visceral organs the including liver and pancreas, the pericardium, bone marrow, kidney and bladder, and male and female reproductive organs.[51,52]

The initial antifungal therapy recommended is fluconazole or itraconazole. However, the preferred treatment of osseous coccidioidomycosis is itraconazole.[53] For patients with disseminated infections that seem to be worsening rapidly or who do not respond to initial oral azole therapy, strategies include switching therapy to another azole, or to AmB deoxycholate (AmB-d), or a lipid-based AmB, or even an azole in combination with AmB. These choices are frequently based on case reports and the clinical experience of the treating physician. Treatment duration is prolonged; often several years until disease is inactive both clinically and serologically with close follow-up for relapses.

Coccidioidal Meningitis

The most deleterious EP dissemination is the spread of *Coccidioides* spp to the central nervous system (CNS) causing meningitis. A lumbar puncture with analysis of CSF should be done in any patient with suspected or previously diagnosed coccidioidomycosis presenting with a headache, blurry vision, photophobia, meningismus, decline in cognition, hearing changes, and focal neurologic deficit. As illustrated in a recent retrospective study, there is no evidence to support routine CSF analysis in patients in at-risk groups (age, ethnicity, CF titer, and so forth) if they do not have CNS symptoms.[54] The diagnosis of coccidioidal meningitis (CM) is based on a positive serologic testing (ID/CF) or culture of CSF. CSF analysis typically shows an elevated white blood cell count with a mixed or lymphocytic pleocytosis, a high level of protein (sometimes measurable in grams per deciliter rather than milligrams per deciliter), and a low level of glucose. Imaging studies are helpful in evaluating complications associated with meningitis. Initial features of illness may be difficult to distinguish from other causes without detailed testing, notably tuberculosis and even autoimmune illnesses.

When left untreated, CM is uniformly fatal.[55] In a historical series reported by Vincent and colleagues,[55] before the availability of antifungals, 17 patients with CM were followed, all of whom died within 31 months. This review also commented on the combined survival statistics described in 5 reports of 117 patients whereby 91% of patients with CM died within 1 year and all died within 2 years. Although the fatality has improved with the use of AmB and azoles, morbidity is still substantial because of complications from the disease, devices used for treatment management, and side effects of the medications, as much higher recommended doses are necessary for a prolonged period of time.[56]

The most common life-threatening complications of meningitis include hydrocephalus, CNS vasculitis, cerebral ischemia, infarction, vasospasm, and hemorrhage. Basilar meningitis and spinal cord involvement may also be encountered. In patients with hydrocephalus, a ventricular shunt is necessary for decompression. Such shunts, often placed distally into the abdominal cavity, may develop secondary infections, obstruction due to persistent coccidioidomycosis, and/or abdominal pseudocysts.[57] It is not uncommon for patients to require multiple shunt revisions. As illustrated in several case reports, repeated obstruction of the shunt and isolation of fungus should alert one to seek alternate antifungal therapy. Some clinicians have used steroids for vasculitis, though this is considered anecdotal.

For the treatment of CM, most clinicians prefer therapy with oral fluconazole.[38] Although the dose studied in an uncontrolled clinical trial was 400 mg, it is common to begin therapy with 800 to 1200 mg per day of fluconazole.[56,58] Before the advent of azoles, AmB was the only drug of choice but was ineffective when given intravenously and required frequent administrations via the intrathecal (IT) route. Because of challenges of administration, toxicity associated with this route, and lack of experience in using this method, current practitioners seldom resort to recommending AmB as initial therapy, although lipid formulations have been used in the salvage setting successfully.[59] Although there are no trials comparing IT AmB and fluconazole, the response rate of IT AmB has ranged from 51% to 100% in studies published before 1986 and with fluconazole the rate is near 79%.[58,60] With fluconazole symptoms resolve within 4 to 8 months, though there is a delay in normalization of CSF abnormalities, which may persist in the presence of a shunt. Based on clinical experience and because of an extremely high relapse of 78% noted in a small series when therapy is discontinued, lifelong treatment with azoles is recommended.[61]

Assessing a patient's response to therapy is primarily a matter of serial evaluation and clinical judgment. Favorable signs include return to premorbid functioning, decreasing CF titers, and excellent adherence to medical care and therapy. Some patients with chronic meningitis have refractory illness with poor recovery or exceptionally slow improvement. A combination of serology and repeated CSF evaluation may be necessary to assess microbiologic and serologic improvement. Adherence counseling, assessment of drug-drug interactions, therapeutic drug monitoring, and consideration of alternative antifungal therapy may be necessary. For patients with CM who are failing treatment and/or have refractory coccidioidal disease, salvage regimens may be necessary. Both voriconazole and posaconazole have been used in this situation, with a growing body of case series and clinical experience to support their use.

