

Coccidioidomycosis-2008

L. Joseph Wheat, M.D.

History

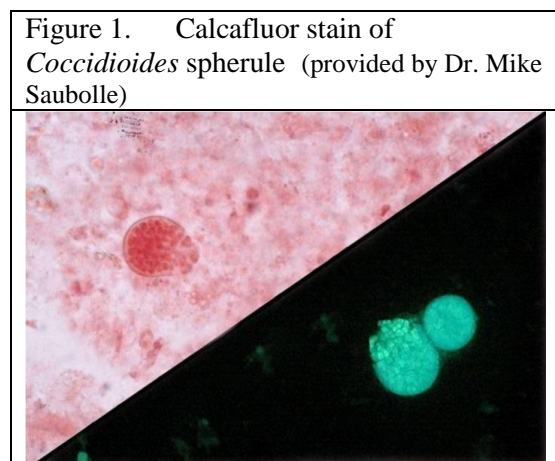
The early history of coccidioidomycosis was reviewed by Hirschmann [1] and provides insight into the discovery of a new disease. As with the other endemic mycoses, coccidioidomycosis was first thought to be a protozoan disease. Once the organism was isolated from patients, only the severe and almost always fatal cases were recognized. Not until the discovery of the high rates of skin test reactivity in residents of endemic areas was it determined that coccidioidomycosis was common and usually asymptomatic or clinically self-limited.

Several individuals contributed to the early history of the disease, most notably Dr. Charles E. Smith, whose work included development of skin test reagents [2], discovery of the benign course in most patients [3], and development of serologic methods for diagnosis [4,5]. Smith's dedication and discoveries paved the way for other investigators. For example, Dr. Demosthenes Pappagianis published his first of over 100 papers on coccidioidomycosis in 1956 which described the virulence properties of *Coccidioides immitis* [6] and his most recent in 2007 describes possible vaccine candidates [7]. His reviews serve as classic references on serologic testing for coccidioidomycosis [8-10]. Hans Einstein published an article in 1956 entitled "Cortisone in coccidioidomycosis" [11] and his most recent article in 2007 entitled "Amphotericin B and coccidioidomycosis" [12].

Others who have contributed to our understanding of the disease include Milton Huppert, Hillard Levine, and Rebecca Cox in the early days, and David Stevens, John Galgiani, Neil Ampel, Antonino Catanzaro, Royce Johnson, Gary Cole, Theodore Kirkland, Josh Fierer, Karl Clemons, Nancy Crum-Cianflone, Janis Blair, and Suzanne Johnson more recently. These individuals have been gracious in assisting others in their research and management of patients and have created a productive collaborative organization, the "Coccidioidomycosis Study Group".

Mycology

Coccidioidomycosis is caused by the pathogenic fungus, *Coccidioides immitis* or *posadasii*. It grows as a mold with septate hyphae in the soil and on culture media. The arthroconidia are 2.5 to 4 by 3 to 6 μm in size and are described as "barrel-shaped".



The arthroconidia convert to a spherule at 37 to 40° C in the laboratory, and in the tissues. Spherules measure 30 to 60 μm in diameter and contain endospores, which are 2 to 5 μm in diameter (Figure 1). Growth on fungal media occurs within a week after inoculation of the specimen, at which time identification using nucleic acid probes is possible. Laboratory employees working with the mold are at risk for development of coccidioidomycosis if they are not careful to observe the appropriate biosafety procedures [13,14].

Coccidioides is the only fungus listed as a select agent of bioterrorism [15].

Epidemiology

Coccidioidomycosis is endemic in the hot, semi-arid southwestern United States, northern Mexico and Central America (Figure 2). Growth in the soil is enhanced by rodent droppings, and requires specific temperature and texture characteristics [16].

Exposure is heaviest in the late summer and fall when dusty conditions exist following rainy winters. There have been several outbreaks in the southwest United States [17-22] and the incidence has been increasing in Arizona and California [19,23]. Of note is that the highest attack rate in Arizona occurred in individuals over 65 years old, who experienced 43 cases per 100,000 persons [19]. This high rate may result from relocation of individuals who were not previously exposed to *Coccidioides* to communities with high rates of exposure, as a consequence of construction for urban expansion. Age was a risk factor for hospitalization [19,24]. Coccidioidomycosis also is common in animals [25].

Figure 2. Endemic area in North America



Recent discovery of a site outside the endemic area in Northeastern Utah highlights the highly focal distribution of the organism [20]. *Coccidioides* was postulated to have been distributed through the travel of Native Americans. Of note is that some arthroconidia have persisted for over 40 years in a particular site that has been investigated repeatedly [16], and presumably has existed for thousands of years [20].

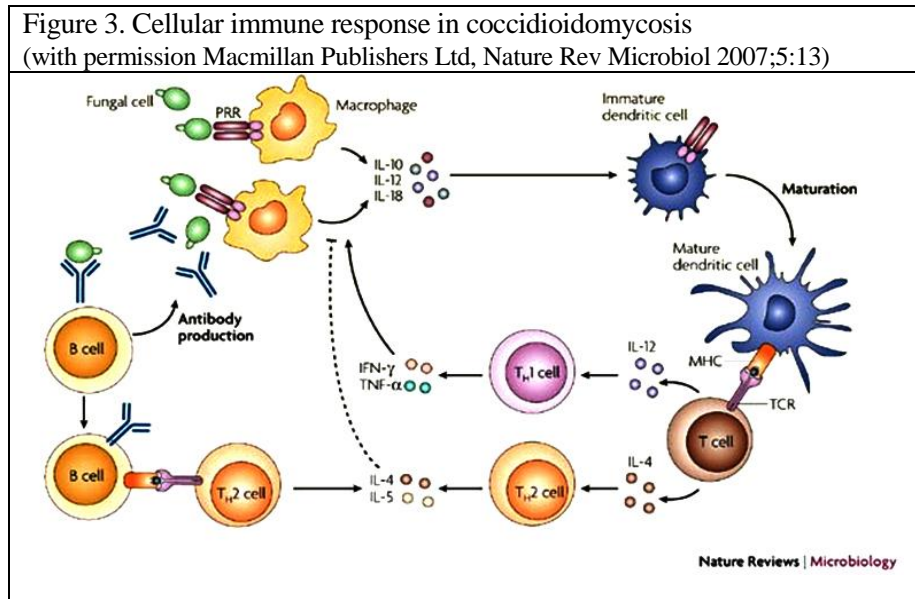
While coccidioidomycosis is widely recognized in endemic areas, it may not be suspected in non-endemic areas. Most cases in non-endemic areas occur in travelers who have visited endemic areas [26]. Also, arthroconidia may be spread by the wind for hundreds of miles from the site of the disturbance affecting individuals without direct exposure to these environmental niches [27,28]. In a review of cases at one institution, a long time interval from the onset of symptoms to diagnosis was attributed, in part, to the low index of suspicion among physicians in non-endemic areas [29].

