

Coccidioidomycosis

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Panel's Recommendations
<ul style="list-style-type: none"> • Routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended (BIII). • Amphotericin B is recommended as initial therapy for the treatment of diffuse pulmonary or disseminated coccidioidomycosis (in the absence of central nervous system involvement) (AII*). • There is no evidence that lipid preparations of amphotericin B are more effective than amphotericin B deoxycholate for the treatment of coccidioidomycosis in children. Lipid preparations are often preferred because they are better tolerated and associated with less nephrotoxicity than amphotericin B deoxycholate (AII*). • A triazole agent such as fluconazole or itraconazole should be used as consolidation therapy at the completion of amphotericin B therapy (BIII). Alternatively, some experts initiate therapy with amphotericin B combined with a triazole, such as fluconazole, in patients with disseminated disease and continue the triazole after amphotericin B is stopped (BIII). • For patients with mild disease (e.g., focal pneumonia), initial therapy with fluconazole or itraconazole is appropriate (AII*). • Itraconazole is preferred for treatment of skeletal infections (AII*). • Voriconazole (as a single agent or in combination with caspofungin), posaconazole, isavuconazole, and amphotericin B have been used as salvage therapy in patients with refractory disease (AII*). • Because absorption varies from patient to patient, serum itraconazole, voriconazole, and posaconazole levels should be measured to ensure effective and nontoxic concentrations, monitor drug levels following changes in dosage, and assess compliance (BIII). • Fluconazole is the preferred agent for treating coccidioidal meningitis (AII*). Intravenous amphotericin B preparations are not preferred for treating coccidioidal meningitis (AII*). Intrathecal, intracisternal, or intraventricular amphotericin B deoxycholate has been used to treat people with refractory disease (AIII). • Lifelong antifungal suppression (secondary prophylaxis) with either fluconazole or itraconazole is recommended for children with HIV after disseminated, diffuse pulmonary, and/or meningeal coccidioidomycosis, even if immune reconstitution is achieved with antiretroviral therapy (AII*). • Lifelong secondary prophylaxis should be considered for children with mild disease and CD4 T lymphocyte (CD4) cell count <250 cells/mm³ or CD4 percentage <15% (BIII). Despite immune reconstitution, relapse of coccidioidomycosis may occur in children with HIV who initiated secondary prophylaxis due to mild disease and immunosuppression. Therefore, lifelong azole prophylaxis should be considered (BIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</p> <p>[†]Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents.</p>

Introduction

Coccidioidomycosis is an endemic mycosis of considerable clinical significance in the Western Hemisphere, including among adults with HIV. Disease syndromes are well-described in adults and immunocompetent children. Because coccidioidomycosis in children with HIV has been significantly less common than in adults, data are limited on specific clinical manifestations and treatment and preventive strategies in this patient population. Therefore, many of our guidelines are based on experience and case reports in adults and limited cases in children without HIV.

Epidemiology

Coccidioidomycosis is caused by the endemic, soil-dwelling dimorphic fungus, *Coccidioides*. Two genetically distinct species, *Coccidioides posadasii* and *C. immitis*, have been identified using molecular and biogeographic characteristics. *C. posadasii* is widely distributed throughout the southwestern United States, northern Mexico, and Central and South America. *C. immitis* is confined mainly to the western United States, with most cases reported in California, Arizona, Utah, and Washington State.¹⁻³ Clinical illness caused by each species is indistinguishable. Infection usually results from inhalation of spores (arthroconidia) produced by the mycelial form, which grows most readily in arid, windy environments, especially when hot summers are preceded by rainy seasons.⁴ Due to projected changes in temperature and precipitation secondary to climate changes, the areas of endemicity are estimated to expand north and farther east and along the Pacific coast.^{5,6} Rates of coccidioidomycosis disease have increased significantly in California in recent years, likely associated with climate change. Disease in non-endemic regions is usually the result of reactivation of a previous infection or from infection acquired during travel to an endemic region.^{7,8} Contaminated fomites such as dusty clothing or agricultural products have been implicated as rare sources of infection.^{9,10}

Most cases of coccidioidomycosis are caused by primary infection. Incidence is influenced by both conducive environmental conditions and activities that predispose people to the inhalation of spores. Increased infection rates have been attributed to population shifts to endemic regions, climatic conditions, construction,¹¹ dust storms, and better recognition of disease manifestations.^{5,12} Surveillance in California revealed an increase in pediatric coccidioidomycosis (also known as San Joaquin Valley Fever) cases from 2000 to 2016, with a higher incidence among those aged 12 to 17 years.¹³ A review of coccidioidomycosis hospitalizations at children's hospitals in the United States from 2002 to 2007 found that most hospitalizations (96%) occurred in endemic areas, with 6% identified as having a primary or acquired immunodeficiency. During the study period, an increased incidence occurred from 2005 to 2006, especially among children with comorbid conditions. A case series of pediatric coccidioidomycosis in an infectious disease clinic in California highlighted delays in diagnosis, even in endemic regions.¹⁴ A median delay of 57 days from symptoms onset to diagnosis was observed in children with disseminated disease, and 16 days in children with acute/pulmonary disease. Before diagnosis, most children received antibiotics for suspected bacterial infections.

