Coccidioidomycosis

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Epidemiology

Coccidioidomycosis is caused by either of two soil-dwelling dimorphic fungi: *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in people with HIV have been reported in the areas in which the disease is highly endemic.[1] Cases also may be identified outside of these areas when a person gives a history of having traveled through an endemic region. In the United States, these areas include the lower San Joaquin Valley and other arid regions in southern California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.[2] Several cases of coccidioidomycosis in individuals who acquired the infection in eastern Washington state have been reported. One of these cases was phylogenetically linked to local *Coccidioides immitis* isolates.[2] These observations suggest that the coccidioidal endemic range may be expanding.

The risk of developing symptomatic coccidioidomycosis after infection is increased in patients with HIV who have CD4 T lymphocyte (CD4) counts <250 cells/mm^3, those who are not virologically suppressed, or those who have AIDS.[3] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[4,5]

Clinical Manifestations

Four common clinical syndromes of coccidioidomycosis have been described: focal pneumonia; diffuse pneumonia; extrathoracic involvement, including meningitis, osteoarticular infection, and other extrathoracic sites; and positive coccidioidal serology tests without evidence of localized infection.[6] In patients with HIV, lack of viral suppression and CD4 count <250 cells/mm^3 are associated with increased severity of the presentation of coccidioidomycosis.[7]

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. Focal pneumonia can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] However, coccidioidomycosis may present with hilar or with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile in meningitis demonstrates low glucose levels, elevated protein levels, and a lymphocytic pleocytosis. mediastinal adenopathy, upper lobe infiltrates, nodules, and peripheral blood eosinophilia—all of which are uncommon in bacterial pneumonia and should make one think of coccidioidomycosis, particularly in patients who reside in, previously resided in, or have travelled to a known endemic area.

Diffuse pneumonia and extrathoracic disease usually occur in more immunocompromised patients. Diffuse pulmonary disease presents with fever and dyspnea with a diffuse reticulonodular pattern on chest imaging, and in some instances may be difficult to distinguish clinically from *Pneumocystis* pneumonia.[9] Hypoxemia may be severe and serological tests are frequently negative at presentation.

Patients with meningitis present with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile in meningitis demonstrates low glucose levels, elevated protein levels, and a lymphocytic pleocytosis.

Elevated coccidioidal antibody titers even without symptoms can indicate risk of subsequent symptomatic disease in patients with advanced HIV. A study conducted prior to the advent of potent ART described 13 patients with HIV who had CD4 counts <350 cells/mm^3 and positive coccidioidal serologic tests without an anatomic site of infection. Five patients subsequently developed clinical illness when their median CD4 count fell to 10 cells/mm^3.[10]

Diagnosis

The diagnosis of coccidioidomycosis is based on serology, histology, culture, and clinical presentation. Culture of the organism from clinical specimens or by demonstration of spherules on histopathological examination of infected tissue confirms the diagnosis. Positive blood cultures are rare and usually found only in those with diffuse pulmonary disease. CSF cultures are positive in fewer than one-third of patients with coccidioidal meningitis.

Unlike other endemic fungi, *Coccidioides* spp. grow relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a non-pigmented mold may be observed in as few as 3 to 7 days and can be confirmed as *Coccidioides* by gene probe. *Coccidioides* growth on an agar plate is a significant laboratory biosafety hazard because of the risk of inhalation of dislodged arthroconidia. When a specimen is sent for culture, laboratory personnel should be alerted to the possibility that *Coccididoides* spp. may be present, and in the laboratory, the culture plate lid should be kept secured with tape.[11] Identification of the fungus should be performed only in a biosafety level 3 containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test and a compatible clinical syndrome. However, it may take several weeks for antibodies to develop, and negative serology cannot be used to rule out disease. Repeat testing every 1-2 weeks should be considered if the patient is ill and the diagnosis has not been established. Patients with past coccidioidal infection and without disease activity usually have negative serological tests. Screening with an enzyme immunoassay (EIA) for IgM and IgG antibody is recommended. It has a rapid turnaround time and is available in many clinical laboratories. These tests are very sensitive but occasionally have been associated with false positive results, particularly for IgM.[12] If either EIA test is positive, antibody assays by immunodiffusion (ID) and by complement fixation (CF) should be obtained to confirm the result and be used for further follow-up. A lateral flow assay (LFA) recently has become available but is far less sensitive than EIA.[13]

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[14] serum,[15] and other body fluids in samples from individuals with active coccidioidomycosis. The assay is most useful in diagnosing extrathoracic disseminated coccidioidomycosis. A recent study suggests that detection of coccidioidal antigen in CSF has a very high sensitivity and specificity for diagnosing coccidioidal meningitis.[16]

In addition, real-time polymerase chain reaction (RT-PCR) testing, if available, can be used on unfixed clinical specimens and on formalin-fixed tissue to aid in the diagnosis of coccidioidomycosis. A *Coccidioides* RT-PCR assay is commercially available but not Food and Drug Administration (FDA)-approved nor tested in patients with HIV.[17]

Preventing Exposure

Individuals with HIV living in or visiting areas in which *Coccidioides* spp. are endemic cannot avoid exposure to the fungus. They should, however, avoid extensive exposure to disturbed native soil, such as at building excavation sites, and they should stay inside during dust storms **(BIII).** No evidence indicates that gardening in cultivated soil in the coccidioidal endemic region increases the risk of acquiring coccidioidomycosis.