Pathogenesis

Infection occurs following inhalation of arthroconidia. In the host, the arthroconidia swell and form spherules which develop endospores during their maturation. Subsequently, the spherules rupture, releasing the endospores which spread locally and disseminate to extra pulmonary sites. Although neutrophils participate in the early inflammatory response to *Coccidioides*, the predominant tissue reaction is granulomatous.

Cellular immunity is the key defense mechanism in coccidioidomycosis, serving to arm macrophages to halt progression of the infection (Figure 3). Individuals with impaired cellular immunity experience severe progressive forms of coccidioidomycosis. Immunosuppressive conditions predisposing to severe coccidioidomycosis include AIDS [30], solid organ transplantation[31], and immunosuppressive therapy for chronic inflammatory or malignant

conditions [32,33]. Coccidioidomycosis also is more severe in the elderly, those who are pregnant [34], African Americans, Filipinos, and persons with a few other conditions [35,36].



Reactivation of latent disease may occur in some immunosuppressed patients [37,38]. Two of 13 patients who developed coccidioidomycosis during a prospective study in an endemic area demonstrated positive spherulin skin tests as evidence for prior coccidioidomycosis [38].

Clinical Findings

Coccidioidomycosis, although often asymptomatic, is a common cause of pneumonia in patients from endemic areas [39]. In a review of over 200 cases of coccidioidomycosis at a single institution, 58% presented with pulmonary disease, 22% with disseminated disease, and 5% with unclassified disease [40]. Frequently, patients are suspected to have community acquired pneumonia, and coccidioidomycosis is not considered. In a survey of cases of community acquired pneumonia in Arizona, coccidioidomycosis accounted for 29% of cases [41]. A septic shock syndrome, including ARDS and multi-organ failure, also has been described and often has been attributed to bacterial infection, delaying the diagnosis of coccidioidomycosis [42-46]. Mortality was a more over 50%.

Symptomatic disease, which often is severe, is more common following direct disturbance of soil. For example, attack rates in workers at archeological sites have ranged from 50% to 90% and the illness was usually severe enough to require hospitalization [20].

Pulmonary. The diagnosis of pulmonary coccidioidomycosis is often overlooked. Among cases presenting in non-endemic areas following return from an endemic area, health-care providers did not consider coccidioidomycosis in the differential diagnosis despite their awareness of travel history [17]. Similarly, among patients with miliary coccidioidomycosis occurring within a heavily endemic area, the diagnosis was suspected in only 25% of cases [47]. The pulmonary syndromes have been reviewed [40,48]. Over half of acute infections are judged to be asymptomatic, while the others present with a variety of clinical manifestations. "Valley

fever" manifestations include fever, chills, headache, nonproductive cough, chest pain, erythema nodosum, erythema multiforme, and arthralgia. In one review, 12 to 16% of patients with pulmonary coccidioidomycosis exhibited arthralgia or rash [40]. The illness usually resolves spontaneously in otherwise healthy individuals, but may lead to chronic complications.

Figure 4. Diffuse infiltrates in coccidioidomycosis



The illness may be more severe following heavy exposure. In one outbreak, all 10 cases reported dyspnea, had bilateral patchy infiltrates, and eight were hospitalized, indicating the severity of the illness [20]. Complications may include acute respiratory distress syndrome (ARDS), fibrocavitary disease, pleural disease and persistent cavities [48]. Pneumonia is more severe in diabetics and cigarette smokers [36]. Cavitory disease also is more common in diabetics [49].

A miliary pattern is felt to result from hematogenous dissemination, Figure 4 [47]. In a review of cases occurring in immune-competent individuals in a highly endemic area, most were rapidly progressive and were complicated by respiratory failure. Coccidioidomycosis was not suspected in most of the cases.

Disseminated disease. Risk factors for disseminated disease include pregnancy (odds ratio 7.3), black race (odds ratio 4.6), and diabetes (odds ratio 2.7) and smoking cigarettes (odds ratio 2.3) [36]. There were too few immunosuppressed individuals for assessment of the effect of immunosuppression on risk for disseminated disease in that study. Others have confirmed a higher incidence of disseminated disease in patients with diabetes [49].

Bone or joint involvement is common, occurring in about 20% of the cases [40]. Joint disease may be complicated by osteomyelitis. About 15% of patients with disseminated coccidioidomycosis have skin involvement. A variety of manifestations may be seen in patients with coccidioidomycosis [50].

Meningitis. Meningitis is more common in coccidioidomycosis than in other endemic mycoses, and has been reviewed [51]. Meningitis was present in about 3% of patients in one study [40]. Headache, personality and/or mental status abnormalities and focal neurologic deficits are common, as are findings of increased intracranial pressure. Cerebrospinal fluid shows lymphocytic pleocytosis in most cases [51,52].

Abnormalities can be identified by magnetic resonance imaging in three quarters of patients, most often showing hydrocephalus, basilar meningitis or cerebral infarction [53]. The mortality rate was twofold higher in patients with neuroimaging abnormalities, and hydrocephalus was associated with a 12 fold increased mortality.

Diagnosis is usually made by demonstration of anti-*Coccidioides* antibodies in the CSF [51] In a review of 25 cases, CSF antibodies were detected in all cases in which testing was performed [54] and 84% in another [55]. Cultures are positive in less than one third of cases [55], and organisms may be seen on direct examination only if the fungal burden is high [51]. *Coccidioides* galactomannan also may be detected in the CSF (Wheat, unpublished).

The natural history of untreated coccidioidal meningitis has been reported [54]. Survival for patients with meningitis was dramatically shorter than that of patients without meningitis, but nearly 20% survived for more than four years. Also the CSF leukocyte count declined without treatment. Following treatment, the relapse rate is higher in patients with meningitis (71%) than in patients with disseminated disease without meningitis (24%) [40].

Immunosuppressed patients.

Acquired immunodeficiency syndrome (AIDS). Coccidioidomycosis is a common opportunistic infection in patients with AIDS from endemic areas [30,56]. The average annual incidence of coccidioidomycosis in Arizona was 4.1% in one report[57]. In another, about one quarter of AIDS patients in Phoenix developed coccidioidomycosis [58]. Coccidioidomycosis tends to be more severe in patients with AIDS. For example AIDS was associated with a 31 fold higher likelihood for hospitalization [24]. Among cases in patients with AIDS in Arizona, 52% exhibited diffuse infiltrates, 42% extra pulmonary disease, and 25% died [57]. Reviewing the experience at a single institution, 65% exhibited diffuse pulmonary infiltrates, 15% meningitis, and 60% died [59]. Common sites of dissemination included the central nervous system, lymph nodes, liver, skin, peritoneum, kidneys, thyroid, adrenal, heart, pituitary, esophagus, and pancreas.

