



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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## Coccidioidomycosis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended **(BIII)**.
- Diffuse pulmonary or disseminated infection (not involving the central nervous system) should be treated initially with amphotericin B **(AII\*)**. After completion of amphotericin B, treatment with fluconazole or itraconazole should begin **(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)**.
- There is no evidence that lipid preparations of amphotericin are more effective than amphotericin B deoxycholate for the treatment of coccidioidomycosis. Lipid preparations are often preferred because they are better tolerated and associated with less nephrotoxicity than amphotericin B deoxycholate **(AII\*)**.
- For patients with mild disease (e.g., focal pneumonia), monotherapy with fluconazole or itraconazole is appropriate **(BII\*)**.
- Itraconazole is preferred for treatment of skeletal infections **(AII\*)**.
- Because absorption of itraconazole varies from patient to patient, serum concentrations should be measured to ensure effective, non-toxic levels of drug, monitor drug levels following changes in dosage, and assess compliance **(BIII)**.
- Amphotericin B preparations are not the drugs of choice for treating coccidioidal meningitis; fluconazole is the preferred drug for treating coccidioidal meningitis **(AII\*)**.
- Lifelong antifungal suppression (secondary prophylaxis) with either fluconazole or itraconazole is recommended for treating HIV-infected children after disseminated, diffuse pulmonary, and/or meningeal coccidioidomycosis **(AII\*)**, even if immune reconstitution is achieved with combination antiretroviral therapy (cART). Lifelong secondary prophylaxis should be considered for children with mild disease and CD4 T lymphocyte cell count <250 cells/mm<sup>3</sup> or <15%, even if immune reconstitution is achieved with cART **(BIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> 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*<sup>†</sup> 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*<sup>†</sup> 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*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Epidemiology

Coccidioidomycosis is caused by the endemic,<sup>1,2</sup> soil-dwelling dimorphic fungus, *Coccidioides* spp. Two species, *Coccidioides posadasii* and *C. immitis*, have been identified using molecular and biogeographic characteristics. *C. immitis* appears to be confined mainly to California; *C. posadasii* is more widely distributed through the southwestern United States, northern Mexico, and Central and South America. Clinical illnesses caused by each are indistinguishable. Infection usually results from inhalation of spores (arthroconidia) produced by the mycelial form which grows in arid, windy environments with hot summers preceded by rainy seasons.<sup>3,4,5,6</sup> Infection that occurs in non-endemic regions usually results from either re-activation of a previous infection or from acquisition during travel to an endemic region.<sup>7</sup> Contaminated fomites, such as dusty clothing or agricultural products,<sup>8</sup> also have been implicated as infrequent sources of infection.<sup>9</sup>

Most illnesses are primary infections with rates governed by both environmental conditions that are conducive to fungal growth and to activities/conditions that predispose to inhalation of spores. Increased infection rates have been attributed to population shifts to endemic regions, climatic conditions, and better recognition.<sup>10-12</sup> A review of hospitalizations for coccidioidomycosis at children's hospitals from 2002 to 2006 found an increased incidence in 2005 to 2006, especially among patients with comorbid conditions.<sup>13</sup>

Impairment of cellular immunity is a major risk factor for severe primary coccidioidomycosis or relapse of past infection. In HIV-infected adults, both localized pneumonia and disseminated infection usually are observed in individuals with CD4 T lymphocyte (CD4) cell counts  $<250$  cells/mm<sup>3</sup>.<sup>14,15</sup> The threshold for increased risk in HIV-infected children has not been established; systemic fungal infection has occurred when CD4 counts were  $\leq 100$  cells/mm<sup>3</sup> and with CD4 percentages  $<15\%$ , both indicative of severe immunosuppression.<sup>16,17</sup> Although no cases of coccidioidomycosis were reported in HIV-infected children enrolled in the Perinatal AIDS Collaborative Transmission Study, the study sites under-represented geographic regions in which coccidioidomycosis is endemic.<sup>18</sup> Women who acquire coccidioidomycosis late in pregnancy are at risk of dissemination, but infection in their infants is infrequent.<sup>19</sup> Infections in infants usually result from inhalation of spores in the environment. In adults, combination antiretroviral therapy (cART) appears to be responsible for the declining incidence and severity of coccidioidomycosis.<sup>20,21</sup> Data are limited in children.