Preventing Disease

Preventing Coccidioidomycosis
Primary antifungal prophylaxis for individuals with negative serologic tests for *Coccididoides* is not recommended (AIII) except for the following indications: Indication for Primary Prophylaxis • New positive IgM and/or IgG test for *Coccidioides*; and • No sign of active coccidioidomycosis; and • CD4 count <250 cells/mm^3 Preferred Therapy • Fluconazole 400 mg PO once daily (AIII) Discontinuation of Primary Prophylaxis • CD4 count ≥250 cells/mm^3 with virologic suppression on ART (BIII) • Close clinical follow-up is recommended (BIII)

Key: CD4 = CD4 T lymphocyte cell; IgG = immunoglobulin G; IgM = immunoglobulin M; PO = orally

Primary antifungal prophylaxis (i.e., prophylaxis for individuals with negative results on serological tests for *Coccidioides*) does not appear to benefit patients with HIV with low CD4 counts who live in regions in which *Coccidioides* spp. are endemic,[4] and it **is not recommended (AIII).** Yearly or twice-yearly serological testing for coccidioidomycosis is reasonable for serologically negative individuals with HIV who live in endemic areas. Testing is advised also for individuals who have previously traveled to or lived in endemic areas. Both IgM and IgG antibody testing using either an EIA or immunodiffusion technique are recommended. In patients who have CD4 counts <250 cells/mm^3 and who previously tested negative for *Coccidioides*, a new positive serology test suggests possible active disease[10] and should prompt further clinical evaluation. If no signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis are identified, antifungal therapy with fluconazole 400 mg daily is recommended for those with a new positive serological test and CD4 counts <250 cells/mm^3 **(AIII).** This regimen should be continued until the CD4 count is ≥250 cells/mm^3 and virological suppression is documented **(BIII).** For those with CD4 counts already ≥250/mm^3 and with viral suppression on antiretrovirals, close clinical follow-up without antifungal therapy is recommended **(BIII).** For asymptomatic patients who have not lived in or travelled to endemic regions, routine testing does not appear useful and **should not be performed (AIII).**

Treating Disease

Treating Coccidioidomycosis

Treating Mild-to-Moderate Pulmonary Infections

Indications for Treatment

- Patients who have clinically mild infection, such as focal pneumonia;
- Patients with positive coccidioidal serologies but with mild or without clinical illness.

Preferred Therapy

- Fluconazole 400 mg PO once daily (AII), *or*
- Itraconazole 200 mg PO three times daily for 3 days then twice daily (AII)

Alternative Therapy (For Patients Who Failed to Respond to Fluconazole or Itraconazole)

- Voriconazole loading dose of 400 mg twice daily for the first day followed by 200 mg PO twice daily (BIII); or
- Posaconazole (extended-release tablet) 300 mg PO twice daily for the first day and then 300 mg daily (BIII)

Treating Severe Pulmonary or Extrapulmonary Infection (Except Meningitis)

Preferred Therapy

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII)
- Use until clinical improvement, then switch to triazole (BIII).

Alternative Therapy

- Some specialists recommend combining amphotericin B with a triazole (fluconazole or itraconazole 400mg daily) and continue the triazole once amphotericin B is stopped (CIII).

Treatment for Meningeal Infections (Consultation with a Specialist Is Advised)

Preferred Therapy

- Fluconazole 400–800 mg IV or PO once daily (AII)

Alternative Therapy

- Itraconazole 200 mg PO two to three-times daily (BII), *or*
- Voriconazole 200–400 mg PO twice daily (BIII), *or*
- Posaconazole (delayed-release tablet) 300 mg PO once daily after a loading dose (CIII), *or*
- Isavuconazole 372 mg every 8 hr for 6 doses, then 372 mg daily (CIII).
- Intrathecal amphotericin B (AIII) when triazole antifungals are not effective. Use in consultation with a specialist and ensure administration by a clinician experienced in this drug delivery technique.