Solid organ and bone marrow transplantation. Coccidioidomycosis also has been reported in bone marrow and solid organ transplant recipients. Transplant patients may acquire coccidioidomycosis by inhalation or transmission in the donor organ, and rarely by reactivation of the latent infection. Disease caused by transmission by the donor organs has been fulminate in most cases [60-62]. In a study of hematopoietic stem cell transplant patients, coccidioidomycosis was diagnosed in three (2.5%) [63]. Among solid organ transplant patients, the incidence has ranged from 0.5% [64] to nearly 10% [65]. The lungs were involved in nearly two thirds of cases, meninges in one quarter, and a diverse spectrum of tissues in the majority of patients [65,66]. As in patients with AIDS, however, mortality was high, ranging from 25 to 63% [65-67].

Protocols have been developed to screen donors and recipients for coccidioidomycosis and to treat the infection when diagnosed [68]. Lifelong suppressive therapy may be required [69]. Patients should also undergo screening for coccidioidomycosis before beginning immunosuppressive therapy for other conditions [32].

Immunosuppression for chronic inflammatory conditions. Coccidioidomycosis also has been reported in patients receiving anti-inflammatory treatment for chronic inflammatory conditions, most recently including patients receiving tumor necrosis factor (TNF) antagonist [32,33,70]. Coccidioidomycosis occurred as early as one week and as long as two years after beginning TNF antagonist therapy. Screening radiographs and serology were recommended for patients beginning TNF antagonist therapy.

Pregnancy. Coccidioidomycosis is more severe during pregnancy, particularly the third trimester [71]. Disseminated disease occurred in 50% of cases during the first, 62% during the second, and 96% during the third trimester of pregnancy. The risk for dissemination was 13 fold higher in African-American women. Although the placenta often is infected, coccidioidomycosis is rare in neonates, presumably because the organism does not readily cross

the placenta [34]. More often, neonatal infection is thought to occur through exposure in the environment or during vaginal delivery [34]. Despite its rarity, transmission to the neonates may occur and should be excluded if the mother is diagnosed with coccidioidomycosis[72-74].

Diagnosis

Perhaps the most common cause for delays in diagnosis is failure to suspect it. Unfortunately, even in endemic areas, coccidioidomycosis often is overlooked in the evaluation of patients with pneumonia [17,41,47]. In immunocompromised patients, it also may be overlooked in patients with findings suggest of sepsis [44,45,75].

Prompt diagnosis is important for several reasons. In patients presenting with pneumonia, diagnosis may reduce testing and treatment for community acquired pneumonia, and permit treatment for coccidioidomycosis in those with risk factors for severe disease or illness requiring hospitalization.

Once suspected, rapid diagnosis may be made by fungal stain of body fluids or tissues, serology, and antigen detection. Culture and perhaps histopathology, if the findings are clear cut, are the only methods for proving the diagnosis, as the other tests are not specific.

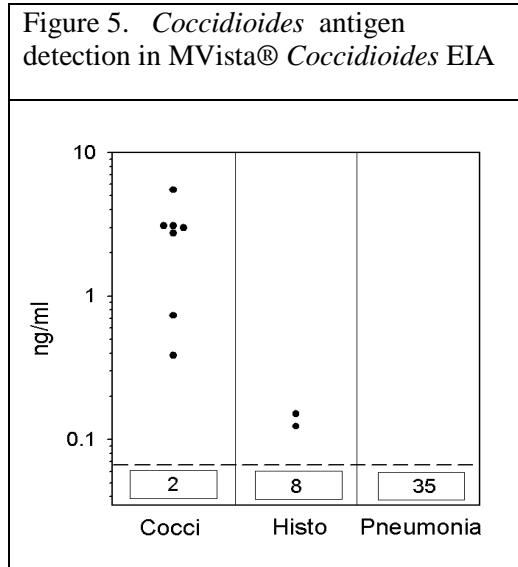
Culture. Cultures are infrequently positive in acute coccidioidomycosis [36]. Cultures are positive more often in patients with severe disease, especially those who are immunosuppressed (Table 1). Delays of a week or more to identify the organism are common, reducing the sensitivity of culture for rapid diagnosis. Thus, non-culture methods are very important for diagnosis of coccidioidomycosis.

Table 1. Sensitivity of diagnostic tests in coccidioidomycosis				
Test	Pulm (N=14)	Pulm (N=54)	Pulm or Dis (N=329)	Pulm or Dis (N=24)
Immunosuppressed	93%	35% HIV	0%	67%
Antigen	ND ¹	ND	ND	71%
Antibody	54%	55%	90%	75%
Cytology or Histopathology	64%	35%	17%	29%
Culture	86%	100%	23%	84%
Reference	[76]	[77]	[49]	Durkin ²
¹ ND=Not done; ² submitted for publication				

Histopathology. Examination of respiratory specimens or tissues may show characteristic spherules (Figure1). However, cytology or histopathology may be falsely negative in a third or more of cases [76,77]. In disseminated cases, cytology of skin lesions may provide a rapid diagnosis [78]. In some cases histopathology may be falsely-positive, even in experienced laboratories.

Antigen detection. Antigen detection was first reported in the early 1980s, demonstrating antigenemia in the half to three quarters of patients with coccidioidomycosis [79-81]. However, those early methods were not adapted for clinical testing. In a more recent report, antigenemia was noted in 47% of seroconverters (CN Miller. Detection of circulating coccidioidal antigen using an inhibition ELISA. American Society for Microbiology general meeting, 2007, abstract

number F.-038). We reported detection of a cross-reactive galactomannan in the urine in 58% of cases using the MVista *Histoplasma* antigen EIA [82].



More recently, a specific *Coccidioides* antigen EIA has been developed and is available for clinical testing (MiraVista Diagnostics, Indianapolis, IN) (Figure 5). The sensitivity in moderately severe or severe coccidioidomycosis was 71% (Table 1). Antigen detection was more sensitive than demonstration of spherules by direct examination, positive in 29% of patients. Specificity was 99% in patients with non-fungal infections, but cross-reactivity was noted in about 11% of patients with other endemic mycoses (M Durkin, submitted for publication, 2008). The sensitivity in milder cases remains to be determined. More information is available at the MiraVista Diagnostic [website](#), which includes a [PowerPoint](#) presentation.

Serology. Serology is highly useful for diagnosis of coccidioidomycosis [83]. The methods for measurement of antibodies to *Coccidioides* spp. include immunodiffusion (ID), complement fixation (CF) and enzyme immunoassay (EIA). Excellent reviews should be consulted for a more thorough understanding of the use of serologic studies in coccidioidomycosis [10]. However, serology is neither entirely sensitive nor specific, and alone cannot be used to establish or exclude the diagnosis. Also, serology may be falsely negative in the first few months of acute infection, and in immunosuppressed patients (Table 1).