Since 2000, cases of coccidioidomycosis have increased in the southwestern United States. California had observed a fivefold increase in cases.¹⁵ Between 2000 and 2012, pediatric cases and hospitalization rates per 100,000 population increased approximately sixfold, with cases rates from 0.7 to 3.9, and hospitalizations from 0.2 to 1.2. Hispanic and African American children were at the highest risk of hospitalization. Approximately 11% of hospitalized children had an

immunocompromising condition. Only 0.2% of children had HIV. Of the 11 reported deaths, only one had an associated immunodeficiency.

Coccidioidal infection resolves once specific T cells mediate macrophage activation that inhibits or kills the fungus. In immunocompetent hosts, infections by *Coccidioides* spp. convey lifelong immunity with no reports of infection.¹⁶ Impaired cellular immunity is the major risk factor for severe primary coccidioidomycosis and relapse of past infection. T lymphocyte-mediated immunity may be impaired by the presence of a primary or acquired immunodeficiency, such as a congenital defect, HIV infection,¹⁷⁻²¹ or by treatment with immunosuppressive medications including corticosteroids^{22,23} and tumor necrosis factor- α inhibitors.^{24,25} Defects in the interferon-gamma/interleukin-12 pathway place children at risk for severe infections.^{26,27} Person-to-person transmission has not been recognized; however, donor-derived coccidioidomycosis through organ donation has been documented.²⁸ In adults with HIV, localized pneumonia and disseminated infection¹⁸ most often occur in individuals with CD4 T lymphocyte (CD4) cell counts <250 cells/mm³. The threshold for increased risk in children with HIV is not well defined, but systemic fungal infections have occurred in children with significant cellular impairment when CD4 counts were ≤ 100 cells/mm³ and CD4 percentages $<15\%$.^{29,30} Few cases of coccidioidomycosis have been reported in immunocompromised children. Not uncommonly, rare types of immunodeficiencies are diagnosed in children, adolescents, and adults with invasive or refractory coccidioidomycosis.³¹⁻³³ No cases of coccidioidomycosis were reported in children enrolled in the Perinatal AIDS Collaborative Transmission Study, but study sites were underrepresented in geographic regions where coccidioidomycosis is endemic.³⁴ Congenital coccidioidomycosis is rare, but infections have occurred following disseminated disease in mothers.³⁵ Infections in infants usually result from inhalation of spores in the environment.³⁶ In adults with HIV, antiretroviral therapy (ART) appears to be responsible for the declining incidence and severity of coccidioidomycosis; however, data are limited in children.^{19,20}

Clinical Manifestations

The symptoms of coccidioidal infection can range from a mild, flu-like illness to more severe focal or disseminated disease, including pneumonia, bone and joint infection, and meningitis. Sixty percent of infected children are asymptomatic. Immunocompromised individuals and previously healthy Black, Hispanic, Native American, and Filipino people with coccidioidomycosis are at increased risk of dissemination, as are pregnant women who become infected during the second or third trimester or the immediate postpartum period.³⁷ The severity of disease in adults with HIV is proportional to the degree of immunosuppression. Severe forms of disease such as diffuse pulmonary infection and extrathoracic dissemination have been associated with low CD4 counts, increased HIV viral load, and a lower likelihood of having received ART. Focal pneumonitis can occur in mild to moderately immunocompromised patients. Pleural inflammation may result in effusion, empyema, and/or pneumothorax. If untreated, a coccidioidal antibody-seropositive HIV individual is at risk of serious disease, with the degree of severity inversely proportional to absolute CD4 count.¹² Bone and joint involvement are rare in people with HIV. Diffuse reticulonodular disease in an immunocompromised child with coccidioidomycosis may radiographically resemble *Pneumocystis jirovecii* pneumonia.³⁸ In addition, people with coccidioidomycosis may also have coinfections such as blastomycosis, toxoplasmosis, and COVID-19.³⁹⁻⁴³ Valley Fever can mimic pulmonary and extrapulmonary tuberculosis (TB); coinfection can also occur in endemic areas.⁴⁴