## Clinical Manifestations

Coccidioidal infection can range from a mild, self-limited, flu-like illness to more severe, focal or disseminated illness, including pneumonia, bone and joint infection and meningitis. Immunocompromised individuals and previously healthy blacks, Hispanics, and Filipinos with coccidioidomycosis are at increased risk of dissemination, as are pregnant women who acquire coccidioidal infection during the second or third trimester<sup>22</sup> or the postpartum period.<sup>23,24</sup> The severity of clinical manifestations in HIV-infected adults varies in direct proportion to the degree of immunocompromise. Diffuse pulmonary infection and extrathoracic dissemination have been associated with decreased CD4 counts, increased HIV RNA levels, and lower likelihood of having received potent antiretroviral therapy (ART).<sup>21</sup> Focal pneumonitis can occur in mild to moderately immunocompromised patients.<sup>15,24</sup> Pleural inflammation may result in effusion, empyema, and/or pneumothorax.<sup>25</sup> If untreated, a coccidioidal antibody-seropositive, HIV-infected individual is at risk of serious disease, with the degree of severity inversely proportional to absolute CD4 counts  $<250$ /mm<sup>3</sup>. Bone and joint involvement is rare in HIV-infected patients.<sup>20,26</sup>

Children with primary pulmonary infection may present with fever, malaise, and chest pain. The presence of cough varies, and hemoptysis is rare. Persistent fever may be a symptom of extrathoracic dissemination. Children with meningitis may present with headaches, altered sensorium, vomiting, and/or focal neurologic deficits.<sup>27-29</sup> Fever is sometimes absent, and meningismus occurs in only 50% of patients. Hydrocephalus complicating basilar inflammation<sup>27,30</sup> occurs in most (83%–100%) children with coccidioidal meningitis.<sup>27,31</sup> Generalized lymphadenopathy, skin nodules, plaques or ulcers,<sup>24,32</sup> peritonitis, and liver abnormalities also may accompany disseminated disease.

## Diagnosis

Because signs and symptoms are non-specific, the diagnosis of coccidioidomycosis should be among those considered in patients who reside in or have visited endemic areas.<sup>25,33</sup> Culture, microscopy, and serology have been the methods used for diagnosis, but newer tests, including coccidioidal galactomannan antigen detection in urine,<sup>1,34</sup> are especially useful for diagnosis in immunocompromised hosts. Polymerase chain reaction (PCR) assays that target specific coccidioidal genes have been developed but are not yet commercially available.<sup>35,36</sup>

In patients with meningitis, cerebrospinal fluid (CSF) 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<sup>37</sup> or other clinical specimens is diagnostic. Stains of CSF in patients with meningitis usually are negative. Pyogranulomatous inflammation with endosporulating spherules is seen in affected tissue specimens with haematoxylin 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.<sup>26</sup> Potassium hydroxide stains are less sensitive and should not be used.<sup>26</sup>

Growth of *Coccidioides* spp. is supported by many conventional laboratory media used for fungal isolation; growth may occur within 5 days at 30°C to 37°C.<sup>26</sup> Blood cultures are positive in <15% of cases; CSF cultures are positive in <50% of children with meningitis.<sup>24,26,38</sup> Cultures of respiratory specimens are often positive in adults with pulmonary coccidioidomycosis. The laboratory should be alerted to clinical suspicion of coccidioidal infection so that specimens can be handled in secure and contained fashion to minimize hazards to laboratory personnel.