The ID test is easiest to perform and the most widely available serodiagnostic method. The ID test can be used to distinguish IgM, more suggestive of recent infection, from IgG antibodies, which may be detected at any stage in the disease process. In healthy subjects, the sensitivity of ID for IgM or IgG was 73%, compared to 75% for CF and 87% for EIA [84]. In immunocompromised subjects, sensitivity was higher by CF (67%) than ID (53%). Others have reported the sensitivity of ID to be 50 to 60% in pulmonary coccidioidomycosis [76,77,82]. The sensitivity of ID may be improved by concentration of the specimen [8]. In an outbreak of acute coccidioidomycosis, IgM antibodies were detected in unconcentrated serum in 10% of cases, compared to 90% following concentration [20].

The CF and EIA are more difficult to perform than ID, and are usually available only at reference laboratories. Although EIA results correlate with CF titers, the correlation is weak [85], and EIA is not as accurate as ID or CF. For example, using one kit (Meridian Bioscience, Cincinnati, OH), the IgM assay was positive in only 54% and the IgG assay in 67% of CF positive specimens [85]. Using another kit measuring IgM, IgA or IgG anti-*Coccidioides* antibodies, EIA was positive in only 71% of CF positive specimens, and was falsely positive in 12% of CF negative specimens (product information, *Coccidioides* Dx Select™, Focus Diagnostics, Cypress California).

Molecular diagnostics. PCR methods have been reported for diagnosis of coccidioidomycosis [86-90]. In an evaluation of fresh clinical specimens, PCR was positive in 13 of 14 (93%) culture positive specimen, but PCR results were not compared to direct examination [89]. In paraffin embedded tissue, PCR was positive on 47 of 64 (73%) of histopathology positive specimens [89]. Specificity was about 98%. However, standardized methods are not commercially available, and too few studies have been conducted to determine the accuracy of the method.

Treatment

The Infectious Diseases Society of America treatment guideline states "Management of coccidioidomycosis first involves recognizing that a coccidioidal infection exists, defining the extent of infection, and identifying host factors that predispose to disease severity" [69]. The guidelines are available at the [IDSA website](#) and will be summarized in this review. Whether all patients with acute coccidioidomycosis should be treated is controversial. While most patients with acute coccidioidomycosis recover without treatment, recovery may be slow and activities may be reduced. Accordingly, some experts recommend treating all symptomatic patients. Unfortunately studies have not been conducted evaluating this approach.

Indications for treatment. Treatment is recommended for all patients with disseminated infection, Table 2.

Acute pneumonia, mild	Observe at 1-3 month intervals for at least 1 year, but some recommend treatment
Acute pneumonia, severe: weight loss >10%, sweats >3 weeks, infiltrates > half of one lung or parts of both lungs, prominent or persistent hilar lymphadenopathy, CF titers > 1:16, inability to work, symptoms > 2 months.	Treat with an azole 200-400 mg daily for 3-6 months, with follow-up at 1-3 month intervals for at least one year
Acute pneumonia, special circumstances: immunosuppression, pregnancy, Filipino or African descent, age > 55 years, other chronic diseases (diabetes, cardio pulmonary disease), symptoms >2 months	Treat with an azole 200-400 mg daily for 3-6 months, with follow-up at 1-3 month intervals for at least 1 year
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia pain	Treat with amphotericin B if significant hypoxia or rapid deterioration followed by an azole for a least 1 year, and an azole for least 1 year in mild cases
Chronic pneumonia	Treat with an azole for least 1 year.
Disseminated disease, non-meningeal	Treat with an azole for a least 1 year except in severe or rapidly worsening cases in whom amphotericin B is recommended.
Disseminated disease, meningeal	Treat with fluconazole 400-1000 mg daily (some also give intrathecal amphotericin B.)

Acknowledging the controversy about treatment of acute coccidioidomycosis, most agree that treatment is recommended in patients who are at risk for severe disease, including these situations: immunosuppression, diabetes mellitus, pre-existing cardio pulmonary disease, pregnancy, Filipino or African descent, age greater than 55 years. Treatment also is recommended for patients with more severe clinical manifestations: weight loss greater than 10%, intense night sweats longer than

three weeks, infiltrates involving more than one half of one lung or parts of both lungs, prominent or persistent hilar lymphadenopathy, anti-coccidioidal complement fixing antibody concentrations in excess of 1:16, inability to work, symptoms longer than two months. Diffuse pneumonia should be treated as it suggests underlying immunodeficiency or exposure to a high inoculum. Some experts recommend use of corticosteroids in patients with ARDS [48].

Cavity formation may occur in coccidioidomycosis, but only requires treatment if symptomatic or otherwise complicated, by cavity rupture or pain. Chronic progressive fibrocavitary pneumonia should be treated. Surgery also may be required in these circumstances. Surgery also may require for drainage of the abscesses, debridement of bone, stabilization of the spine, and relief of increased intracranial pressure.

Selection of antifungal agent. The IDSA guideline states that "Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections"[69]. Indications for amphotericin B include respiratory failure, rapidly progressive infections, and pregnancy. Crum, however, found that azole therapy was inferior to amphotericin B for treatment of disseminated disease, particularly in patients with bone involvement; and recommended amphotericin B for complicated or multi-organ disease [40].

Itraconazole is preferred in patients with bone involvement, and fluconazole in those with meningitis. In a randomized comparison of fluconazole and itraconazole for treatment of non-meningeal coccidioidomycosis, the response was better with itraconazole than fluconazole, 63% compared to 50%, but the difference was not statistically significant[91]. However, for skeletal infection, response to itraconazole was significantly better than to fluconazole. Itraconazole blood levels should be determined to assure concentrations of at least 1 µg/mL.

Newer azoles and echinocandins. Posaconazole is an alternative to itraconazole and fluconazole. The susceptibility of *Coccidioides* to posaconazole and itraconazole is similar [92,93]. Posaconazole was more effective than itraconazole in murine models of coccidioidomycosis[92,93], but the murine model is not optimal for evaluation of itraconazole. Posaconazole achieves better blood and tissue levels in mice than does itraconazole, perhaps accounting for its greater efficacy.

In an early clinical trial using posaconazole in patients with acute coccidioidomycosis the response rate at 12 months was 66% [94]. Subsequent reports described the outcome of posaconazole therapy in patients who failed or intolerant to other treatments [95-97]. The response rate was about 75% , and response was often rapid [95]. Experience using posaconazole for other infections indicates the importance of assuring adequate blood concentrations, with the goal of achieving a level of at least 1 µg/mL [98,99].