Coccidioidomycosis in Immunocompromised Patients

Patients with impaired immune function are at risk for both symptomatic infection as well as reactivation of latent disease. The risks of novel infection are often presumed higher in such a group, but definitive incidence data are limited. In a study of 2246 solid organ transplant (SOT) recipients in Arizona, 239 (10.6%) had positive serologic

testing with nearly all (212 of 239) showing evidence of coccidioidomycosis before transplantation.[62] Posttransplant, an additional 27 of the 2246 patients (1.2%) developed newly acquired, active disease. In a study of allogeneic hematopoietic stem-cell transplant (allo-HSCT) patients, 11 of 426 (2.6%) developed active coccidioidomycosis after transplant.[63] In these groups, the rates of dissemination and mortality are higher than in the general population, with up to 55% mortality observed in allo-HCT recipients and 28% in SOT recipients.[62–64] Observation of such outcomes has led many clinicians to recommend prophylaxis in high-risk transplant recipients. Because of the suboptimal testing sensitivities, achieving a diagnosis can be challenging and may require multiple testing modalities.[62]

Further studies have demonstrated that patients with serologic evidence of prior coccidioidomycosis before organ transplantation have higher rates of posttransplant coccidioidomycosis than others, suggesting that *Coccidioides* may reactivate from latency, with some risk factors including high-dose prednisone, and treatment of rejection.[65] In the aforementioned study of allo-HSCT patients, 8 of 426 (1.9%) had asymptomatic positive serologic tests before transplantation, and 2 (25%) had reactivation following transplantation. Although antifungal prophylaxis has been evaluated and seems effective in some studies, it may not be a panacea. In a study of 100 patients with coccidioidomycosis who underwent SOT, 94% received antifungal prophylaxis; of this group, 5 patients experienced reactivated infection.[66] Notably, all patients survived with modified ongoing antifungal therapies.

It should also be noted that donor-derived coccidioidomycosis is possible.[67] Transmission rates are difficult to determine, but onset of disease has a high mortality in these patients. Pretransplant recipient and donor screening in endemic areas or with a history of travel to endemic areas is recommended. Multiple testing modalities may be considered depending on clinical presentation and may include serology, pathology, culture, PCR, and, in the future, skin-testing. An excellent review has been recently published.[62] In patients with HIV, coccidioidomycosis may be considered an opportunistic infection. Although primary prophylaxis has not been demonstrated to be effective, treatment of primary pulmonary coccidioidomycosis is warranted, especially if CD4+ lymphocyte counts are less than 250 cells per microliter.[68] Secondary prophylaxis may be considered until counts increase greater than 250 cells per microliter.

The advent of biological therapies and targeted chemotherapeutics has resulted in further questions regarding their use in endemic areas. At present, the exact risks of acquiring coccidioidomycosis on any given biological agent are unknown. In a convenience sample in an endemic area, 1.9% of patients in a rheumatology center had evidence of coccidioidomycosis.[69] The prevalence in patients with rheumatoid arthritis (RA) was approximately 3.1%, but use of tumor necrosis factor α inhibitors could not be proven to have association in this study. In contrast, a prior study of patients receiving infliximab and etanercept found 13 cases of coccidioidomycosis (7 of 247 in the infliximab group vs 4 of 738 treated with other modalities, relative risk 5.23, $P<.01$).[70] Screening may be used, but the benefit is unclear. Antifungal prophylaxis is not currently recommended.

ANTIFUNGAL THERAPY

Amphotericin

In severe or refractory coccidioidal disease, intravenous AmB is considered the drug of choice. AmB is a polyene antifungal agent that binds to sterols in the fungal cell membrane causing intracellular components to leak resulting in cell death. Its use came into practice in the mid-1950s; recognition of the poor CNS penetration led to

the development of administering IT AmB via lumbar, cisternal, or ventricular routes in salvage settings.[71] IT treatment changed the outcome of CM; however, numerous surgical, mechanical, and infectious complications along with headaches, paresthesia, nerve palsies, myelopathy, arachnoiditis, hemorrhage, transverse myelitis, and more have led to its use only for those with refractory disease and also with consultation with experienced physicians who have pioneered these techniques.

Data on the use of lipid preparations of AmB are scant and are largely derived from animal models. Clemons and colleagues[72] compared the efficacy of intravenous liposomal AmB with those of oral fluconazole and intravenous AmB-d for the treatment of experimental CM. All regimens reduced the numbers of colony forming units (CFU) in the brain and spinal cord; however, liposomal AmB–treated animals had 3 to 11 fold lower numbers of CFU than fluconazole and 6 to 35 fold lower numbers of CFU than AmB-d-treated rabbits. Another animal model that compared intravenous AmB lipid complex (ABLC), AmB-d, and oral fluconazole showed that ABLC cleared CFU from CSF faster than AmB-d or fluconazole.[73] Although no formal guidelines exist regarding the use of these agents, the data discussed earlier indicate that lipid formulations of AmB may be of benefit, as it can be administered at higher doses with less toxicity.