Serologic assays, performed by enzyme-linked immunoassay (EIA), immunodiffusion, or classical tube precipitin or complement fixation methodology that measure coccidioidal Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibody are valuable aids in diagnosis<sup>39</sup> but may be falsely negative in immunocompromised hosts. 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.<sup>40,41</sup> IgG-specific antibody appears later and persists for 6 to 8 months. A commercial EIA appears more sensitive than the older tube precipitin and complement fixation tests and the immunodiffusion assays, although concern remains about specificity.<sup>42</sup> The EIA, however, is not quantitative.<sup>24</sup> Assays for coccidioidal antibody in serum or body fluids such as CSF provide diagnostic and prognostic information. Cross-reactivity can occur with other endemic mycoses. 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 or detection of IgG-specific antibody in CSF. Serial testing<sup>36</sup> following at least a 2-week interval may be needed to demonstrate this. Antibody titers decline during effective therapy. A *Coccidioides* EIA has been developed that detects and quantifies coccidioidal galactomannan concentrations in urine samples<sup>34,43,44</sup> and is especially useful in serious infections and/or instances in which antibody is undetectable. Dissociation of immune complexes has increased the sensitivity of detection of coccidioidal antigen in serum.<sup>44</sup> Meningitis has been diagnosed using real-time PCR analysis of CSF.<sup>36</sup>

## Prevention Recommendations

### *Preventing Exposure*

HIV-infected patients who reside in or visit regions in which coccidioidomycosis is endemic cannot completely avoid exposure to *Coccidioides* spp., but risk can be reduced by avoiding activities and/or exposure to sites that may predispose to inhalation of spores. These include disturbing contaminated soil, archaeological excavation, and being outdoors during dust storms. If such activities are unavoidable, use of high-efficiency respiratory filtration devices should be considered.<sup>36</sup>

### *Preventing First Episode of Disease*

No prospective studies have been published that examine the role of prophylaxis to prevent development of active coccidioidomycosis in patients without previous (recognized) episodes of coccidioidomycosis. Although some experts would provide prophylaxis with an azole (fluconazole) to coccidioidal antibody-positive HIV-infected patients living in regions with endemic coccidioidomycosis, others would not.<sup>26</sup> Chemoprophylaxis is used for coccidioidal antibody-positive HIV-infected adults living in endemic areas and with CD4 counts <250 cells/mm<sup>3</sup>.<sup>45,46</sup> However, given the low incidence of coccidioidomycosis in HIV-infected children, the potential for drug interactions, potential for development of antifungal drug resistance, and the cost, the routine use of antifungal medications for primary prophylaxis of coccidioidal infections in children is not recommended (BIII).

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

In patients with HIV infection, effective cART, if not being administered at the time of diagnosis of coccidioidomycosis, should be started in concert with initiation of antifungal agents. Treatment protocols that are recommended for HIV-infected children are based on experience in nonrandomized, open-label studies in adults. Physicians who infrequently treat children with coccidioidomycosis should consider consulting with experts.

Antifungal therapy had been a recommendation for all HIV-infected adults with clinically active, mild coccidioidomycosis.<sup>47</sup> More recently, treatment protocols appropriate for patients who are HIV-uninfected have been suggested<sup>47</sup> for HIV-infected adults reliably receiving potent ART and who have CD4 counts >250 cells/mm<sup>3</sup>.<sup>46</sup> That would include patients with mild infections that are not accompanied by signs suggestive of dissemination, diffuse pulmonary infiltrates, or meningitis. In this setting, patients should be closely monitored to ensure compliance with ART, effective HIV suppression, and maintenance of CD4 counts >250 cells/mm<sup>3</sup>. Management should also include education directed at reducing the probability of re-exposure to coccidioidal spores. In children, absent comparable published experience in this setting, expert consultation should be sought and, if treatment is elected, recommendations should be based upon assurance of continued compliance with ART, confirmation of continued HIV suppression, CD4 counts >250/mm<sup>3</sup>, 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 pneumonitis), monotherapy with fluconazole or itraconazole is appropriate given their effectiveness, safety, convenient oral dosing, and pharmacodynamic parameters (**BII**\*). Fluconazole (6–12 mg/kg/day) and itraconazole (5–10 mg/kg/dose twice daily for the first 3 days, followed thereafter by 2–5 mg/kg per dose twice daily) are alternatives 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 treating non-meningeal coccidioidomycosis. Itraconazole (5 mg/kg body weight dose twice daily) appeared to be more effective than fluconazole for treating skeletal infections (**AII**\*).<sup>48</sup>