Voriconazole also is active against *Coccidioides*, exhibiting in vitro susceptibility similar to that of itraconazole [100]. Voriconazole has not been studied in animal models of coccidioidomycosis, however. Furthermore, clinical studies have not been conducted. However, there are a few case reports of success using voriconazole [101-103]. Trough serum concentrations should be monitored to increase the likelihood of success by attaining level of 1 to 5 µg/mL [104-106]. CNS toxicity is more likely with levels above 5 µg/mL [104,107].

Experience with the echinocandins is limited. Caspofungin improved survival and reduced fungal burden in a murine model of coccidioidomycosis [108]. There are a few reports using caspofungin for treatment of patients, with mixed results: success in two [109,110] and failure in another [111]. The patients who responded also received either liposomal amphotericin B or fluconazole and the unsuccessful case presented with meningitis, a manifestation that often fails other therapies, precluding an objective assessment of caspofungin's role. However, these data do not support use of echinocandins in coccidioidomycosis [69].

Meningitis. The IDSA guideline indicates that "fluconazole is currently preferred by most clinicians" [69], a view that is widely shared [51]. In a prospective study fluconazole 400 mg daily was given to 47 patients with *Coccidioides* meningitis [112]. Response was noted in 21 of 24 (88%) "relapse" cases compared to 16 of 23 (70%) initial treatment cases. Two additional initial treatment cases subsequently failed, reducing the response to initial therapy to 14 of 23 (61%). Two of the nine patients failing initial therapy died, six improved when the dosage was increased, and another in response to intrathecal amphotericin B. Causes for failure were not evaluated, but in histoplasmosis development of resistance was an important cause [113], a possibility that has not been investigated in coccidioidomycosis.

The current guidelines [69] do not recommend dosage but one of the panel members indicated "most experts now prefer therapy with high-dose fluconazole (800–1200 mg daily)", and that he recommended 1000 mg once daily [51]. Success also has been reported with itraconazole [114], which was as effective as fluconazole in animal models [115,116]. Itraconazole was more effective than fluconazole in a murine *Histoplasma* meningitis model [117].

Others, however, prefer initial treatment with liposomal amphotericin B for six to ten weeks, followed by fluconazole [52]. The basis for that recommendation was the high levels of liposomal amphotericin B achieved in brain tissue and results of a rabbit meningitis model showing it to be more effective than the deoxycholate amphotericin B or fluconazole [118]. Also of importance is that efficacy of fluconazole at the higher doses has not been studied in *Coccidioides* meningitis, and that patients continue to fail that regimen [101,102,111,119]. Considering these findings, the most effective treatment for *Coccidioides* meningitis may be unknown.

Voriconazole (4 mg/kg q12h orally) was suggested as an alternative in patients who were not responding to fluconazole, and has been used successfully in a few patients [101,102]. Posaconazole also has been used for treatment of *Coccidioides* meningitis [119]. Intrathecal amphotericin B, the old favorite, remains an alternative in patients who fail systemic therapy with an azole or liposomal amphotericin B.

Hydrocephalus is a common complication of coccidioidal meningitis, which requires shunting if there is evidence for increased intracranial pressure [51,52,69,120].

Duration of treatment. The duration of treatment ranges from months to years, and lifelong suppressive therapy is recommended for patients with meningitis, irreversible immunodeficiency states, or relapses despite appropriate treatment [69]. Although the IDSA guideline and other reviews [30] indicate that therapy can be discontinued in patients with AIDS whose CD4 count increased to at least 250 cells/mL in response to antiretroviral therapy, some practitioners

continue to recommend suppressive therapy [121]. Relapse despite immune reconstitution has been reported [122]. More information is needed before an evidence-based recommendation can be made regarding the need for suppressive therapy.

Prevention

Individuals at risk for more severe forms of coccidioidomycosis should be educated about ways to reduce exposure. They should avoid endemic areas during periods of active outbreaks. Some experts recommend that patients with a history of previous coccidioidomycosis or positive serologic test should receive antifungal treatment before organ transplantation. For example, one group evaluates prospective transplant recipients for evidence of prior coccidioidomycosis, and if found, recommends azole prophylaxis [31]. Experts also recommend screening for coccidioidomycosis before implementing immunosuppressive therapy for patients residing in or who have visited endemic areas, but noted most cases represent acute infection and would not have been detected by pre-immunosuppression screening [32]. Thus, physicians and patients should be taught to suspect coccidioidomycosis when unexplained illness develops, especially with pulmonary findings. Efforts to develop a vaccine began in the 1960s [123] and continue today [124].

Durkin, submitted for publication, 2008

Reference List

1. Hirschmann JV. The early history of coccidioidomycosis: 1892-1945. *Clin Infect Dis* 2007; 44:1202-7.
2. Smith CE, Whiting EG, Baker EE, Rosenberger HG, Beard RR, and Saito MT. The use of coccidioidin. *Amer Rev Tuberc* 1948; 57:330-60.
3. Smith CE. Epidemiology of acute coccidioidomycosis with erythema nodosum. *Am J Pub Health* 1940; 30:600-11.
4. Smith CE, Saito MT, Beard RR, Kepp McFadden R, Clark Wheatlake R, and Eddie BU. Serological tests in the diagnosis and prognosis of coccidioidomycosis. *The American Journal of Hygiene* 1950; 52:1-21.
5. Smith CE, Saito MT, and Simons SA. Pattern of 39,500 serologic tests in coccidioidomycosis. *JAMA* 1956; 160:546-52.
6. Pappagianis D, Smith CE, and Kobayashi GS. Relationship of the in vivo form of *Coccidioides immitis* to virulence. *J Infect Dis* 1956; 98:312-9.
7. Haley L. Compensability of, and legal issues related to, coccidioidomycosis. *Ann N Y Acad Sci* 2007; 1111:129-32.
8. Pappagianis D and Zimmer BL. Serology of coccidioidomycosis. *Clin Microbiol Rev* 1990; 3:247-68.