In a retrospective, observational study of 33 children with coccidioidomycosis (median age, 6 years) at a children's hospital in central California, 28 (85%) had pneumonia, 5 (15%) had osteomyelitis,

and 2 (6%) had meningitis/cerebritis.⁴⁵ Mediastinitis was common in younger children, and none of the children were immunocompromised. In another report from California, among 64 children, those with disseminated disease (n = 27) were more likely to be hospitalized. More than one-third had central nervous system (CNS) involvement. Eleven children were immunocompromised and one had HIV; however, HIV was not identified in previously healthy children.⁴⁶ A retrospective study from a tertiary care center in an endemic region of central California described 78 children with extrapulmonary manifestations of coccidioidomycosis.⁴⁷ Of those, 65% were Hispanic, 85% were without comorbid conditions, and 6% were immunocompromised. Along with pulmonary disease, bone and joints, mediastinum, CNS, cervical lymph nodes, larynx, and skin were most affected.

Children with primary pulmonary infection may present with fever, malaise, chest pain, and intermittent cough, with rare cases of hemoptysis possible. Coccidioidomycosis is commonly mistaken for bacterial pneumonia. Like with other endemic mycoses, the presence of erythema nodosum may be a key clinical finding for coccidioidomycosis in an endemic region.⁴⁸⁻⁵⁰ Persistent fever may be a sign of extrathoracic dissemination. Musculoskeletal coccidioidomycosis has been well-described in children.⁵¹ Common symptoms include limb swelling as well as bone and joint pain. Of children with musculoskeletal coccidioidomycosis, 29% had involvement of multiple bones, most commonly involving the craniofacial and metacarpal/metatarsal bones.⁵¹ Children with meningitis may present with headaches, altered sensorium, vomiting, and/or focal neurologic deficits. Fever is sometimes absent, and meningismus occurs in only 50% of patients. Hydrocephalus complicating basilar inflammation, occurs in most (83% to 100%) children with coccidioidal meningitis.⁵²⁻⁵⁴ Generalized lymphadenopathy, skin nodules, plaques or ulcers,⁵⁵ peritonitis,⁵⁶ and liver abnormalities may also accompany disseminated disease.

Diagnosis

Because signs and symptoms are nonspecific, the diagnosis of coccidioidomycosis should be considered in patients who reside in or have visited endemic areas.⁵⁷ The evolving changes in the geographic distribution of coccidioidomycosis may warrant a high degree of suspicion in people with compatible disease syndromes, especially those with community-acquired pneumonia living in areas with newly described cases.^{5,6} Diagnostic algorithms have been developed to assist clinicians in the diagnosis of endemic mycoses, including coccidioidomycosis.⁵⁸ In patients with suspected pulmonary coccidioidomycosis, initial diagnostic testing starts with serologic assays such as enzyme immunoassays, immunodiffusion, and complement fixation. Culture, microscopy, and serology have been the standard methods used for diagnosis, but tests such as coccidioidal galactomannan antigen detection in urine can be useful for diagnosis in immunocompromised hosts.⁵⁹ Nucleic acid amplification tests (NATs) have been developed, and several are commercially available.⁷ NATs and DNA probes have been used to detect *Coccidioides* spp. in tissue and soil samples.⁶⁰⁻⁶²

In patients with meningitis, cerebrospinal fluid (CSF) analysis shows moderate hypoglycorrhachia, elevated protein concentration, and pleocytosis with a predominance of mononuclear cells. CSF eosinophilia may also be present. The observation of distinctive spherules containing endospores in histopathologic tissue or other clinical specimens is diagnostic.⁶³ Stains of CSF in patients with meningitis usually are negative. Pyogranulomatous inflammation with endosporulating spherules is seen in affected tissue specimens stained with hematoxylin and eosin. Spherules can also be observed using Papanicolaou, Gomori methenamine silver nitrate, and periodic acid-Schiff stains. Cytologic stains are less reliable for diagnosing pulmonary coccidioidomycosis, and a negative cytologic stain on a clinical respiratory specimen may not exclude active pulmonary coccidioidomycosis.⁶⁴ Potassium hydroxide stains are less sensitive and should not be used.⁶⁴

Growth of *Coccidioides* spp. is supported by many conventional laboratory media used for fungal isolation and may occur within 5 days at 30°C to 37°C. Blood cultures are positive in <15% of cases.⁶⁵ CSF cultures are positive in <50% of children with meningitis.⁶⁶ In a recent study of CNS coccidioidomycosis, 4 of 30 children (13%) had a positive CSF culture, significantly lower than prior reports.⁵² Cultures of respiratory specimens are often positive in adults with pulmonary disease. The laboratory should be alerted to the clinical suspicion of coccidioidal infection to minimize hazards to laboratory personnel.

