# Coccidioidomycosis

**John N. Galgiani,[1,2,3] Neil M. Ampel,[1,2,3] Janis E. Blair,[4] Antonino Catanzaro,[5] Royce H. Johnson,[6] David A. Stevens,[7,8] and Paul L. Williams[9]**

[1]Valley Fever Center for Excellence, [2]Southern Arizona Veterans Affairs Health Care System, and [3]University of Arizona, Tucson, and [4]Mayo Clinic, Scottsdale, Arizona; and [5]University of California, San Diego, [6]Kern Medical Center, Bakersfield, [7]Santa Clara Valley Medical Center and [8]Stanford University, San Jose, and [9]Kaiser Permanente Medical Center, Fresno, California

## EXECUTIVE SUMMARY

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. After these assessments, patients with localized acute pulmonary infections and no risk factors for complications often require only periodic reassessment to demonstrate resolution of their self-limited process. On the other hand, patients with extensive spread of infection or who are at high risk of complications because of immunosuppression or other preexisting factors require a variety of treatment strategies that may include antifungal drug therapy, surgical debridement, or a combination of both. Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Amphotericin B is now usually reserved for patients with respiratory failure due to infection with *Coccidioides* species, those with rapidly progressive coccidioidal infections, or women during pregnancy. Therapy often ranges from many months to years in duration, and in some patients, lifelong suppressive therapy is needed to prevent relapses.

Received 12 July 2005; accepted 13 July 2005; electronically published 20 September 2005.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

Reprints or correspondence: Dr. John N. Galgiani, Valley Fever Center for Excellence, 3601 S. 6th Ave., VA Med Ctr. and Univ. of Arizona, Tucson, AZ 85723 (spherule@u.arizona.edu).

**Clinical Infectious Diseases 2005; 41:1217–23**

1058-4838/2005/4109-0001$15.00

## INTRODUCTION

Coccidioidomycosis (also known as valley fever) results from inhaling the spores (arthroconidia) of *Coccidioides* species (*Coccidioides immitis* or *Coccidioides posadasii*) [1]. Most infections in the United States are acquired within the major regions of endemicity of southern Arizona, central or other areas of California, southern New Mexico, and west Texas. Travelers who have recently visited the region of endemicity or previously infected patients with immunosuppression who experience reactivation of latent infections can develop clinical disease and require medical management outside of the region of coccidioidal endemicity [2].

The estimated numbers of infections per year has risen to ~150,000 as a result of population increases in southern Arizona and central California. Of these infections, one-half to two-thirds are subclinical, and virtually all patients with these infections are protected from second primary infections. The most common clinical presentation of coccidioidomycosis is a self-limited acute or subacute community-acquired pneumonia that becomes evident 1–3 weeks after infection. Such illnesses are usually indistinguishable from bacterial or other infections without specific laboratory tests, such as fungal cultures or coccidioidal serological testing. For such patients, symptoms—especially fatigue interfering with normal activities—may last for weeks to many months. Approximately 5%–10% of infections result in residual pulmonary sequelae, usually nodules or peripheral thin-walled cavities. An even smaller proportion of all infections result in illnesses related to chronic pulmonary or extrapulmonary infection. For extrapulmonary complications, estimates range as low as 0.5% of infections for persons of Caucasian ancestry, several-fold higher for persons of African or Filipino ancestry (possibly also for persons of Asian, Hispanic,

or Native American ancestry), and as high as 30%–50% of infections for heavily immunosuppressed patients, such as those with AIDS, lymphoma, receipt of a solid-organ transplant, or receipt of rheumatologic therapies, such as high-dose corticosteroids or anti-TNF medications. Disseminated infections also appear to be more frequent in adults than in children. Although virtually any site in the body may be involved, extrapulmonary dissemination most frequently involves the skin, the skeletal system, and the meninges [3–6].

***Objective.*** The objective of this practice guideline is to provide recommendations for which patients with coccidioidomycosis are likely to benefit from treatment and which therapies are most appropriate for various forms of infection.