9. Pappagianis D. Serologic studies in coccidioidomycosis. *Semin Respir Infect* 2001; 16:242-50.
10. Pappagianis D. Current status of serologic studies in coccidioidomycosis. *Current Fungal Infection Reports* 2007; 1:129-34.
11. Levan NE and Einstein HE. Cortisone in coccidioidomycosis. *Calif Med* 1956; 84:193-7.
12. Johnson RH and Einstein HE. Amphotericin B and coccidioidomycosis. *Ann N Y Acad Sci* 2007; 1111:434-41.
13. Johnson JE, Perry JE, Fekety FR, Kadull, P.J., and Cluff LE. Laboratory acquired coccidioidomycosis. *Ann Intern Med* 2008; 60:941-56.
14. Saubolle MA. Laboratory aspects in the diagnosis of coccidioidomycosis. *Ann N Y Acad Sci* 2007; 1111:301-14.
15. Dixon DM. *Coccidioides immitis* as a Select Agent of bioterrorism. *J Appl Microbiol* 2001; 91:602-5.
16. Fisher FS, Bultman MW, Johnson SM, Pappagianis D, and Zaborsky E. *Coccidioides* niches and habitat parameters in the southwestern United States: a matter of scale. *Ann N Y Acad Sci* 2007; 1111:47-72.
17. Cairns L, Blythe D, Kao A et al. Outbreak of coccidioidomycosis in Washington State residents returning from Mexico. *Clinical Infectious Diseases* 2000; 30:61-4.
18. Crum NF, Lederman ER, Hale BR, Lim ML, and Wallace MR. A cluster of disseminated coccidioidomycosis cases at a US military hospital. *Mil Med* 2003; 168:460-4.
19. Park BJ, Sigel K, Vaz V et al. An epidemic of coccidioidomycosis in Arizona associated with climatic changes, 1998-2001. *J Infect Dis* 2005; 191:1981-7.
20. Petersen LR, Marshall SL, Barton-Dickson C et al. Coccidioidomycosis among workers at an archeological site, northeastern Utah. *Emerg Infect Dis* 2004; 10:637-42.
21. Standaert SM, Schaffner W, Galgiani JN et al. Coccidioidomycosis among visitors to a *Coccidioides immitis*-endemic area: an outbreak in a military reserve unit. *J Infect Dis* 1995; 171:1672-5.
22. Werner SB, Pappagianis D, Heindl I, and Mickel A. An epidemic of coccidioidomycosis among archeology students in northern California. *N Engl J Med* 1972; 286:507-12.
23. Laniado-Laborin R. Expanding understanding of epidemiology of coccidioidomycosis in the Western hemisphere. *Ann N Y Acad Sci* 2007; 1111:19-34.
24. Flaherman VJ, Hector R, and Rutherford GW. Estimating severe coccidioidomycosis in California. *Emerg Infect Dis* 2007; 13:1087-90.

25. Shubitz LF. Comparative aspects of coccidioidomycosis in animals and humans. *Ann N Y Acad Sci* 2007; 1111:395-403.
26. Panackal AA, Hajjeh RA, Cetron MS, and Warnock DW. Fungal infections among returning travelers. *Clin Infect Dis* 2002; 35:1088-95.
27. Flynn NM, Hoepfich PD, Kawachi MM et al. An unusual outbreak of windborne coccidioidomycosis. *N Engl J Med* 1979; 301:358-61.
28. Drutz DJ. Urban coccidioidomycosis and histoplasmosis. *N Engl J Med* 1979; 301:381-2.
29. Desai SA, Minai OA, Gordon SM, O'Neil B, Wiedemann HP, and Arroliga AC. Coccidioidomycosis in non-endemic areas: a case series. *Respir Med* 2001; 95:305-9.
30. Ampel NM. Coccidioidomycosis in persons infected with HIV-1. *Ann N Y Acad Sci* 2007; 1111:336-42.
31. Blair JE. Coccidioidomycosis in patients who have undergone transplantation. *Ann N Y Acad Sci* 2007; 1111:365-76.
32. Bergstrom L, Yocum DE, Ampel NM et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2004; 50:1959-66.
33. Mertz LE and Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. *Ann N Y Acad Sci* 2007; 1111:343-57.
34. Arnold CA, Rakheja D, Arnold MA et al. Unsuspected, disseminated coccidioidomycosis without maternofetal morbidity diagnosed by placental examination: case report and review of the literature. *Clin Infect Dis* 2008; 46:e119-e123.
35. Shubitz LF, Galgiani JN, Tian ZQ, Zhong Z, Timmermans P, and Katz L. Efficacy of ambruticin analogs in a murine model of coccidioidomycosis. *Antimicrob Agents Chemother* 2006; 50:3467-9.
36. Rosenstein NE, Emery KW, Werner SB et al. Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995-1996. *Clin Infect Dis* 2001; 32:708-15.
37. Galgiani JN and Ampel NM. Coccidioidomycosis in human immunodeficiency virus-infected patients. *J Infect Dis* 1990; 162:1165-9.
38. Ampel NM, Dols CL, and Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: Results of a prospective study in a coccidioidal endemic area. *Am J Med* 1993; 94:235-40.
39. Anstead GM and Graybill JR. Coccidioidomycosis. *Infect Dis Clin North Am* 2006; 20:621-43.

40. Crum NF, Lederman ER, Stafford CM, Parrish JS, and Wallace MR. Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and current controversies. *Medicine (Baltimore)* 2004; 83:149-75.
41. Valdivia L, Nix D, Wright M et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis* 2006; 12:958-62.
42. Lopez A and Williams PMD. Acute Pulmonary Coccidioidomycosis Mimicking Bacterial Pneumonia and Septic Shock: A Report of Two Cases. *The Amer Journ of Med* 1993; 95:236-9.
43. Arsura EL, Bellinghausen PL, Kilgore WB, Abraham JJ, and Johnson RH. Septic shock in coccidioidomycosis. *Crit Care Med* 1998; 26:62-5.
44. Ampel NM, Ryan KJ, Carry PJ, Wieden MA, and Schiffman RB. Fungemia due to *coccidioides immitis*. *Medicine* 1999; 65:312-21.
45. Rempe S, Sachdev MS, Bhakta R, Pineda-Roman M, Vaz A, and Carlson RW. *Coccidioides immitis* fungemia: Clinical features and survival in 33 adult patients. *Heart Lung* 2007; 36:64-71.
46. Wilke E, Ardiles T, and Carlson RW. A case of coccidioidal fungemia initially diagnosed as rhinosporidiosis. *Heart Lung* 2005; 34:217-21.
47. Arsura EL and Kilgore WB. Miliary coccidioidomycosis in the immunocompetent. *Chest* 2000; 117:404-9.
48. Spinello IM, Munoz A, and Johnson RH. Pulmonary coccidioidomycosis. *Semin Respir Crit Care Med* 2008; 29:166-73.
49. Santelli AC, Blair JE, and Roust LR. Coccidioidomycosis in patients with diabetes mellitus. *Am J Med* 2006; 119:964-9.
50. Crum-Cianflone NF, Truett AA, Teneza-Mora N et al. Unusual presentations of coccidioidomycosis: a case series and review of the literature. *Medicine (Baltimore)* 2006; 85:263-77.
51. Johnson RH and Einstein HE. Coccidioidal meningitis. *Clin Infect Dis* 2006; 42:103-7.
52. Davis LE and Porter BS. Central Nervous System *Coccidioides immitis* Infections. *Curr Treat Options Neurol* 2005; 7:157-65.
53. Arsura EL, Johnson R, Penrose J et al. Neuroimaging as a guide to predict outcomes for patients with coccidioidal meningitis. *Clin Infect Dis* 2005; 40:624-7.
54. Vincent T, Galgiani JN, Huppert M, and Salkin D. The Natural History of Coccidioidal Meningitis: VA-Armed Forces Cooperative Studies, 1955-1958. *Clinical Infectious Diseases* 1993; 16:247-54.