Serologic assays performed by enzyme-linked immunoassay (EIA), immunodiffusion, or classical tube precipitin or complement fixation (CF) methodology that measure coccidioidal immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are valuable diagnostic aids but may be falsely negative in immunocompromised hosts.⁶⁷ Presence of IgM-specific coccidioidal antibody suggests active or recent infection, although in instances in which IgG-specific antibody is absent, data are conflicting about potential false positives.^{68,69} IgG-specific antibodies appear later and persist for 6 to 8 months. A commercial EIA appears to be more sensitive than the older tube precipitin and CF tests and the immunodiffusion assays, although concern remains about specificity.⁶² CF appears to be a more specific assay. Assays for coccidioidal antibodies in serum or body fluids such as CSF provide diagnostic and prognostic information. Cross-reactivity can occur with other endemic mycoses such as blastomycosis and histoplasmosis. Patients with coccidioidomycosis have been observed to have positive *Histoplasma* antigen results.⁷⁰ A study of 19 patients from three clinical practices in Arizona and California with acute or chronic coccidioidomycosis found 11 patients (58%) with a positive *Histoplasma* urine antigen assay.⁷⁰ In patients with acute disease, antigenuria was detected in 79% of patients. Based on these data, this assay may offer an indirect method for diagnosis. A recently developed rapid lateral flow assay is now available, but its sensitivity appears to be lower than EIA.⁷¹ IgG-specific antibody titers often become undetectable in several months if the infection resolves. The diagnosis of meningitis is established with either a positive CSF culture, detection of IgG-specific antibodies in CSF, or positive antigen.⁶¹ Among 36 patients with coccidioidal meningitis, antigen testing of CSF demonstrated a sensitivity of 93% and specificity of 100%, while CSF cultures were positive for antigens in 7% of patients. Additionally, antibodies were identified by immunodiffusion in 67% of patients, complement fixation in 70%, and enzyme-linked immunosorbent assay–detected IgM and IgG antibodies in 8% and 85% of patients, respectively.⁷²

An elevated opening pressure is often observed in patients with meningitis. Immunocompromised hosts may not have a reliable serologic response.

A *Coccidioides* EIA has been developed that detects and quantifies coccidioidal galactomannan concentrations in urine samples and is especially useful in serious infections and/or instances in which the antibody is undetectable.⁵⁹ Dissociation of immune complexes has increased the sensitivity of coccidioidal antigen detection in serum.⁷³ The serologic diagnosis of coccidioidomycosis might also be complicated in the presence of very high antibody levels, inducing false negative results due to a prozone phenomenon.^{74,75} This occurs in assays that involve antibody–antigen binding when antibody levels are overwhelming. This effect occurs more frequently in patients with HIV and other immunodeficiencies, as well as during pregnancy.⁷⁶ Although the prozone phenomenon is most commonly associated with syphilis, it is also observed in coccidioidomycosis-endemic regions and co-occurring with various other infections. The prozone phenomenon can be overcome by testing serial serum dilutions.⁷⁷ Molecular methods of detection are commercially available at reference laboratories and may be a valuable means of confirming a diagnosis.⁷⁸ For example, meningitis has been diagnosed using real-time polymerase chain reaction (PCR) analysis of CSF.⁶¹

Prevention

Preventing Exposure

Patients with HIV who reside in or visit regions in which *Coccidioides* spp. are endemic cannot completely avoid infection, but the risk can be reduced by avoiding activities that may increase exposure to inhalation of spores. These activities include disturbing contaminated soil, including sports in dusty terrain, archaeological excavation, construction, and being outdoors during dust storms **(BIII)**.^{11,79,80} If such activities are unavoidable, use of high-efficiency respiratory filtration devices should be considered.

