



## Complete Summary

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### GUIDELINE TITLE

Practice guidelines for the treatment of coccidioidomycosis.

### BIBLIOGRAPHIC SOURCE(S)

Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guidelines for the treatment of coccidioidomycosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr; 30(4):658-61. [32 references]

## COMPLETE SUMMARY CONTENT

SCOPE  
METHODOLOGY - including Rating Scheme and Cost Analysis  
RECOMMENDATIONS  
EVIDENCE SUPPORTING THE RECOMMENDATIONS  
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
QUALIFYING STATEMENTS  
IMPLEMENTATION OF THE GUIDELINE  
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
CATEGORIES  
IDENTIFYING INFORMATION AND AVAILABILITY

## SCOPE

### DISEASE/CONDITION(S)

Coccidioidomycosis (inhalation of Coccidioides immitis spores)

### GUIDELINE CATEGORY

Management  
Treatment

### CLINICAL SPECIALTY

Infectious Diseases  
Internal Medicine

### INTENDED USERS

Physicians

### GUIDELINE OBJECTIVE(S)

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

#### TARGET POPULATION

Patients with coccidioidomycosis

#### INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment

1. Periodic reassessment of symptoms, physical examination, laboratory studies, and radiographic studies (without antifungal treatment)
2. Pharmacotherapy (antifungal therapy)
  - Amphotericin B
  - Azole antifungals (ketoconazole, fluconazole, itraconazole)
3. Surgical management (resection, debridement, lobectomy)
4. Shunt for hydrocephalus

#### MAJOR OUTCOMES CONSIDERED

- Resolution of signs and symptoms of infection
- Reduction of serum concentrations of antibodies to *Coccidioides immitis*
- Return of function of involved organs
- Prevent relapse of illness upon discontinuation of therapy

## METHODOLOGY

#### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

#### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

#### NUMBER OF SOURCE DOCUMENTS

Not stated

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grades reflecting the quality of evidence on which recommendations are based:

- I. Evidence from at least one properly randomized, controlled trial
- II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
- III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

#### METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

#### METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

#### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of recommendation:

- A. Good evidence to support a recommendation for use
- B. Moderate evidence to support a recommendation for use
- C. Poor evidence to support a recommendation
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

#### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

#### METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

#### DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The recommendations for the management of several manifestations of coccidioidomycosis were developed through a series of drafts revised by a writing committee. 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.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are repeated at the end of the Major Recommendations field.

#### Primary Respiratory Infection

##### Uncomplicated

Management of primary respiratory infections due to *Coccidioides 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., human immunodeficiency virus [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 *Coccidioides immitis* of >1:16, as determined by a reference method or an equivalent titer (Pappagianis & Zimmer, 1990), 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 miliary infiltrates are produced by *Coccidioides 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 *Coccidioides 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 *Coccidioides 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 *Coccidioides 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 *Coccidioides 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 (Cunningham & Einstein, 1982). 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  $\geq 1$  week or in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin 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/day 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/day (Galgiani et al., 1998) (AII). Some physicians begin therapy with 800 or 1000 mg/day of fluconazole (BIII). Dosages of itraconazole of 400–600 mg/day have also been reported to be comparably effective (Tucker et al., 1990) (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 (Dewsnup et al., 1996) (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.

## Definitions of Strength of Recommendation and Quality of Evidence Ratings:

### Quality of evidence:

- I. Evidence from at least one properly randomized, controlled trial

- II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
- III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Strength of recommendation:

- A. Good evidence to support a recommendation for use
- B. Moderate evidence to support a recommendation for use
- C. Poor evidence to support a recommendation
- D. Moderate evidence to support a recommendation against use
- E. Good evidence to support a recommendation against use

CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early identification and treatment of complications will decrease the amount of tissue destruction and resulting morbidity. Effective therapy is potentially lifesaving.

Subgroups Most Likely to Benefit:

Persons of African and Filipino descent have a higher risk for dissemination.

POTENTIAL HARMS

Antifungal Therapy

- Conventional amphotericin B is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity.

- Lipid formulations of amphotericin B, although offering several therapeutic advantages over conventional amphotericin B, are considerably more expensive, ranging from 10- to 20-fold higher in cost.
- One potential limitation of the azole antifungal drugs is the frequency of their interactions with coadministered drugs, which results in adverse clinical consequences. One type of azole-drug interaction may lead to decreased plasma concentration of the azole, related to either decreased absorption or increased metabolism of the azole. A second type of azole-drug interaction may lead to an unexpected toxicity of the coadministered drug, relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system.
- A second potential limitation of the azoles is the emergence of resistance of fungal organisms, especially *Candida* species, to fluconazole.

#### Cost

- 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.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

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. Treatment of coccidioidal meningitis with intrathecal amphotericin B has been reported as accumulated experience of individual investigators.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guidelines for the treatment of coccidioidomycosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr; 30(4):658-61. [32 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2000 Apr

### GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

### SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

### GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Practice Guidelines Committee

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: John N. Galgiani, Neil M. Ampel, Antonino Catanzaro, Royce H. Johnson, David A. Stevens, and Paul L. Williams.

### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

### GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Infectious Diseases Society of America \(IDSA\) Web site](#). Also available in [HTML format](#).

Print copies: Available from the University of Chicago Press; fax: (773) 702-6096.

#### AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. *Clinical Infectious Diseases* 2001; 32: 851-4.
- Gross PA. Practice guidelines for infectious diseases: Rationale for a work in progress. *Clin Infect Dis.* 1998 May; 26(5): 1037-41.
- Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of quality standards for infectious diseases. *Infectious Diseases Society of America. Clin Infect Dis* 1994 Mar; 18(3): 421.

Electronic copies: Available from the [Infectious Diseases Society of American \(IDSA\) Web site](#).

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

#### PATIENT RESOURCES

None available

#### NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001.

#### COPYRIGHT STATEMENT

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