***Treatment options.*** Coccidioidomycosis encompasses a broad spectrum of illness. At one end of that spectrum, it may produce a mild respiratory syndrome or an uncomplicated community-acquired pneumonia, either of which may resolve spontaneously. At the other end of that spectrum, infection may result in progressive pulmonary destruction or lesions in other parts of the body. Because severity varies widely, the optimal management strategies also vary widely among individual patients. Although the vast majority of patients who present with early infections will resolve their infection without specific antifungal therapy, management should routinely include repeated patient encounters every 3–6 months for up to 2 years, either to document radiographic resolution or to identify evidence of pulmonary or extrapulmonary complications as early as possible. Patients who present with severe pneumonia soon after infection warrant antifungal therapy. Patients who develop chronic pulmonary or disseminated disease also warrant antifungal therapy, which is typically prolonged—potentially lifelong—especially in patients with overt immunocompromising conditions. Exact management guidelines for these clinical forms will vary according to disease type and, to an extent, must be individualized. For example, the role of surgical debridement, which, in some patients, is a critical component of therapy, is not addressed in this guideline. However, all patients with progressive or disseminated disease will require some combination of periodic physical examinations, laboratory studies, and imaging studies to guide management decisions.

Specific antifungal drugs and their usual dosages for treatment of coccidioidomycosis include amphotericin B deoxycholate (0.5–1.5 mg/kg per day or alternate day administered intravenously), lipid formulations of amphotericin B (2.0–5.0 mg/kg or greater per day administered intravenously), ketoconazole (400 mg every day administered orally), fluconazole (400–800 mg/day administered orally or intravenously), and itraconazole (200 mg twice per day or 3 times per day administered orally). If itraconazole is used, measurement of itraconazole concentration in serum samples may determine if absorption is satisfactory. Cyclodextrin suspensions of itraconazole afford greater absorption, although published clinical trials of itraconazole for the treatment of coccidioidomycosis have not used this formulation. In general, the more rapidly progressing a coccidioidal infection, the more likely amphotericin B will be selected by most authorities for initial therapy. Conversely, subacute or chronic presentations are more likely to be treated initially with an azole antifungal.

Newly available antifungal agents of possible benefit for the treatment of refractory coccidioidal infections are voriconazole and caspofungin. Voriconazole has not been approved by the United States Food and Drug Administration (FDA) for the treatment of coccidioidomycosis. Although there are no reports of voriconazole therapy for experimental coccidioidal infections, case reports have suggested that voriconazole may be effective in selected patients [7–9]. Caspofungin has been effective in treating experimental murine coccidioidomycosis [10], but in vitro susceptibility of isolates varies widely [11], and there is only 1 report regarding its value [12]. Posaconazole, not yet approved by the FDA, was shown to be an effective treatment in a small clinical trial [13] and in patients with refractory infections [14]. Its efficacy relative to other triazole antifungals is unknown.

Combination therapy with members of different classes of antifungal agents has not been evaluated in patients, and there is a hypothetical risk of antagonism [15]. However, some clinicians feel that outcome in severe cases is improved when amphotericin B is combined with an azole antifungal. If the patient improves, the dosage of amphotericin B can be slowly decreased while the dosage of azole is maintained.

Despite there being several antifungal therapies available for treatment of coccidioidomycosis, occasional patients have exceptionally widespread, debilitating, and potentially life-threatening complications, either at the time of first diagnosis or despite therapy. This is especially true for patients with coccidioidal meningitis. Because of the regional nature of coccidioidomycosis, many of the clinicians most familiar with such problems practice in the southwestern regions of endemnicity. Occasionally seeking advice or obtaining a second opinion from a specialist who is particularly familiar with coccidioidomycosis may be of benefit in formulating a treatment plan that best fits a specific clinical situation.

***Outcomes.*** Desired outcomes of treatment are resolution of signs and symptoms of infection, reduction of serum concentrations of anticoccidioidal antibodies, and return of function of involved organs. It would also be desirable to prevent relapse of illness on discontinuation of therapy, although current therapy is often unable to achieve this goal.

***Evidence to support recommendations.*** Before the availability of antifungal therapy, initial uncomplicated pulmonary infections in the absence of comorbidity resolved in at least

95% of patients. Randomized, prospective clinical trials of antifungal drugs have not been completed to determine whether drug therapy hastens the resolution of immediate symptoms or prevents subsequent complications.