Preventing First Episode of Disease

No prospective studies have been published that examine the role of prophylaxis in preventing the development of active coccidioidomycosis in patients without previous (recognized) episodes of coccidioidomycosis. Some, but not all experts would provide prophylaxis with an azole (fluconazole) to coccidioidal antibody–positive patients with HIV living in regions with endemic coccidioidomycosis.⁶⁴ In a retrospective analysis of liver transplant patients residing in an endemic area, antifungal prophylaxis with fluconazole prevented coccidioidomycosis.⁸¹ Chemoprophylaxis has been used for coccidioidal antibody–positive adults with HIV and CD4 counts <250 cells/mm³ and who live in endemic areas.^{19,30} However, given the low incidence of coccidioidomycosis in children with HIV, the potential for drug interactions, cost, and development of antifungal drug resistance, the routine use of antifungal medications for primary prophylaxis of coccidioidomycosis in children with HIV is not recommended **(BIII)**.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment

Treating Disease

Treatment protocols that are recommended for children with HIV with coccidioidomycosis are based on experience in studies in adults. Physicians who infrequently treat children with coccidioidomycosis should consider consulting with experts. Children with HIV who are not receiving ART at the time of diagnosis of coccidioidomycosis should receive ART along with antifungal therapy.

For years, antifungal therapy was recommended for all adults with HIV with clinically active, mild coccidioidomycosis.⁸² More recently, treatment protocols used for patients without HIV have been suggested for adults with HIV⁸² who are reliably receiving potent ART and who have CD4 counts >250 cells/mm³. This applies to patients with mild infections that are not accompanied by signs suggestive of dissemination, diffuse pulmonary infiltrates, or meningitis; patients should be closely monitored to ensure ART adherence, effective HIV suppression, and maintenance of CD4 counts >250 cells/mm³. Management should also include education directed at reducing the probability of re-exposure to coccidioidal spores. Given that comparable published experience in this setting is lacking in children, expert consultation should be sought; if treatment is elected, recommendations should be based on the assurance of continued adherence to ART, confirmation of

continued HIV suppression, maintenance of CD4 counts >250 cells/mm³, education directed at decreasing the likelihood of exposure to coccidioidal spores, and close medical follow up.

For patients with mild, non-meningitic disease (e.g., focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate given their effectiveness, safety, convenient oral dosing, and pharmacodynamic parameters (**AII***). Fluconazole (6–12 mg/kg/day, maximum dose 400 mg) and itraconazole (5–10 mg/kg/dose twice daily for the first 3 days, followed thereafter by 2–5 mg/kg/dose twice daily, maximum dosing, 200 mg every 12 hours) are preferred to amphotericin B for children who have mild, non-meningitic disease (**BIII**). In a randomized, double-blind trial in adults, fluconazole and itraconazole were equivalent for non-meningeal coccidioidomycosis. Itraconazole (5 mg/kg body weight dose twice daily) appeared to be more effective than fluconazole for skeletal infections (**AII***).⁸³ Two children with osteoarticular coccidioidomycosis who failed to respond to fluconazole monotherapy had an excellent response to itraconazole.⁸⁴ Due to increased efficacy, itraconazole is recommended for skeletal infections (**AII***). In a 2022 study in which 83% of children received fluconazole, only 15% failed this therapy and required an alternative regimen.⁵¹ Fluconazole is frequently used as an initial agent because it does not require therapeutic drug monitoring, it is better tolerated than itraconazole suspension, and is more likely to be covered by insurance than itraconazole suspension (**AIII**). In addition, fluconazole has fewer drug–drug interactions than itraconazole.

Severely ill patients with diffuse pneumonia and/or other signs of disseminated infection (not involving the CNS) should initially be treated with an amphotericin B preparation because these agents appear to evoke a faster therapeutic response than azoles (**AII***).⁸² Although there is no evidence that lipid preparations are more effective than amphotericin B deoxycholate, lipid formulations often are used because they are better tolerated (**AII***). The length of amphotericin B therapy is determined by both the severity of initial symptoms and the pace of clinical improvement. Thereafter, amphotericin B is stopped, and treatment with fluconazole or itraconazole is initiated (**BIII**). Some experts initiate therapy with both amphotericin B and triazole (e.g., fluconazole) in patients with severe disseminated disease and continue the triazole after amphotericin B is stopped (**BIII**). The duration of therapy should be ≥1 year.^{64,82} Lifelong maintenance therapy is recommended for immunocompromised people.

Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease and is continued lifelong for meningeal disease (**BIII**).

Itraconazole solution is preferred to the capsule formulation because it is better absorbed and can achieve serum concentrations 30% higher than those achieved with the capsules. Serum concentrations of itraconazole should be monitored and achieve a level ≥1 mcg/mL at steady state. Levels exceeding 10 mcg/mL should be followed by dose reduction (**AIII**).⁸⁵ Absorption of itraconazole solution is improved when taken with an empty stomach, while the capsule should be taken with food and acidic beverages.

