

Practice Guidelines for the Treatment of Coccidioidomycosis

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Executive Summary

Management of patients diagnosed with coccidioidomycosis involves defining the extent of infection and assessing host factors that predispose to disease severity. Patients with relatively 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 at high risk of complications because of immunosuppression or other pre-existing factors require a variety of treatment strategies that may include antifungal therapy, surgical debridement, or both. Amphotericin B is often selected for treatment of patients with respiratory failure due to *Coccidioides immitis* or rapidly progressive coccidioidal infections. With other more chronic manifestations of coccidioidomycosis, treatment with fluconazole, itraconazole, or ketoconazole is common. Duration of therapy often ranges from many months to years, and, for some patients, chronic suppressive therapy is needed to prevent relapses.

Introduction

Coccidioidomycosis results from inhaling the spores (arthroconidia) of *Coccidioides immitis*. Most infections in the United States occur within the major regions of endemicity in southern Arizona, central California, southern New Mexico, and west Texas. Travelers who visit these regions of endemicity and immunosuppressed patients in whom latent infections reactivate can require medical management in other parts of the country [1].

Of the estimated 100,000 infections per year, one-half to two-thirds are subclinical, and most patients with these infections are protected from second primary infections. The most common clinical presentation in diagnosed cases of coccidioidomycosis is acute or subacute pneumonic illness. Approximately 5%–10% of infections result in residual pulmonary sequelae,

usually nodules or peripheral thin-walled cavities. An even smaller proportion of all infections, perhaps 0.5%–1.0%, result in illnesses related to chronic pulmonary or extrapulmonary infection. Although virtually any site in the body may be involved, extrapulmonary dissemination most frequently involves the skin, the skeletal system, and the meninges [2–4].

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

Treatment options. Coccidioidomycosis encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection. For this reason, management strategies vary widely from patient to patient. Although disease will resolve in most patients who present with early infections without specific antifungal therapy, management should routinely include repeated patient encounters for 1–2 years, either to document resolution or to identify, as early as possible, evidence of pulmonary or extrapulmonary complications. Patients who develop progressive pulmonary disease or disseminated disease warrant antifungal therapy, which is typically prolonged—potentially lifelong—especially for patients with overt immunocompromised 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 cases is a critical component of therapy, is not addressed in this practice guideline. However, all patients with progressive or disseminated disease will require some combination of periodic physical examinations, laboratory studies, and radiological studies to guide management decisions.

Specific antifungals (and their usual dosages) for treatment of coccidioidomycosis include amphotericin B (0.5–0.7 mg/kg/d iv), ketoconazole (400 mg/d po), fluconazole (400–800 mg/d po or iv), and itraconazole (200 mg b.i.d. po). If itraconazole is used, measurement of serum concentrations of itraconazole after 2 weeks may determine if absorption is satisfactory. In general, the more rapidly progressive a coccidioidal infection is, 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.

Outcomes. Desired outcomes of treatment are resolution of signs and symptoms of infection, reduction of serum con-

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centrations of antibodies to *C. immitis*, and return of function of involved organs. It would also be desirable to prevent relapse of illness upon discontinuation of therapy, although current therapy is often unable to achieve this goal.

Evidence. Before the availability of antifungal therapy, the natural history of initial pulmonary infections revealed that these infections resolved in at least 95% of patients. Randomized, prospective clinical trials of antifungals have not been completed to determine whether drug therapy hastens the resolution of immediate symptoms or prevents subsequent complications.

Published reports of iv amphotericin B treatment of chronic pulmonary or extrapulmonary nonmeningeal coccidioidomycosis are limited to small numbers of patients treated in open-label, nonrandomized studies [5]. Treatment of coccidioidal meningitis with intrathecal amphotericin B has been reported as accumulated experience of individual investigators [6–11].

The response of symptomatic chronic pulmonary and extrapulmonary disseminated infections to several oral azole antifungals has been studied in large multicenter, open-label, nonrandomized trials by the Mycoses Study Group, as well as other investigators [12–25]. Most patients in these studies were treated for periods ranging from months to years, and had exhibited decreased number of symptoms, improved appearance on chest radiographs or of extrapulmonary lesions, decreased concentrations of CF-type antibodies in serum or CSF, and conversion of sputum cultures from positive to negative for *C. immitis*. Follow-up cultures of specimens 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 [26]. A randomized trial of itraconazole versus fluconazole has been completed, and the results will be available soon.

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

Benefits, harms, and costs. 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 is high, in the range of \$5000–\$20,000 per year of treatment. For managing critically ill patients with coccidioidomycosis, there are considerable additional costs including intensive care support for many days or weeks.

Management of Clinical Entities

In the following sections, there are descriptions of management strategies for several manifestations of coccidioidomy-

cosis. Each recommendation is followed by a parenthetical reference to the category and grade of disease. The category (A–E) indicates the strength of each recommendation for or against use, and the grade (I, II, or III) indicates the quality of evidence on which the recommendation is based (see Sobel [27] for definitions of categories and grades).

The descriptions were developed through a series of drafts revised by a writing committee composed of the major contributors of patients to clinical trials for new therapies for *C. immitis* infections. The penultimate draft was reviewed for comment by health care professionals in an open session on 3 April 1998, in association with the annual meeting of the Coccidioidomycosis Study Group in Visalia, California.