Published reports of intravenous amphotericin B treatment of chronic pulmonary or extrapulmonary nonmeningeal coccidioidomycosis are limited to small numbers of patients treated in open-label, nonrandomized studies [13]. Coccidioidal meningitis treatment with intrathecal amphotericin B has been reported as the accumulated experience of individual investigators [16].

The response of symptomatic chronic pulmonary and extrapulmonary disseminated infections to several oral azole antifungal agents has been studied in large, multicentered, open-label, nonrandomized trials by the Mycoses Study Group, as well as by other investigators [17–26]. The majority of patients in these studies were treated for periods ranging from months to years and exhibited decreased numbers of symptoms, improved appearance of chest radiographs or extrapulmonary lesions, decreased concentrations of complement fixing-type antibodies in their serum or CSF samples, and sputum cultures that converted from positive for *Coccidioides* species to negative. Follow-up cultures of samples obtained from extrapulmonary lesions often would have required invasive procedures and frequently were not carried out. Moreover, when therapy was stopped, these abnormalities often recurred, suggesting that sterilization of lesions was not accomplished. A randomized trial of oral itraconazole (200 mg administered twice per day) versus oral fluconazole (400 mg administered every day) has been published [27]. In the primary analysis, there was no difference between these 2 treatments when analyzed at the 8-month time point. Subanalyses indicated that itraconazole therapy may be more potent in the treatment of skeletal lesions and superior when analyzed at 12 months overall.

***Values.*** Principal value is afforded to patients who receive treatment. Coccidioidomycosis is not contagious by the respiratory route and therefore control of individual infections will not have additional public health benefit.

***Benefits, harms, and costs.*** A diagnosis of coccidioidomycosis in itself may benefit a patient by (1) reducing the use of unnecessary antibacterial therapies, (2) avoiding further diagnostic evaluations, (3) allaying patient anxiety about an otherwise uncertain respiratory condition, and (4) affording patients prognostic information. Early identification and treatment of complications will decrease the amount of tissue destruction and resulting morbidity. Effective therapy is potentially lifesaving.

Use of amphotericin B often engenders untoward effects. Surgical risks depend on the specific procedure.

The cost of antifungal medication can be as high as $20,000 per year of treatment. Recently, generic fluconazole has become available at considerably lower cost. For managing critically ill patients with coccidioidomycosis, there are considerable additional costs, including intensive care support for many days or weeks. In a recent Centers for Disease Control and Prevention (CDC) analysis, hospital costs in Arizona during 1998–2001 were a mean of $33,762 per patient with coccidioidomycosis [28].

***Validation.*** Below are descriptions of management strategies for several manifestations of coccidioidomycosis. A revision of the original Practice Guidelines for Coccidioidomycosis [29] was circulated among the authors. Subsequently revised drafts were reviewed for comment by members of the Arizona Infectious Diseases Society (6–7 March 2004) and by health care professionals who attended the 48th Annual Coccidioidomycosis Study Group Meeting (held on 3 April 2004). The strength of and evidence for recommendations, expressed using the Infectious Diseases Society of America–US Public Health Service grading system for ranking recommendations in clinical guidelines (table 1), is shown following each specific recommendation.

## MANAGEMENT OF CLINICAL ENTITIES

### Primary Respiratory Infection

Primary infections due to *Coccidioides* species most frequently manifest as community-acquired pneumonia 1–3 weeks after exposure [30, 31]. Distinguishing coccidioidomycosis from other etiologies is usually difficult without specific laboratory confirmation, such as detection of anticoccidioidal antibodies in serum samples [32] or identification of *Coccidioides* species in sputum samples or another respiratory specimen. Therefore, residents of and recent travelers to regions where community-acquired pneumonia is endemic should be evaluated for *Coccidioides* species as a possible etiologic agent. *Coccidioides* species are listed by the CDC as Select Agents, and their growth in culture requires handling in a secure and contained fashion [33].