55. Bouza E, Dreyer JS, Hewitt WL, and Meyer RD. Coccidioidal meningitis. An analysis of thirty-one cases and review of the literature. *Medicine (Baltimore)* 1981; 60:139-72.
56. Ampel NM. Coccidioidomycosis in persons infected with HIV type 1. *Clin Infect Dis* 2005; 41:1174-8.
57. Woods CW, McRill C, Plikaytis BD et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994-1997: Incidence, risk factors, and prevention. *J Infect Dis* 2000; 181:1428-34.
58. Bronnimann DA, Adam RD, Galgiani JN et al. Coccidioidomycosis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; 106:372-9.
59. Singh VR, Smith DK, Lawrence J et al. Coccidioidomycosis in patients infected with human immunodeficiency virus: Review of 91 cases at a single institution. *Clinical Infectious Diseases* 1996; 23:563-8.
60. Wright PW, Pappagianis D, Wilson M et al. Donor-related coccidioidomycosis in organ transplant recipients. *Clin Infect Dis* 2003; 37:1265-9.
61. Tripathy U, Yung GL, Kriett JM, Thistlethwaite PA, Kapelanski DP, and Jamieson SW. Donor transfer of pulmonary coccidioidomycosis in lung transplantation. *Ann Thorac Surg* 2002; 73:306-8.
62. Miller MB, Hendren R, and Gilligan PH. Posttransplantation disseminated coccidioidomycosis acquired from donor lungs. *J Clin Microbiol* 2004; 42:2347-9.
63. Glenn TJ, Blair JE, and Adams RH. Coccidioidomycosis in hematopoietic stem cell transplant recipients. *Med Mycol* 2005; 43:705-10.
64. Williams JC. Mucormycosis of the genitourinary tract. *Infect Urol* 1997; 10:178-82.
65. Blair JE and Logan JL. Coccidioidomycosis in solid organ transplantation. *Clin Infect Dis* 2001; 33:1536-44.
66. Cohen IM, Galgiani JN, Potter D, and Ogden DA. Coccidioidomycosis in renal replacement therapy. *Arch Intern Med* 1982; 142:489-94.
67. Holt CD, Winston DJ, Kubak B et al. Coccidioidomycosis in liver transplant patients. *Clinical Infectious Diseases* 1997; 24:216-21.
68. Gullberg RM, Quintanilla A, Levin ML, Williams J, and Phair JP. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. *Rev Infect Dis* 1987; 9:369-75.
69. Galgiani JN, Ampel NM, Blair JE et al. Coccidioidomycosis. *Clin Infect Dis* 2005; 41:1217-23.

70. Dweik M, Baethge BA, and Duarte AG. Coccidioidomycosis pneumonia in a nonendemic area associated with infliximab. *South Med J* 2007; 100:517-8.
71. Crum NF and Ballon-Landa G. Coccidioidomycosis in pregnancy: case report and review of the literature. *Am J Med* 2006; 119:993-7.
72. Charlton V, Ramsdell K, and Sehring S. Intrauterine transmission of coccidioidomycosis. *Pediatr Infect Dis J* 1999; 18:561-3.
73. Linsangan LC and Ross LA. *Coccidioides immitis* infection of the neonate: two routes of infection. *Pediatr Infect Dis J* 1999; 18:171-3.
74. Bernstein DI, Tipton JR, Schott SF, and Cherry JD. Coccidioidomycosis in a neonate; maternal-infant transmission. *J Pediatr* 1981; 99:752-4.
75. Arsura EL, Bellinghausen PL, Kilgore WB, Abraham JJ, and Johnson RH. Septic shock in coccidioidomycosis. *Crit Care Med* 1998; 26:62-5.
76. Sarosi GA, Lawrence JP, Smith DK, Thomas A, Hobohm DW, and Kelley PC. Rapid diagnostic evaluation of bronchial washings in patients with suspected coccidioidomycosis. *Semin Respir Infect* 2001; 16:238-41.
77. DiTomasso JP, Ampel NM, Sobonya RE, and Bloom JW. Bronchoscopic diagnosis of pulmonary coccidioidomycosis. Comparison of cytology, culture, and transbronchial biopsy. *Diagn Microbiol Infect Dis* 1994; 18:83-7.
78. Meyer KC, McManus EJ, and Maki DG. Overwhelming pulmonary blastomycosis associated with the adult respiratory distress syndrome. *N Engl J Med* 1993; 329:1231-6.
79. Weiner MH. Antigenemia detected in human coccidioidomycosis. *J Clin Microbiol* 1983; 18:136-42.
80. Galgiani JN, Grace GM, and Lundergan LL. New serologic tests for early detection of coccidioidomycosis. *J Infect Dis* 1991; 163:671-4.
81. Galgiani JN, Dugger KO, Ito JI, and Wieden MA. Antigenemia in primary coccidioidomycosis. *Am J Trop Med Hyg* 1984; 33:645-9.
82. Kuberski T, Myers R, Wheat LJ, Kubak BM, Bruckner D, and Peuges D. Diagnosis of coccidioidomycosis by antigen detection using cross-reaction with a *Histoplasma* antigen. *Clinical Infect Diseases* 2007; 44:e50-e54.
83. Pappagianis D. *Coccidioides immitis* antigen. *J Infect Dis* 1999; 180:243-4.
84. Blair JE, Coakley B, Santelli AC, Hentz JG, and Wengenack NL. Serologic testing for symptomatic coccidioidomycosis in immunocompetent and immunosuppressed hosts. *Mycopathologia* 2006; 162:317-24.