Azoles

The introduction of azoles was a significant breakthrough in the treatment of coccidioidomycosis for both meningeal and nonmeningeal disease. These agents act by inhibiting the synthesis of ergosterol in the fungal cell membrane.[74] The first trials with azoles included clotrimazole, then miconazole whose use quickly faded because of toxicity, frequency of dosing, ineffectiveness, and lack of oral availability. Ketoconazole was the first oral agent to be used in the treatment of coccidioidomycosis, although only 20% to 30% of patients demonstrated a clinical response to 200 to 400 mg/d. Dose escalation was attempted to increase drug efficacy; however, gastrointestinal intolerance, adrenal insufficiency, and gynecomastia ultimately limited the use of this agent.[75,76]

Third-generation azoles, the triazoles, were introduced in the 1980s and showed promising efficacy with less toxicity, especially with higher dosing and prolonged use. First was itraconazole with excellent in vitro activity against *Coccidioides* spp.[77] The Mycosis Study Group documented its tolerance and efficacy in which 57% of the 47 patients with nonmeningeal coccidioidomycosis achieved remission.[78] In one randomized double-blind placebo-controlled trial for nonmeningeal coccidioidomycosis, patients with skeletal infections responded twice as frequently to itraconazole than fluconazole, though the study dose of fluconazole was lower than is currently used.[53] Itraconazole CSF penetration is not optimal; but it does concentrate in fatty tissues, including the brain, and has demonstrated efficacy in the treatment of CM.[79] Among its different formulations, itraconazole solution has greater bioavailability than capsules and is maximally absorbed in the fasting state.[74] For the maximum absorption of the capsular form, an acidic environment with intake of a high-fat meal is preferred. At doses of 800 mg and higher, adverse effects included adrenal insufficiency, hypertension, hypokalemia, and edema. Negative inotropic effects have also been reported,[80] but this is uncommon in clinical practice.

Fluconazole was the next to be developed, and it still remains the preferred triazole because of its excellent bioavailability, tolerability, CNS penetration, slow clearance (24- to 30-hour half-life), little hepatotoxicity, renal clearance, no endocrine side effects, reasonable response rates in prior reports, and generally lower costs. In a multicenter, open-label, single-arm study, among 75 evaluable patients, a satisfactory

response was observed in 12 (86%) of the 14 patients with skeletal, 22 (55%) of the 40 patients with chronic pulmonary, and 16 (76%) of the 21 patients with soft tissue disease.[81] Forty-one patients who responded were followed off the drug, and 15 (37%) of them experienced reactivation of infection. Tucker and colleagues[82,83] identified fluconazole to have potential use in coccidioidal meningitis. This study was followed by the landmark study by Galgiani and colleagues[58] that showed fluconazole to achieve the same response rate for CM as its historical counterpart IT AmB. Thus, because of its favorable activity and minimal toxicity, current guidelines recommend fluconazole (800–1200 mg) as the preferred agent for meningeal infection. Daily doses up to 2000 mg have been used in some cases. With improving host control of the infection, fluconazole doses may be decreased slowly over time; but a specific effective maintenance dose for meningeal and/or disseminated disease is not well established.

The disadvantage of azole therapy is the inability to eradicate the fungus, which seems to be a class effect; thus, treatment is continued indefinitely as a suppressive rather than curative therapy for CM, although newer formulations and agents may offer mean fungicidal concentrations achievable in clinical care. Therapeutic drug monitoring of fluconazole can be done in patients with complicated courses of illness or who are not responding clinically. Commonly encountered adverse effects with higher doses ($\geq$400 mg) of fluconazole include dry mouth, dry skin, nausea, reversible alopecia, and abnormal liver function tests.

Newer Triazoles

Voriconazole and posaconazole are newer triazoles and are primarily used in patients whose coccidioidal infection is refractory to first-line azole therapy. They both have excellent activity in vitro against *Coccidioides* spp (**Table 1**).[84] In vitro concentration studies are frequently based on mycelial phase fungal growth, and extrapolation to human disease is the subject of ongoing evaluation. Similar to fluconazole, voriconazole is an attractive choice because of its favorable pharmacokinetic/pharmacodynamics in the CSF. Voriconazole is available in parenteral and oral formulations with excellent oral bioavailability. Therapeutic drug monitoring should be considered, as voriconazole serum concentrations can vary between individuals.[74] Administration of voriconazole may be complicated by drug-drug interactions as a result of its inhibition of CYP2C9, CYP2C19, and CYP3A4 enzymes. Adverse effects may also limit use; besides the visual disturbance, neurotoxicity, hepatotoxicity, photopsia, and QTc prolongation, concerns have been raised with long-term use of voriconazole for the

Table 1
In vitro susceptibility of *Coccidioides* isolates to selected antifungal agents

Coccidioides spp 30 Isolates	MIC Range	Geometric Mean MIC	MIC_{50}	MIC_{90}
Amphotericin B	0.03–0.125	0.056	0.06	0.125
Itraconazole	0.03–0.5	0.149	0.125	0.5
Fluconazole	2–64	8.774	8	32
Voriconazole	0.06–1.0	0.193	0.125	0.5
Posaconazole	0.06–1.0	0.183	0.125	0.5
Isavuconazole	0.125–1.0	0.28	0.25	0.5

Abbreviation: MIC, minimal inhibitory concentration.