***Uncomplicated acute coccidioidal pneumonia.*** How best to manage primary respiratory coccidioidal infections is an unsettled issue because of the lack of prospective controlled trails. For many (if not most) patients, management may rely on periodic reassessment of symptoms and radiographic findings to assure resolution without antifungal treatment. On the other hand, some authorities propose treatment of all symptomatic patients to decrease the intensity or duration of symptoms. Although physicians speculate that early treatment may decrease the frequency or severity of dissemination, there are no data to support this speculation (C-III). Several special circumstances are usually considered to warrant initiation of therapy. Chief among these is concurrent immunosuppression, such as that which accompanies AIDS, receipt of an organ transplant, therapy with high-dose corticosteroids, or receipt of inhibitors

**Table 1. Infectious Diseases Society of America–US Public Health Service Grading System for ranking recommendations in clinical guidelines.**

| Category, grade | Definition |
|---|---|
| Strength of recommendation | |
| A | Good evidence to support a recommendation for use; should always be offered |
| B | Moderate evidence to support a recommendation for use; should generally be offered |
| C | Poor evidence to support a recommendation; optional |
| D | Moderate evidence to support a recommendation against use; should generally not be offered |
| E | Good evidence to support a recommendation against use; should never be offered |
| Quality of evidence | |
| I | Evidence from ⩾1 properly randomized, controlled trial |
| II | Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments |
| III | Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees |

of TNF (such as etanercept or infleximab). Also, other patients who are likely to handle pulmonary coccidioidal infection less well include those with diabetes mellitus or preexisting cardiopulmonary disease (A-II). The diagnosis of primary infection during pregnancy, especially in the third trimester or immediately postpartum, frequently prompts the initiation of treatment (A-III). During pregnancy, amphotericin B is the treatment of choice because fluconazole (and likely other azole antifungals) are teratogenic (A-III). Persons of Filipino or African descent have a higher risk for dissemination, and this may also be taken into consideration (B-III). Finally, patients who are judged to have exceptionally severe primary infections may be more likely to benefit from treatment than those patients with a more mild illness. Although opinion varies as to the most-relevant factors for judging severity of illness, commonly used indicators include weight loss of >10%, intense night sweats persisting longer than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, anticoccidiodial complement-fixing antibody concentrations in excess of 1:16 (as determined by a reference method or equivalent titer) [32], inability to work, symptoms that persist for >2 months, or age >55 years. Commonly prescribed therapies include currently available oral azole antifungal agents at dosages of 200–400 mg per day. Courses of typically recommended treatment range from 3 to 6 months.

As the patient's illness improves, either with or without antifungal therapy, continued monitoring at 1–3-month intervals for 1 year or longer is advised to assess the resolution of pulmonary infiltrates and to identify, as early as possible, those patients who develop infection outside of the chest. Monitoring usually should include patient interviews, physical examinations (as appropriate), serologic tests, and radiographic examinations. Determining pulmonary lesions that evolve into residual nodules is useful because it obviates the need for establishing the nodule's etiology at a future time. Identifying dissemination is accomplished with histologic examination and culture of suspicious skin lesions, analysis of aspirates of joint effusions, and lumbar puncture of patients who develop progressively severe or persistent headaches, mental status changes, or other meningeal signs. Although extrapulmonary dissemination is infrequent, early detection of patients in whom dissemination does occur would afford benefit by earlier initiation of treatment and a resulting reduction in tissue destruction.

***Diffuse pneumonia.*** Bilateral reticulonodular or miliary infiltrates produced by *Coccidioides* species suggest either an underlying immunodeficiency state with concurrent fungemia or an exposure to a high inoculum of fungal spores, as may occur as a result of laboratory accidents or at archeology sites. In such patients, therapy is usually begun either with amphotericin B or high-dose fluconazole. Amphotericin B is more frequently used as initial therapy if significant hypoxia is present or if deterioration is rapid (A-III). Several weeks of therapy are often required to produce clear evidence of improvement. After this time, during convalescence, amphotericin B therapy may be discontinued and replaced with treatment with an oral azole antifungal (B-III). In combination, the total length of therapy should be at least 1 year, and for patients with severe immunodeficiency, oral azole therapy should be continued as secondary prophylaxis (A-III). Because diffuse pneumonia due to *Coccidioides* species is usually a manifestation of fungemia, patients should be evaluated for the possibility of other extrapulmonary lesions that may also require attention.