85. Martins TB, Jaskowski TD, Mouritsen CL, and Hill HR. Comparison of commercially available enzyme immunoassay with traditional serological tests for detection of antibodies to *Coccidioides immitis*. *J Clin Microbiol* 1995; 33:940-3.
86. de Aguiar CR, Nogueira Brilhante RS, Gadelha Rocha MF, Araujo Moura FE, Pires DC, and Costa Sidrim JJ. Rapid diagnosis of coccidioidomycosis by nested PCR assay of sputum. *Clin Microbiol Infect* 2007.
87. Assi MA, Binnicker MJ, Wengenack NL, Deziel PJ, and Badley AD. Disseminated coccidioidomycosis in a liver transplant recipient with negative serology: Use of polymerase chain reaction. *Liver Transpl* 2006; 12:1290-2.
88. Bialek R, Kern J, Herrmann T et al. PCR assays for identification of *Coccidioides posadasii* based on the nucleotide sequence of the antigen 2/proline-rich antigen. *J Clin Microbiol* 2004; 42:778-83.
89. Binnicker MJ, Buckwalter SP, Eisberner JJ et al. Detection of coccidioides species in clinical specimens by real-time PCR. *J Clin Microbiol* 2007; 45:173-8.
90. Johnson SM, Simmons KA, and Pappagianis D. Amplification of coccidioidal DNA in clinical specimens by PCR. *J Clin Microbiol* 2004; 42:1982-5.
91. Galgiani JN, Catanzaro A, Cloud GA et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis - A randomized, double-blind trial. *Ann Intern Med* 2000; 133:676-86.
92. Gonzalez GM, Tijerina R, Najvar LK et al. In vitro and in vivo activities of posaconazole against *Coccidioides immitis*. *Antimicrob Agents Chemother* 2002; 46:1352-6.
93. Lutz JE, Clemons KV, Aristizabal BH, and Stevens DA. Activity of the triazole SCH 56592 against disseminated murine coccidioidomycosis. *Antimicrob Agents Chemother* 1997; 41:1558-61.
94. Hostetler JS, Catanzaro A, Stevens DA et al. Treatment of coccidioidomycosis with SCH 39304. *J Med Vet Mycol* 1994; 32:105-14.
95. Anstead GM, Corcoran G, Lewis J, Berg D, and Graybill JR. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis* 2005; 40:1770-6.
96. Catanzaro A, Cloud GA, Stevens DA et al. Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. *Clin Infect Dis* 2007; 45:562-8.
97. Stevens DA, Rendon A, Gaona-Flores V et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest* 2007; 132:952-8.

98. Walsh TJ, Raad I, Patterson TF et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; 44:2-12.
99. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, and Patino H. Pharmacokinetics of Oral Posaconazole in Allogeneic Hematopoietic Stem Cell Transplant Recipients with Graft-versus-Host Disease. *Pharmacotherapy* 2007; 27:1627-36.
100. Li RK, Ciblak MA, Nordoff N, Pasarell L, Warnock DW, and McGinnis MR. In vitro activities of voriconazole, itraconazole, and amphotericin B against *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*. *Antimicrob Agents Chemother* 2000; 44:1734-6.
101. Prabhu RM, Bonnell M, Currier BL, and Orenstein R. Successful treatment of disseminated nonmeningeal coccidioidomycosis with voriconazole. *Clin Infect Dis* 2004; 39:e74-e77.
102. Proia LA and Tenorio AR. Successful Use of Voriconazole for Treatment of *Coccidioides Meningitis*. *Antimicrob Agents Chemother* 2004; 48:2341.
103. Cortez KJ, Walsh TJ, and Bennett JE. Successful treatment of coccidioid meningitis with voriconazole. *Clin Infect Dis* 2003; 36:1619-22.
104. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, and Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; 46:201-11.
105. Smith J, Safdar N, Knasinski V et al. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006; 50:1570-2.
106. Trifilio SM, Bennett CL, Yarnold PR et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. *Bone Marrow Transplant* 2007; 39:425-9.
107. Zonios DI, Gea-Banacloche J, Childs R, and Bennett JE. Hallucinations during voriconazole therapy. *Clin Infect Dis* 2008; 47:e7-e10.
108. Gonzalez GM, Gonzalez G, Najvar LK, and Graybill JR. Therapeutic efficacy of caspofungin alone and in combination with amphotericin B deoxycholate for coccidioidomycosis in a mouse model. *J Antimicrob Chemother* 2007.
109. Antony S. Use of the Echinocandins (Caspofungin) in the Treatment of Disseminated Coccidioidomycosis in a Renal Transplant Recipient. *Clin Infect Dis* 2004; 39:879-80.
110. Park DW, Sohn JW, Cheong HJ et al. Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole. *BMC Infect Dis* 2006; 6:26.

111. Hsue G, Napier JT, Prince RA, Chi J, and Hospenthal DR. Treatment of meningeal coccidioidomycosis with caspofungin. *J Antimicrob Chemother* 2004; 54:292-4.
112. Galgiani JN, Catanzaro A, Cloud GA et al. Fluconazole therapy for coccidioidal meningitis. *Ann Intern Med* 1993; 119:28-35.
113. Wheat LJ, Connolly P, Smedema M, Brizendine E, and Hafner R. Emergence of resistance to fluconazole as a cause of failure during treatment of histoplasmosis in patients with acquired immunodeficiency disease syndrome. *Clin Infect Dis* 2001; 33:1910-3.
114. Tucker RM, Denning DW, Dupont B, and Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med* 1990; 112:108-12.
115. Kamberi P, Sobel RA, Clemons KV, Stevens DA, Pappagianis D, and Williams PL. A murine model of coccidioidal meningitis. *J Infect Dis* 2003; 187:453-60.
116. Sorensen KN, Sobel RA, Clemons KV, Pappagianis D, Stevens DA, and Williams PL. Comparison of fluconazole and itraconazole in a rabbit model of coccidioidal meningitis. *Antimicrob Agents Chemother* 2000; 44:1512-7.
117. Haynes RR, Connolly PA, Durkin MM et al. Antifungal therapy for central nervous system histoplasmosis, using a newly developed intracranial model of infection. *J Infect Dis* 2002; 185:1830-2.
118. Clemons KV, Sobel RA, Williams PL, Pappagianis D, and Stevens DA. Efficacy of intravenous liposomal amphotericin B (AmBisome) against coccidioidal meningitis in rabbits. *Antimicrob Agents Chemother* 2002; 46:2420-6.
119. Pitisuttithum P, Negroni R, Graybill JR et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother* 2005; 56:745-55.
120. Romeo JH, Rice LB, and McQuarrie IG. Hydrocephalus in coccidioidal meningitis: case report and review of the literature. *Neurosurgery* 2000; 47:773-7.
121. Carmichael JK. Coccidioidomycosis in HIV-infected persons. *Clin Infect Dis* 2006; 42:1059-60.
122. Mathew G, Smedema M, Wheat LJ, and Goldman M. Relapse of coccidioidomycosis despite immune reconstitution after fluconazole secondary prophylaxis in a patient with AIDS. *Mycoses* 2003; 46:42-4.
123. Levine HB, Pappagianis D, and Cobb JM. Development of vaccines for coccidioidomycosis. *Mycopathol Mycol Appl* 1970; 41:177-85.
124. Hector R and Rutherford GW. The public health need and present status of a vaccine for the prevention of coccidioidomycosis. *Ann N Y Acad Sci* 2007; 1111:259-68.