Treatment in Pregnancy

- Azole antifungal agents are contraindicated and should be avoided in the first trimester of pregnancy because of potential teratogenic effect and risk of spontaneous abortion (AIII).
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII), *or*

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII)

Discontinuing Therapy

Focal Coccidioidal Pneumonia, Therapy Can Be Stopped If (AII)

- Clinically responded to 3 to 6 months of antifungal therapy, *and*
- CD4 count ≥250 cells/mm^3, *and*
- Virologic suppression on ARVs, *and*
- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis

- Relapse can occur in 25% to 33% of patients without HIV and can occur in patients with HIV who have CD4 count >250 cells/mm^3.
- Therapy duration is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts (BIII).

Coccidioidal Meningitis

- Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong (AII).

Other Considerations

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.
- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Adult and Adolescent Antiretroviral Guidelines DDI Tables list these interactions and recommend dosage adjustments where feasible.

Key: ARVs = antiretrovirals; CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; DDI = drug–drug interaction; IV = intravenous; PO = orally

Treatment of mild-to-moderate pulmonary coccidioidal infection: Therapy with a triazole antifungal agent given orally is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII).** Fluconazole should be given as 400 mg daily **(AII);** itraconazole should be given in divided doses of 200 mg three times daily for 3 days, followed by 200 mg twice daily **(AII)**.[18,19] Itraconazole is preferred for those who have bone or joint disease **(AI).**[20] Serum itraconazole concentrations should be measured after the drug reaches steady state at 2 weeks to ensure adequate absorption. Target serum concentration (the sum of the parent itraconazole and hydroxyl itraconazole metabolite levels) is at least >1mcg/mL and preferably >2mcg/mL.

Data to support clinical efficacy for treatment with posaconazole[21,22] and voriconazole are limited, but these agents are useful for patients who do not respond to fluconazole or itraconazole **(BIII).** Voriconazole is given as a loading dose of 400 mg twice daily on Day 1, followed thereafter by 200 mg twice daily. Trough serum voriconazole concentrations should be measured to ensure efficacy and avoid toxicity; a concentration of 1 to 5 mcg/mL is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used **(BIII),**[22] but the current extended-release tablet formulation of posaconazole at a dosage of 300 mg twice daily for the first day, then 300mg once daily is better tolerated by patients and provides more reliable serum concentrations. Recently, a

syndrome of mineralocorticoid excess manifesting as hypertension with hypokalemia was reported in some patients taking posaconazole.[23] Monitoring of blood pressure and serum potassium levels is appropriate in patients taking posaconazole.

No data have been published on the use of the antifungal isavuconazole for coccidioidomycosis in patients with HIV. Among nine patients with pulmonary disease without HIV, initial therapy with isavuconazole resulted in complete or partial treatment success in five patients (56%).[24]

All triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents and other anti-infective agents. Drug–drug interaction (DDI) tables in the Adult and Adolescent ARV Guidelines list such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Treatment of severe pulmonary coccidioidal infection or extrapulmonary infection: Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or who are severely ill with extrathoracic disseminated disease **(AII).**[19] Most experience has been with the deoxycholate formulation using a dose of amphotericin B of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are only anecdotal reports[25] from studies that used lipid formulations of amphotericin B for the treatment of coccidioidomycosis. Lipid formulations are likely to be as effective as the deoxycholate formulation and should be considered as equivalent alternative initial therapy, particularly in patients with underlying renal dysfunction **(AIII).** For lipid formulations, a daily dose of amphotericin B of 3 to 5 mg/kg is appropriate. Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII).**

Some specialists recommend combining amphotericin B with a triazole antifungal (400 mg of fluconazole or itraconazole daily) at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII).**[19]

Treatment of patients with coccidioidal meningitis: Treatment of coccidioidal meningitis requires consultation with a specialist **(AIII).** Intravenous amphotericin B alone is ineffective as treatment for coccidioidal meningitis. Treatment with a triazole antifungal is recommended. Fluconazole (400 to 800 mg daily) is the preferred regimen (AII),[18,26] but itraconazole 400 to 600 mg daily also has been successfully used (BII).[27] Therapy with voriconazole **(BIII),**[28-30] posaconazole **(CIII),**[22,31] and isavuconazole **(CIII)** has been described in individual cases and has been successful.[32] Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B is recommended **(AIII).** When required, intrathecal therapy should be administered by someone very experienced in this drug delivery technique.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Monitoring the CF antibody titer is useful to assess response to therapy, and this titer should be measured every 12 weeks. More than a twofold rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. Immune reconstitution inflammatory syndrome (IRIS) has been reported infrequently in patients with HIV and coccidioidomycosis.[33-35] In general, delaying initiation of ART while treating coccidioidomycosis **is not recommended (AIII).** Conversely, a recent case series[36] and a single case report[37] suggested that, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm^3) with disseminated disease, clinical

decline may occur with initiation of ART. These findings suggest that it might be prudent to delay ART for 4 to 6 weeks after initiating antifungal therapy in severely immunosuppressed patients who have disseminated or central nervous system disease **(BIII).** However, delay may not prevent IRIS, as reported in at least one patient with disseminated disease, who had received treatment with fluconazole for 28 days but who still had worsening symptoms within a week after starting ART.[38] Close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed people who have HIV and who have disseminated coccidioidomycosis.[13]