### Pulmonary Nodule, Asymptomatic

If a stable solitary nodule is determined to be due to *Coccidioides* species by noninvasive means or by fine-needle aspiration, specific antifungal therapy or resection is unnecessary (E-II). Similarly, in the absence of significant immunosuppression, anti-

fungal therapy is not recommended if the lesion is completely resected and the diagnosis is determined from the excised tissue. Stability can be determined by repeated radiographic examination of the chest for 2 years demonstrating no change in the size of the nodule. Should enlargement of the nodule occur, reevaluation with sputum cultures and measurement of coccidioidal serum antibodies may help to determine whether the patient's infection is active and warrants therapy. Consideration also should be given to the possibility of cancer coexistent with the coccidioidal infection, in which case resection of the nodule would usually be necessary.

### Pulmonary Cavity

***Asymptomatic.*** Many cavities caused by *Coccidioides* species are benign in their course and do not require intervention. Such cavities may harbor viable fungus, and cultures of samples of sputum or other respiratory secretions commonly yield colonies of *Coccidioides* species. Many authorities do not consider these characteristics of asymptomatic cavities sufficient reason to initiate treatment. Moreover, in the absence of controlled clinical trials, evidence is lacking that antifungal therapy has a salutary effect on the course of asymptomatic coccidioidal cavities (B-III). With the passage of time, some cavities disappear, obviating the need for intervention. Although an indefinite follow-up period without intervention is appropriate for many patients, eventual resection from 1 to several years after the cavity is identified may be recommended to avoid future complications, especially if the cavity is still detectable after 2 years, if it demonstrates progressive enlargement, or if it is immediately adjacent to the pleura (B-III).

***Symptomatic.*** Complications of coccidioidal cavities include local discomfort, superinfection with other fungi or possibly bacteria, or hemoptysis. Should these complications occur, oral therapy with azole antifungals may result in improvement, although recurrence of symptoms (at least in some patients) may occur on cessation of therapy. If a bacterial superinfection is present, treatment for several weeks with an oral antibacterial may also reduce symptoms. However, such therapies usually do not result in the closure of the cavity. In cases in which the surgical risks are not unusually high, resection of localized cavities is likely to resolve the problem and may be recommended as an alternative approach to chronic or intermittent therapy.

***Ruptured.*** Rupture of a coccidioidal cavity into the pleural space, resulting in a pyopneumothorax, is an infrequent but serious complication of a necrotizing coccidioidal pneumonia [34]. In young, otherwise-healthy patients, surgical closure by lobectomy with decortication is the preferred management (A-II). Antifungal therapy is recommended for treatment, particularly in cases with delay of diagnosis and coexistent diseases (C-III). For patients in whom the diagnosis was delayed a week or more or for patients in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin B or oral azole antifungal drugs prior to surgery or chest tube drainage without surgery (C-III).

### Chronic Progressive Fibrocavitary Pneumonia

Initial treatment with oral azole antifungal agents is recommended (A-II). If the patient improves sufficiently, therapy should be continued for at least 1 year. If therapy is not satisfactory, switching to an alternative azole antifungal, raising the dosage of the azole, or therapy with amphotericin B are alternative strategies (B-III). Surgical resection may be a useful option for refractory lesions that are well localized or in cases in which significant hemoptysis has occurred.

### Disseminated Infection (Extrapulmonary)

***Nonmeningeal.*** Initial therapy is usually initiated with oral azole antifungal agents, most commonly fluconazole or itraconazole (A-II). Clinical trials have used 400 mg per day of ketoconazole, itraconazole, or fluconazole. Some experts recommend higher dosages (up to 2000 mg per day of fluconazole; up to 800 mg per day of itraconazole, administered in 200-mg doses) (B-III). Amphotericin B is recommended for alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations, such as the vertebral column (B-III). Amphotericin B dosage is similar to that for diffuse coccidioidal pneumonia, although the duration of therapy may be longer. In patients experiencing failure of conventional deoxycholate amphotericin B therapy or experiencing intolerable drug-related toxicities, lipid amphotericin B formulations have been demonstrated to be safe and to cause less nephrotoxicity and may be considered. Animal model studies have indicated that the higher amphotericin B dosages that can be given via lipid formulations produce results superior to those seen with the maximally tolerated deoxycholate amphotericin B [35–37]. However, there have been no clinical trials assessing the efficacy of lipid formulations of amphotericin B.