Primary Respiratory Infection

Uncomplicated. Management of primary respiratory infections due to *C. immitis* is very controversial because of the lack of prospective, controlled trials. 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 (CIII). Concurrent risk factors (i.e., HIV infection, organ transplant, or high doses of corticosteroids) or evidence of unusually severe infections should lead to the initiation of antifungal therapy (AII). Diagnosis of primary infection during the third trimester of pregnancy or immediately in the postpartum period should raise consideration for treatment (AIII). During pregnancy, amphotericin B is the treatment of choice because fluconazole and likely other azole antifungals are teratogenic (AIII).

Although opinion varies on the most relevant factors to judge severity, commonly used indicators are weight loss of >10%, intense night sweats persisting for >3 weeks, infiltrates involving more than one-half of 1 lung or portions of both lungs, prominent or persistent hilar adenopathy, concentrations of CF antibody to *C. immitis* of >1 : 16, as determined by a reference method or an equivalent titer [28], failure to develop dermal hypersensitivity to coccidioidal antigens, inability to work, or symptoms that persist for >2 months. Persons of African or Filipino descent have a higher risk for dissemination, and this fact may also be taken into consideration (BIII). Commonly prescribed therapies include currently available oral azole antifungals at their recommended doses. Courses of typically recommended treatment range from 3 to 6 months.

Diffuse pneumonia. When bilateral reticulonodular or milary infiltrates are produced by *C. immitis*, there is probably an underlying immunodeficiency state. Therapy usually starts with amphotericin B (AIII). Several weeks of therapy are often required to produce clear evidence of improvement. After this time during convalescence, amphotericin B treatment may be discontinued and replaced with oral azole antifungal therapy (BIII). 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 (AIII). Because diffuse pneumonia due to *C. immitis* is usually a manifestation of fungemia, patients should be evaluated for other extrapulmonary lesions that may also require attention.

Pulmonary Nodule, Asymptomatic

If a solitary nodule is determined to be due to *C. immitis* by noninvasive means or by fine-needle aspiration, specific antifungal therapy or resection is unnecessary (EIII). Similarly, in the absence of significant immunosuppression, antifungal therapy is not recommended if the lesion is completely resected and the diagnosis is determined from examination of the excised tissue.

Pulmonary Cavity

Asymptomatic. Many cavities due to *C. immitis* are benign in their course and do not require intervention. Such cavities harbor viable fungus, and cultures of sputum or other respiratory secretions commonly yield colonies of *C. immitis*. Most authorities do not consider these characteristics of asymptomatic cavities sufficient reason to initiate treatment. Moreover, in the absence of controlled clinical trials, we lack evidence that antifungal therapy has a salutary effect on the course of asymptomatic coccidioidal cavities (BIII). With the passage of time, some cavities disappear, obviating the need for intervention. Although indefinite follow-up 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 (BIII).

Symptomatic. Complications of coccidioidal cavities are 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, occurs upon cessation of therapy. Where the surgical risks are not unusually high, resection of localized cavities will probably 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 that results in pyopneumothorax is an infrequent but well-recognized complication [29]. For young, otherwise healthy patients, surgical closure by lobectomy with decortication is the preferred management (AII). Antifungal therapy is recommended for coverage, particularly in acute cases with active disease, delay of diagnosis, or coexistent diseases (CIII). For patients for whom the diagnosis was delayed ≥ 1 week or in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with am-

photericin B or oral azole antifungals before surgery, or chest tube drainage without surgery (CIII).

Chronic Fibrocavitary Pneumonia

Initial treatment of chronic fibrocavitary pneumonia is with oral azole antifungals (AII). If the patient's condition improves sufficiently, therapy should be continued for at least 1 year. If therapy is not satisfactory, alternatives are switching to an alternative azole antifungal, raising the dose of fluconazole if it was the oral azole initially selected, and administering therapy with amphotericin B (BIII). Surgical resection may be a useful option for refractory lesions that are well localized or where significant hemoptysis has occurred.

Disseminated Infection, Extrapulmonary

Nonmeningeal. Therapy is usually initiated with oral azole antifungals (AII). Clinical trials have used 400 mg/d of ketoconazole, itraconazole, or fluconazole. Some experts recommend higher dosages of fluconazole (BIII). Amphotericin B is alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations such as the vertebral column (BIII). The dosage of amphotericin B is similar to that for treatment of diffuse coccidioidal pneumonia, although the duration may be longer. Surgical debridement or stabilization is an occasionally important if not critical adjunctive measure.

Meningitis. Therapy with oral fluconazole is currently preferred. The dosage used in reported clinical trials was 400 mg/d (AII) [30]. Some physicians begin therapy with 800 or 1000 mg/d of fluconazole (BIII). Dosages of itraconazole of 400–600 mg/d have also been reported to be comparably effective [31] (BII). Some physicians 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 have not been defined (CIII). Patients who respond to azole therapy should continue this treatment indefinitely [32] (AIII).

Hydrocephalus nearly always requires a shunt for decompression (AIII). Hydrocephalus may develop regardless of the therapy being used, and switching to alternative therapy is not required (BIII). Patients who do not respond to fluconazole or itraconazole treatment are candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment. The intrathecal dose of amphotericin B normally ranges from 0.01 to 1.5 mg; it is administered at intervals ranging from daily to weekly, beginning at a low dose and increasing until patient intolerance appears.

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