A newer formulation of itraconazole called SUBA-itraconazole has been used to treat endemic mycoses. Experience in adults demonstrates similar efficacy but with less pharmacologic variability and fewer adverse events than “conventional” itraconazole.⁸⁶ Data in children are limited.⁸⁷

Meningitis is a life-threatening manifestation of coccidioidomycosis, and consultation with experts should be considered (**BIII**). Successful treatment requires an antifungal agent that achieves effective

concentrations in CSF. Intravenous amphotericin B achieves poor CSF concentrations and is therefore not recommended for treating coccidioidal meningitis **(AIII)**. The relative safety and comparatively superior ability of fluconazole to penetrate the blood–brain barrier have made it the treatment of choice for coccidioidal meningitis **(AII*)**. An effective dose of fluconazole in adults is 400 mg/day, but some experts begin therapy with 800 to 1,200 mg/day.⁸² Children usually receive 12 mg/kg/dose once daily (800 mg/day maximum) **(AII)**. The 12 mg/kg dose may be required to attain serum concentrations equivalent to those in adults receiving 400 mg/day.^{88,89} Some experts would begin at a dose of 15 to 23 mg/kg/day.⁶⁶ Successful therapy with posaconazole⁹⁰⁻⁹² and voriconazole⁹³⁻⁹⁵ has been described in adults, but there is limited experience in children. Some experts have used intrathecal amphotericin B deoxycholate in addition to systemic azole therapy.⁹⁶ Intrathecal amphotericin B administration adds additional morbidity and is not used as part of initial therapy **(CIII)**.⁸² Despite the benefits afforded by the azoles for treating meningitis, a retrospective analysis of outcomes in adults treated for coccidioidal meningitis in the pre-azole era (earlier than 1980) compared with outcomes in the azole era found that a similar percentage developed serious complications, including stroke and hydrocephalus. Risk factors for acquiring coccidioidal meningitis in the azole era included an immunocompromised state, with one-third of patients in this group having HIV or AIDS.⁹⁷

Monitoring and Adverse Events

In addition to monitoring patients for clinical improvement, some experts have recommended monitoring coccidioidal IgG antibody titers once monthly to assess response to therapy **(AIII)**. If therapy is succeeding, titers should decrease progressively. A rise in titer suggests recurrence of clinical disease. However, if serologic tests initially were negative, titers during effective therapy, may initially increase briefly and thereafter decrease. This lag in response during the first 2 months of therapy should not necessarily be construed as treatment failure.

Adverse effects of amphotericin B are primarily those associated with nephrotoxicity (including hypokalemia). Infusion-related fevers, chills, as well as nausea and vomiting also can occur, although they are less frequent in children than in adults. Lipid formulations of amphotericin B have lower rates of nephrotoxicity. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) can also occur but are very rare in children. Intrathecal injection of amphotericin B may result in arachnoiditis.^{98,99}

Triazoles can interact with other drugs metabolized by cytochrome P450-dependent hepatic enzymes, and the potential for drug interactions should be assessed before initiation of therapy **(AIII)**.⁸⁵ Use of fluconazole and itraconazole appears to be safe in combination with ART. Voriconazole should be avoided in patients receiving protease inhibitors **(BIII)** or non-nucleoside reverse transcriptase inhibitors.¹⁰⁰ The most frequent adverse effects of fluconazole are nausea and vomiting followed by skin rash and pruritus, and some cases of Stevens-Johnson syndrome have been reported. Chronic paronychia associated with fluconazole may be associated with long-term use in children with coccidioidomycosis.¹⁰¹ Resolution was observed after cessation of therapy. Asymptomatic increases in transaminases occur in 1% to 3% of patients receiving azole drugs. In patients with HIV, fluconazole at high doses can cause adrenal insufficiency. Because absorption of itraconazole varies from patient to patient, measure serum concentrations to ensure effective and nontoxic drug levels, monitor changes in dosage, and assess compliance **(BIII)**.⁸⁵

Itraconazole solution is preferred to the capsule formulation because it is better absorbed and can achieve serum concentrations 30% higher than those achieved with capsules. Serum concentrations

of itraconazole should be monitored and achieve a level ≥ 1 $\mu\text{g/mL}$ at steady state. Levels exceeding 10 $\mu\text{g/mL}$ should be followed by dose reduction **(AIII)**.⁸⁵ Absorption of itraconazole solution is improved when taken on an empty stomach, whereas the capsule should be taken with food and acidic beverages.