Combination therapy with amphotericin B and an azole has been administered to some patients, especially when infection is widespread or in cases in which there has been disease progression during treatment with a single agent. Although combination therapy may improve responses, there is no evidence that such an approach is superior to treatment with a single agent, and for other fungal infections, there are examples of antagonism with combination therapy [38], as has been demonstrated in vitro with *Coccidioides* species [11].

Surgical debridement or stabilization is an occasionally important, if not critical, adjunctive measure. Factors that favor a recommendation for surgical intervention are large size of abscesses, progressive enlargement of abscesses or destructive lesions, presence of bony sequestrations, instability of the spine,

or impingement on critical organs (such as a pericardial effusion on the heart) or tissues (such as an epidural abscess on the spinal cord).

***Meningitis.*** Therapy with oral fluconazole is currently preferred by most clinicians. The dosage used in reported clinical trials was 400 mg per day (A-II). Some physicians begin therapy with 800 or 1000 mg per day of fluconazole (B-III). Itraconazole, administered in dosages of 400–600 mg per day, has also been reported to be comparably effective [39] (B-II). Some physicians also initiate therapy with intrathecal amphotericin B in addition to an azole on the basis of their belief that responses are more prompt with this approach. The dose and duration of intrathecal amphotericin B in this circumstance ranges between 0.1 mg and 1.5 mg per dose (C-III). Patients who respond to azole therapy should continue this treatment indefinitely [40] (A-III). Hydrocephalus nearly always requires a shunt for decompression (A-III). Hydrocephalus may develop regardless of the therapy being used and need not require switching to alternative therapy (B-III). Patients who do not respond to fluconazole or itraconazole would be candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment. The intrathecal dosage of amphotericin B normally ranges between 0.1 mg and 1.5 mg per dose, administered at intervals ranging from daily to weekly, beginning at a low dosage and increasing the size of the dosage until the appearance of patient intolerance (indicated by severe vomiting, prostration, or transient dose-related mental status) [16].

The most common life-threatening complication of coccidioidal meningitis in the modern era is CNS vasculitis leading to cerebral ischemia, infarction, and hemorrhage [41]. Some physicians have personal experience demonstrating the efficacy of administering high-dose, intravenous, short-term corticosteroids for this condition, whereas other physicians have not noted similar benefit.

### Prophylaxis for Coccidioidomycosis in Solid-Organ Transplant Recipients

The risk of coccidioidomycosis among solid-organ transplant recipients in an area of endemicity was 4%–9% [42], with the majority of infections occurring within 1 year after transplantation [43]. Because infection in such patients frequently disseminates and carries a high risk of mortality, there is interest in reducing the number of these complications in patients from or within the regions of endemicity by use of preemptive prophylactic antifungal therapy. One transplantation program in the area of endemicity has employed a strategy of targeted prophylaxis, whereby patients with certain risk factors for coccidioidomycosis (a positive serological test result prior to receipt of a transplant or a history of coccidioidomycosis) receive prophylactic fluconazole at the time of transplantation, and thus far, the results are encouraging [44].

### Management of Patients Infected with HIV-1

Before the introduction of HAART, coccidioidomycosis was a major opportunistic infection in the area of endemicity among individuals infected with HIV-1 [45]. The incidence of clinically apparent coccidioidal infection has since decreased. Prevention of coccidioidomycosis among HIV-1–infected patients living in the area of coccidioidal endemicity by prophylactic use of an antifungal is not effective for most patients [46]. Treatment is recommended for all patients with HIV-1 infection and peripheral blood $CD4^+$ lymphocyte counts <250 cells/$\mu$L who have clinically active coccidioidomycosis. Therapy should be continued as long as the $CD4^+$ cell count is <250 cells/$\mu$L [45, 47]. However, it may be reasonable to stop therapy in those patients with higher $CD4^+$ cell counts if there is clinical evidence of control of the coccidioidal infection (except for patients with meningitis, for whom therapy should be life-long).

