Complete Summary

GUIDELINE TITLE

Coccidioidomycosis.

BIBLIOGRAPHIC SOURCE(S)

Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Coccidioidomycosis. Clin Infect Dis 2005 Nov 1;41(9):1217-23. [47 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: 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.

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
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Coccidioidomycosis (inhalation of *Coccidioides immitis* or *C. posadasii* spores, [also known as valley fever])

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 which therapies are most appropriate for various forms of infection

TARGET POPULATION

Patients with coccidioidomycosis

INTERVENTIONS AND PRACTICES CONSIDERED

1. Periodic reassessment of symptoms, physical examination, sputum cultures, measurement of coccidioidal serum antibodies, fine needle aspiration of lung nodules, identification of dissemination (culture of suspicious skin lesions, analysis of aspirates of joint effusions, and lumbar puncture), laboratory studies, and radiographic studies (without antifungal treatment)
2. Pharmacotherapy (antifungal therapy)
    - Amphotericin B deoxycholate, lipid formulations of amphotericin B
    - Azole antifungals
3. Surgical management (resection, debridement, lobectomy)
4. Shunt for hydrocephalus
5. Prophylactic fluconazole therapy for solid-organ transplant recipients
6. Management of coccidioidomycosis in patients infected with human immunodeficiency virus-1 (HIV-1)

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

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-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 stated

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; 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

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

A revision of the original Practice Guidelines for Coccidioidomycosis 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).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are provided at the end of the "Major Recommendations" field.

Primary Respiratory Infection

Primary infections due to *Coccidioides* species most frequently manifest as community-acquired pneumonia 1 to 3 weeks after exposure. Distinguishing coccidioidomycosis from other etiologies is usually difficult without specific laboratory confirmation, such as detection of anticoccidioidal antibodies in serum samples 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 Centers for Disease Control and Prevention (CDC) as Select Agents, and their growth in culture requires handling in a secure and contained fashion.

Uncomplicated Acute Coccidioidal Pneumonia

How best to manage primary respiratory coccidioidal infections is an unsettled issue 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 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 acquired immune deficiency syndrome (AIDS), receipt of an organ transplant, therapy with high-dose corticosteroids, or receipt of inhibitors of tumor necrosis factor (TNF) (such as etanercept or infliximab). 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), 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 to 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 to 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 military 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, antifungal 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 harbor viable fungus, and cultures of samples of sputum or other respiratory secretions commonly yield colonies of *Coccidioides* species. Most 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. 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 for 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. 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, as has been demonstrated in vitro with *Coccidioides* species.

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 to 600 mg per day has also been reported to be comparably effective **(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 **(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 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).

The most common life-threatening complication of coccidioidal meningitis in the modern era is central nervous system (CNS) vasculitis leading to cerebral ischemia, infarction, and hemorrhage. 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% to 9%, with the majority of infections occurring within 1 year after transplantation. 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.

Management of Patients Infected with HIV-1

Before the introduction of highly active antiretroviral therapy (HAART), coccidioidomycosis was a major opportunistic infection in the area of endemicity among individuals infected with human immunodeficiency virus (HIV)-1. 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. Treatment is recommended for all patients with HIV-1 infection and

peripheral blood CD4+ lymphocyte counts <250 cells/microL who have clinically active coccidioidomycosis. Therapy should be continued as long as the CD4+ cell count is <250 cells/microL. 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).

Definitions:

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 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; should always be offered
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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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations" field).

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

- Side effects of and drug interactions associated with antifungal therapy
- Risks associated with surgery

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.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Coccidioidomycosis. Clin Infect Dis 2005 Nov 1;41(9):1217-23. [47 references] PubMed

ADAPTATION

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

DATE RELEASED

2000 Apr (revised 2005 Nov 1)

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

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FINANCIAL DISCLOSURES/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.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: 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.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Disease Society of America (IDSA) Web site.

Print copies: Available from Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Kish MA. Guide to development of practice guidelines. Clin Infect Dis 2001 Mar 15;32(6):851-4.

Electronic copies: Available from the Clinical Infectious Diseases Journal Web site.

Print copies: Available from Infectious Diseases Society of America, 1300 Wilson Boulevard, Suite 300, Arlington, VA 22209.

A PDA version of the original guideline document is available from www.idsaguidelinesforhandhelds.org.

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. This summary was updated by ECRI on November 14, 2005.

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