Coccidioidomycosis-associated immune reconstitution inflammatory syndrome (IRIS) following the initiation of ART has not been reported in children and is rarely reported in adults.¹⁰²⁻¹⁰⁴

Managing Treatment Failure

The treatment of coccidioidomycosis unresponsive to standard therapy has been reviewed, with the majority of experience occurring in adults. Often patients with invasive, refractory disease may not respond to fluconazole and itraconazole treatment and may harbor resistant strains. In these situations, treatment with other azoles such as posaconazole, voriconazole, or isavuconazole may be warranted **(AII*)**.⁸² Posaconazole was effective in 6 adults with disease refractory to treatment with other azole, and amphotericin B and was used successfully in 11 of 15 adults (73%) whose infections were refractory to previous therapy. Posaconazole has also been effective for chronic refractory meningitis unresponsive to fluconazole.⁹⁰⁻⁹² Voriconazole was effective in treating coccidioid meningitis and non-meningeal disseminated disease in adults who did not respond to fluconazole or were intolerant of amphotericin B.⁹³⁻⁹⁵ Isavuconazole has been used as salvage therapy in coccidioid meningitis.¹⁰⁵ Monotherapy with caspofungin was successful in treating disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and other adults in whom conventional therapy failed. Others have used caspofungin in combination with fluconazole and voriconazole, though some experts would not recommend echinocandins, including caspofungin. Voriconazole has been used in combination with caspofungin to treat refractory coccidioidomycosis after failing conventional therapies.¹⁰⁶ However, echinocandins have limited activity against *Coccidioides* spp. The use of these agents is not recommended by fungal experts as frontline therapy. Azoles remain the preferred agents for salvage therapy **(AII*)**.¹⁰⁷

Adjunctive interferon-gamma (IFN- γ) has been successful in treating people with refractory coccidioidomycosis who failed other therapies.^{108,109} A work-up for underlying immunodeficiencies is generally recommended in children who were previously healthy and who develop invasive, severe coccidioidomycosis disease. Recent studies have investigated the use of monoclonal antibodies in children with disseminated coccidioidomycosis with impaired cytokine receptor signaling, with protocols developed for the use of dupilumab—a monoclonal antibody that blocks the alpha chain common to the interleukin-4 and interleukin-13 receptors—and interferon-gamma treatment as adjunctive therapy to antifungals.³³ Interferon- γ in combination with dupilumab has been successful in treating disseminated coccidioidomycosis in a previously healthy child.³³ However, no controlled clinical studies or data exist for children; thus IFN- γ is not recommended for use in children with HIV **(BIII)**.

In instances in which patients with coccidioid meningitis fail to respond to treatment with azoles, both systemic amphotericin B and direct instillation of amphotericin B deoxycholate into the intrathecal, ventricular, or intracisternal spaces, with or without concomitant azole treatment, have been used successfully **(AIII)**. Liposomal amphotericin B has been used to treat relapsed coccidioid meningitis.¹¹⁰ A consensus panel of experts recommended a trial of liposomal amphotericin B based on case reports with documented efficacy, but amphotericin B deoxycholate was not recommended **(AIII)**.¹¹¹ When patients receiving liposomal amphotericin B are being transitioned to an azole agent, many experts discontinue the amphotericin B formulation only once

azole serum levels have reached steady state and are therapeutic. The basilar inflammation that characteristically accompanies coccidioidal meningitis often results in obstructive hydrocephalus requiring the placement of a CSF shunt. Thus, development of hydrocephalus in coccidioidal meningitis does not necessarily indicate treatment failure. Response rates with the azoles can be excellent, but cures are infrequent. Relapse after cessation of therapy is common, occurring in as many as 80% of patients.¹¹² Thus, indefinite continuation of fluconazole therapy is recommended for patients who have coccidioidal meningitis **(AII)**.

Preventing Recurrence

Lifelong suppression (secondary prophylaxis) is recommended for patients following successful treatment of meningitis. Relapse after successful treatment of disseminated disease can occur, and lifelong antifungal suppression with either fluconazole or itraconazole should be used **(AII*)**. Secondary prophylaxis should be considered for children with mild disease and CD4 counts $<250/\text{mm}^3$ or CD4 percentages $<15\%$ **(BIII)**.⁸²

Discontinuing Secondary Prophylaxis

In disseminated infection, continuing suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is recommended after completion of initial therapy. Patients with diffuse pulmonary disease, disseminated disease, or meningeal infection should remain on lifelong prophylaxis, even if immune reconstitution is achieved with ART, because of the high risk of relapse **(AII*)**. In adults with HIV and focal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 counts $>250/\text{mm}^3$ on ART, some experts would discontinue secondary prophylaxis after 12 months of antifungal therapy with careful monitoring for recurrence with chest radiographs and coccidioidal serology. The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children has not been studied. Therefore, in children with HIV, once secondary prophylaxis is initiated for an acute episode of milder, non-meningeal coccidioidomycosis, lifelong suppressive therapy should be considered, regardless of ART and immune reconstitution **(BIII)**.