## Acknowledgments

***Financial support.*** Supported in part by the US Office of Veterans Affairs.

***Potential conflicts of interest.*** A.C. has received grant support from Schering and has lectured for Pfizer. J.N.G. has received research support or has been a consultant for Pfizer, Janssen, Merck, Schering, Enzon, and Lilly. R.H.J. has received grant support from Pfizer; is a member of the speakers' bureaus for Sanofi-Aventis, Enzon, and Merck; and has been on the speakers' bureau of Bristol Myers-Squibb and Bayer. D.A.S. has received research support from and has been a consultant for Janssen, Ortho-McNeil, Pfizer, Gilead, Enzon, and Schering. All other authors: no conflicts.

## References

1. Fisher MC, Koenig GL, White TJ, Taylor JT. Molecular and phenotypic description of *Coccidioides posadasii* sp nov., previously recognized as the non-California population of *Coccidioides immitis*. Mycologia **2002**; 94:73–84.
2. Galgiani JN. Coccidioidomycosis: a regional disease of national importance—rethinking approaches for control. Ann Intern Med **1999**; 130:293–300.
3. Chiller TM, Galgiani JN, Stevens DA. Coccidioidomycosis. Infect Dis Clin North Am **2003**; 17:41–57, viii.
4. Stevens DA. Current concepts: coccidioidomycosis. N Engl J Med **1995**; 332:1077–82.
5. Drutz DJ, Catanzaro A. Coccidioidomycosis: part II. Am Rev Respir Dis **1978**; 117:727–71.
6. Drutz DJ, Catanzaro A. Coccidioidomycosis: part I. Am Rev Respir Dis **1978**; 117:559–85.
7. Caraway NP, Fanning CV, Stewart JM, Tarrand JJ, Weber KL. *Coccidioidomycosis osteomyelitis* masquerading as a bone tumor: a report of 2 cases. Acta Cytol **2003**; 47:777–82.
8. Prabhu RM, Bonnell M, Currier BL, Orenstein R. Successful treatment of disseminated nonmeningeal coccidioidomycosis with voriconazole. Clin Infect Dis **2004**; 39:e74–7.
9. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of *Coccidioides* meningitis. Antimicrob Agents Chemother **2004**; 48:2341.
10. Gonzalez GM, Tijerina R, Najvar LK, et al. Correlation between antifungal susceptibilities of *Coccidioides immitis* in vitro and antifungal treatment with caspofungin in a mouse model. Antimicrob Agents Chemother **2001**; 45:1854–9.
11. Stevens DA. Drug interaction of caspofungin with conventional agents against pathogens of endemic mycoses [abstract 863]. In: Program and abstracts of the 42nd Interscience Conference on Antimicrobial Agents