Data from Gonzalez GM. In vitro activities of isavuconazole against opportunistic filamentous and dimorphic fungi. Medical Mycol 2009;47(1):74.

development of periostitis because of hyperfluorosis and melanoma in situ.[85–87] However, a small study of nontransplant patients with chronic coccidioidomycosis on long-term fluorinated triazole therapies did not identify significant long-term osseous effects despite elevated plasma fluoride levels.[85]

Posaconazole has also been shown to have potent in vitro and in vivo activity against *Coccidioides* spp. It has been tested in murine models and shown to be 200 fold or greater as potent as fluconazole and 50 fold or greater potent as itraconazole along with having fungicidal activity in vivo against *C immitis*.[88] Posaconazole is available in liquid, capsule, and intravenous formulations. Historically, it was available in liquid form only, requiring it be taken with a fatty meal and acidic beverage, which limited optimal absorption in severely ill patients. Most reported studies on the use of posaconazole were done before the advent of capsule and intravenous formulations. Adverse events include gastrointestinal effects, rash, and elevated transaminases.[89] Drug cost remains a significant problem for many patients.

Isavuconazole is a newly available extended-spectrum triazole with in vitro activity against *Coccidioides* spp.[84] Limited clinical data have been presented to date regarding the in vivo efficacy, and thus far it has been prescribed only to patients with primary coccidioidal pneumonia. It has been effectively used for other invasive fungal infections, including *Aspergillus*, Mucorales, and other endemic fungi as well; a clinical trial for the treatment of nonmeningeal disseminated and chronic coccidioidomycosis is currently underway.

Echinocandins

The echinocandins have little inherent activity against *Coccidioides* spp in the mycelial phase; however, the potential efficacy has been demonstrated in murine models of infection.[90] There are case reports of caspofungin being used in combination with azole- or amphotericin-based therapies. In a series of 9 pediatric patients, Levy and colleagues[91] have reported clinical improvement in 8 cases in which a salvage regimen of caspofungin plus voriconazole was used following treatment failures. As publications describing the potential efficacy of these agents are limited, this class should not be used as monotherapy in the treatment of coccidioidomycosis at this time.

Interferon Gamma Therapy

In vitro studies have demonstrated interferon (IFN)-γ production by peripheral blood mononuclear cells is reduced in patients with chronic coccidioidomycosis,[92–94] and defects within interleukin 12/IFN-γ have been reported in several patients with disseminated coccidioidal infection.[95,96] These findings have encouraged the use of adjunctive exogenous IFN-γ along with antifungal use in patients with refractory disseminated coccidioidomycosis, although its use is limited by patient tolerability, expense, and a lack of a clear benefit in the absence of compelling clinical data.[97]

Future Therapies

Future innovative ways to target this disease are in development. Nikkomycin Z has shown promise with a possibility of cure in murine models of infection. Safety trials have been conducted, and clinical trials are anticipated in 2016 or shortly thereafter.

As this organism is capable of eliciting a wide range of immunologic reactions, further research in the areas of immunotherapy and vaccination will be of great importance. It is well known that some hosts are able to effectively control infection, whereas others develop severe complications. The current knowledge of host risk factors and immunogenetics is in the early stages, and a better understanding of the

mechanisms for effective host control of disease may allow the possibility of intervention.[46,98]

SUMMARY

The management of coccidioidomycosis depends on the last 6 decades of clinical experience. For most human infections, the disease is relatively benign. However, for others, the outcome is one of severe debility and even death. Even in cases of relatively benign disease, the possibility of recurrence is problematic. For clinicians both in endemic areas and elsewhere, knowledge of the identification and management of this illness will continue to be necessary. Although there is an increasing experience with several highly active antifungal therapies, it is still not possible to reliably eradicate infection and prevent relapses with chronic disseminated coccidioidomycosis. CM is one of a few infectious diseases that require lifetime suppressive therapy for CM because of its devastating results. Although newer and more effective treatments are needed and in development, for now fluconazole and itraconazole remain the predominant therapy along with AmB formulations. The correlation of failures with reliable susceptibility data may also enable better treatment decisions, keeping in consideration the newer triazoles for refractory disease.

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