Dosing Recommendations for Prevention and Treatment of Coccidioidomycosis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	N/A	N/A	Primary prophylaxis not routinely indicated in children.
Secondary Prophylaxis	<ul style="list-style-type: none"> Fluconazole 6 mg/kg body weight (maximum 400 mg) per dose IV or PO once daily, <i>or</i> For Coccidioidal Meningitis: <ul style="list-style-type: none"> Continue initial treatment with fluconazole (12 mg/kg body weight per dose IV or PO once daily) 	Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily	<p>Secondary Prophylaxis Indicated</p> <ul style="list-style-type: none"> Prior meningitis or disseminated disease Milder disease if CD4 count <250 cells/mm³ or CD4 percentage <15%. <p>Criteria for Discontinuing Secondary Prophylaxis</p> <ul style="list-style-type: none"> Lifelong therapy for meningitis or disseminated disease Consider lifelong therapy for milder disease, regardless of ART or immune reconstitution
Treatment	<p>Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease</p> <ul style="list-style-type: none"> Liposomal amphotericin B preparation at a dose of 5 mg/kg body weight IV once daily (dose can be increased to as much as 10 mg/kg body weight IV once daily for life-threatening infections) Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily, until clinical improvement Liposomal amphotericin B is the treatment of choice with similar efficacy with fewer adverse events. After the patient is stabilized, therapy with an azole (fluconazole or itraconazole) can be substituted and continued to complete a 1-year 	<p>Severe Illness With Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease</p> <p><i>If unable to use amphotericin B:</i></p> <ul style="list-style-type: none"> Fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or by mouth once daily. Treatment is continued for a total of 1 year, followed by secondary prophylaxis. 	<p>Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful.</p> <p>Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent.</p> <p>Some experts initiate an azole during amphotericin B therapy. Others defer initiation of the azole until after amphotericin B is stopped.</p> <p>For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children. Options should be discussed with an expert in the treatment of coccidioidomycosis.</p> <p>Chronic suppressive therapy (secondary prophylaxis) with fluconazole or itraconazole is routinely recommended following initial induction therapy for disseminated disease.</p>

Dosing Recommendations for Prevention and Treatment of Coccidioidomycosis

Indication	First Choice	Alternative	Comments/Special Issues
	course of antifungal therapy.		Therapy with amphotericin B results in a more rapid clinical response in severe, non-meningeal disease.
	Mild-to-Moderate Non-Meningeal Coccidioidal Infection <ul style="list-style-type: none"> Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily for 6–12 months and clinical improvement 	Mild-to-Moderate Non-Meningeal Coccidioidal Infection <ul style="list-style-type: none"> Itraconazole 2–5 mg/kg body weight (maximum dose 200 mg) per dose IV or PO three times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) PO per dose twice daily thereafter for 6–12 months and clinical improvement Age ≥13 Years: Posaconazole oral (delayed-release tablets), 300 mg twice daily for two doses, followed by 300 mg daily for 6–12 months and clinical improvement 	<p>Surgical debridement of bone, joint, and/or excision of cavitary lung lesions may be helpful.</p> <p>Itraconazole is the preferred azole for treatment of bone infections. Fluconazole can be used as an alternative agent.</p> <p>For treatment failure, can consider voriconazole, isavuconazole, caspofungin, or posaconazole (or combinations). However, experience is limited in children.</p> <p>Options should be discussed with an expert in the treatment of coccidioidomycosis.</p> <p>Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm³ or CD4 percentage <15%.</p>
	Coccidioidal Meningitis <ul style="list-style-type: none"> Lifelong fluconazole 12 mg/kg body weight (maximum 800–1,200 mg) per dose IV or PO once daily 	Coccidioidal Meningitis <ul style="list-style-type: none"> IV liposomal amphotericin B plus intrathecal amphotericin B deoxycholate followed by secondary prophylaxis 	<p>For treatment failure, can consider posaconazole, isavuconazole, or voriconazole.</p> <p>Chronic suppressive therapy (secondary prophylaxis) with fluconazole is continued lifelong for meningeal disease.</p> <p>Options for treatment and secondary prophylaxis should be discussed with an expert in the treatment of coccidioidomycosis in children.</p>

Key: CD4 = CD4 T lymphocyte; IV = intravenous; PO = oral

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