Managing Treatment Failure

Serum drug concentrations should be checked in patients with severe coccidioidomycosis who do not respond to treatment with itraconazole. In case of confirmed treatment failure with adequate serum concentrations of the azole, treatment should be changed to IV amphotericin B, either deoxycholate or a lipid formulation for patients who are severely ill (AIII). For those who are not severely ill, posaconazole (BIII) and voriconazole (BIII) are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir- or cobicistat-boosted regimens (see the DDI tables in the Adult and Adolescent Antiretroviral Guidelines). Posaconazole and isavuconazole have fewer known drug interactions with antiretrovirals than voriconazole. In certain situations, surgical intervention may be indicated.[18]

Therapy After Immune Reconstitution

Patients with peripheral blood CD4 count ≥250 cells/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[39] Moreover, a prospective study has demonstrated that coccidioidomycosis is less severe in those with lower HIV RNA and higher CD4 counts.[5] Given these facts, in patients with HIV who have undetectable HIV RNA on potent ART and who have CD4 count ≥250cells/mm^3, coccidioidomycosis should be managed no differently than it is in patients in the general population **(AII).**

For patients with focal pulmonary disease who meet the above criteria, treatment with a triazole antifungal agent should continue for a minimum of 3 to 6 months **(AII).** For patients with diffuse pulmonary disease and those with extrathoracic dissemination, antifungal therapy should continue for at least 12 months and usually much longer. Therapy should be discontinued based on clinical and immunological response and in consultation with an expert. For patients with detectable HIV viremia or CD4 count <250/mm^3, antifungal therapy at full dose should continue **(BIII).**

Preventing Relapse

Relapse of coccidioidomycosis occurs in 25% to 33% of individuals without HIV who have diffuse pulmonary coccidioidomycosis or nonmeningeal disseminated coccidioidomycosis[40,41] and may occur in people with HIV who have CD4 counts ≥250 cells/mm^3 and are virologically suppressed on antiretrovirals.[1,36] During and after coccidioidomycosis therapy, patients should have serial chest radiographs and coccidioidal serology tests every 3 to 6 months. Relapses have been reported in ≥80% of patients with meningitis in whom triazoles have been discontinued.[42] Therefore, therapy for coccidioidal meningitis should be continued for life **(AII).**

Special Considerations During Pregnancy

Women are generally at lower risk than men for severe coccidioidomycosis, and disease does not appear to reactivate or worsen in women with prior coccidioidomycosis during pregnancy. However, when coccidioidomycosis is acquired during the second or third trimester of pregnancy, the infection is more likely to be severe and disseminated.[43]

Congenital malformations, including craniofacial and limb abnormalities, similar to those observed in animals exposed to fluconazole, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[44]

A recent systematic review and meta-analysis of cohort or case control studies (n = 6 studies) that analyzed more than 16,000 exposures and reported fetal outcomes after exposure to fluconazole used in the first trimester of pregnancy, found a marginal association with increased risk of congenital malformations (odds ratio 1.09; 95% CI, 0.99–1.2, *P* = 0.088), including heart defects, as well as spontaneous abortion; exposure to more than 150 mg was associated with an overall increase in congenital malformations. One registry-based cohort study (included in the systematic review)[5,37] and a more recent large population-based case-control study[45] specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

A nationwide cohort study in Denmark reported that the risk of spontaneous abortion was greater in women exposed to oral fluconazole in pregnancy than in women who had not been exposed or those with topical azole exposure only.[46] A cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use in pregnancy and risk of stillbirth or neonatal death.[47] Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short-term exposure. Responding to the reported birth defects, the FDA has changed the pregnancy category for fluconazole from C to D for any use other than a single 150 mg dose of fluconazole to treat vaginal candidiasis.[48] Although cases of birth defects in infants exposed to itraconazole have been reported, prospective cohort studies of >300 women with first trimester exposure did not show an increased risk of malformation.[49,50] However, in general, all azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII).** One problematic area is coccidioidal meningitis, for which the only alternative treatment to triazole antifungals is IV or intrathecal amphotericin B. In such situations, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the mother, the infectious diseases consultant, and the obstetrician.[43] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies; for voriconazole, these occurred at doses lower than recommended for humans; however, adequately controlled studies in humans have not been conducted. Therefore, use of voriconazole and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII).**

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII).** Extensive clinical use of amphotericin B has not been associated with teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. One study suggested that the treatment regimen for women who develop coccidioidomycosis in the second or third trimester can be similar to that for nonpregnant women with coccidioidomycosis **(CIII).**[18]

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