and Chemotherapy. Washington, DC: American Society for Microbiology, **2002**.
12. 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.
13. Blum D, Catanzaro A, Cloud G. Safety and tolerance of posaconazole (SCH 56592) in patients with nonmeningeal disseminated coccidioidomycosis [abstract 1417]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy.Washington, CD: American Society for Microbiology, **2000**.
14. Stevens DA, Rendon A, Gaona V, et al. Posaconazole therapy for chronic refractory coccidioidomycosis [abstract 663]. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2004**.
15. Sugar AM. Use of amphotericin B with azole antifungal drugs: what are we doing. Antimicrob Agents Chemother **1995**; 39:1907–12.
16. Stevens DA, Shatsky SA. Intrathecal amphotericin in the management of coccidioidal meningitis. Semin Respir Infect **2001**; 16:263–9.
17. Galgiani JN, Stevens DA, Graybill JR, Dismukes WE, Cloud GA. Ketoconazole therapy of progressive coccidioidomycosis: comparison of 400- and 800-mg doses and observations at higher doses. Am J Med **1988**; 84:603–10.
18. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NAIAD Mycoses Study Group. Am J Med **1990**; 89:282–90.
19. Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. Am J Med **1995**; 98:249–56.
20. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis: the NIAID-Mycoses Study Group. Ann Intern Med **1993**; 119:28–35.
21. Diaz M, Negroni R, Montero-Gei F, et al. A pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Clin Infect Dis **1992**;14(Suppl 1):S68–S76.
22. Tucker RM, Galgiani JN, Denning DW, et al. Treatment of coccidioidal meningitis with fluconazole. Rev Infect Dis **1990**; 12(Suppl 3):S380–S9.
23. Tucker RM, Denning DW, Arathoon EG, Rinaldi MG, Stevens DA. Itraconazole therapy for nonmeningeal coccidioidomycosis: clinical and laboratory observations. J Am Acad Dermatol **1990**; 23:593–601.
24. Stevens DA, Stiller RL, Williams PL, Sugar AM. Experience with ketoconazole in three major manifestations of progressive coccidioidomycosis. Am J Med **1983**; 74:58–63.
25. Brass C, Galgiani JN, Campbell SC, Stevens DA. Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. Rev Infect Dis **1980**; 2:656–60.
26. Stevens DA. Azoles in the treatment of coccidioidomycosis. In: Einstein HE, Pappagianis D, Catanzaro A, eds. Coccidioidomycosis: proceedings of the 5th International Conference on Coccidioidomycosis. Washington: National Foundation for Infectious Diseases, **1996**:255–64.
27. Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis: a randomized, double-blind trial. Mycoses Study Group. Ann Intern Med **2000**; 133:676–86.
28. Park BJ, Sigel K, Vaz V, et al. An epidemic of coccidioidomycosis in Arizona associated with climate changes, 1998–2001. J Infect Dis **2005**; 191:1981–7.
29. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. Clin Infect Dis **2000**; 30:658–61.
30. Panackal AA, Hajjeh RA, Cetron MS, Warnock DW. Fungal infections among returning travelers. Clin Infect Dis **2002**; 35:1088–95.
31. Feldman BS, Snyder LS. Primary pulmonary coccidioidomycosis. Semin Respir Infect **2001**; 16:231–7.
32. Pappagianis D. Serologic studies in coccidioidomycosis. Semin Respir Infect **2001**; 16:242–50.
33. Centers for Disease Control and Prevention Select Agent Program Web page. Available at: http://www.cdc.gov/od/sap/. Accessed 30 August 2005.
34. Cunningham RT, Einstein H. Coccidioidal pulmonary cavities with rupture. J Thorac Cardiovasc Surg **1982**; 84:172–7.
35. Clemons KV, Stevens DA. Efficacies of amphotericin B lipid complex (ABLC) and conventional amphotericin B against murine coccidioidomycosis. J Antimicrob Chemother **1992**; 30:353–63.
36. Clemons KV, Hanson LH, Perlman AM, Stevens DA. Efficacy of SCH39304 and fluconazole in a murine model of disseminated coccidioidomycosis. Antimicrob Agents Chemother **1990**; 34:928–30.
37. Clemons KV, Sobel RA, Williams PL, Pappagianis D, Stevens DA. Efficacy of intravenous liposomal amphotericin B (AmBisome) against coccidioidal meningitis in rabbits. Antimicrob Agents Chemother **2002**; 46:2420–6.
38. Steinbach WJ, Stevens DA, Denning DW. Combination and sequential antifungal therapy for invasive aspergillosis: review of published in vitro and in vivo interactions and 6281 clinical cases from 1966–2001. Clin Infect Dis **2003**; 37(Suppl 3):S188–S224.
39. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. Ann Intern Med **1990**; 112:108–12.
40. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for *Coccidioides immitis* meningitis? Ann Intern Med **1996**; 124:305–10.
41. Williams PL. Vasculitic complications associated with coccidioidal meningitis. Semin Respir Infect **2001**; 16:270–9.
42. Blair JE, Logan JL. Coccidioidomycosis in solid organ transplantation. Clin Infect Dis **2001**; 33:1536–44.
43. Cohen IM, Galgiani JN, Potter D, Ogden DA. Coccidioidomycosis in renal replacement therapy. Arch Intern Med **1982**; 142:489–94.
44. Awasthi S, Cox RA. Transfection of murine dendritic cell line (JAWS II) by a nonviral transfection reagent. Biotechniques **2003**; 35:600–2, 604.
45. Ampel NM, Dols CL, 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.
46. 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.
47. Ampel NM. Delayed-type hypersensitivity, in vitro T-cell responsiveness and risk of active coccidioidomycosis among HIV-infected patients living in the coccidioidal endemic area. Med Mycol **1999**; 37:245–50.