Severely ill patients with diffuse pneumonia and/or other signs of probable disseminated infection (not involving the CNS) are initially treated with an amphotericin B preparation because these appear to evoke a faster therapeutic response than do the azoles.<sup>49,50</sup> Although there is no evidence that the lipid preparations are more effective than amphotericin B deoxycholate, lipid formulations often are used because they are better tolerated (**AIII**). The length of amphotericin B therapy is governed by both the severity of initial symptoms and the pace of the clinical improvement. Thereafter, amphotericin B is stopped and treatment with fluconazole or itraconazole begun (**BIII**). Some experts initiate therapy with both amphotericin B and a triazole, such as fluconazole, in patients with severe disseminated disease and continue the triazole after amphotericin B is stopped (**BIII**).<sup>26,48</sup> The total duration of therapy should be ≥ 1 year.<sup>26</sup>

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 1000 mg/day.<sup>47</sup> Children usually receive 12 mg/kg/dose once daily (800 mg/day maximum) (**AII**\*).<sup>51,52</sup> The 12 mg/kg dosage may be required to attain serum concentrations equivalent to those in adults receiving 400 mg/day.<sup>53</sup> Some experts would begin at a dose of 15 to 23 mg/kg/day.<sup>24</sup> Successful therapy with posaconazole<sup>54</sup> and voriconazole has been described in adults but there is no published experience in children.<sup>55</sup> Some experts use amphotericin B administered intrathecally<sup>50,56</sup> in addition to an azole. Intrathecal amphotericin administration adds additional toxicity and is not used as part of initial therapy (**CIII**). 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 (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 immunocompromised state, with one-third of patients in this group having HIV/AIDS.<sup>28</sup>

### ***Monitoring and Adverse Events (Including IRIS)***

In addition to monitoring patients for clinical improvement, some experts<sup>26</sup> have recommended monitoring coccidioidal IgG antibody titers to assess response to therapy. Titers should be obtained every 12 weeks (**AIII**). If therapy is succeeding, titers should decrease progressively; a rise in titers suggests recurrence of clinical disease. However, if serologic tests initially were negative, titers during effective therapy may increase briefly and then decrease.<sup>26</sup> 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. Infusion-related fevers, chills, 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) also can occur (see discussion on monitoring and adverse events in *Candida* infection). Intrathecal injection of amphotericin B may result in arachnoiditis.<sup>57,58</sup>

Triazoles can interact with other drugs metabolized by CYP450-dependent hepatic enzymes,<sup>59,60</sup> and the potential for drug interactions should be assessed before initiation of therapy (**AIII**). Use of fluconazole or itraconazole appears to be safe in combination with ART. Voriconazole should be avoided in patients receiving protease inhibitors (**BIII**)<sup>61</sup> or non-nucleoside reverse transcriptase inhibitors.<sup>15</sup> The most frequent adverse effects of fluconazole are nausea and vomiting. Skin rash and pruritus may be observed, and cases of Stevens-Johnson syndrome have been reported. Asymptomatic increases in transaminases occur in 1% to 13% of patients receiving azole drugs. In HIV-infected patients, fluconazole at high doses can cause adrenal insufficiency.<sup>62</sup>

Because absorption of itraconazole varies from patient to patient, serum concentrations should be measured to ensure effective, non-toxic levels of drug, monitor changes in dosage, and assess compliance (**BIII**).

Coccidioidomycosis-associated immune reconstitution inflammatory syndrome following the initiation of ART has not been reported in children and is rarely reported in adults.<sup>63</sup>

### ***Managing Treatment Failure***

The treatment of coccidioidomycosis unresponsive to standard therapy has been reviewed; the majority of experience has been in adults.<sup>55</sup> Posaconazole was effective in 6 adults with disease refractory to treatment with other azoles and to amphotericin B<sup>64</sup> and has been used successfully in 73% of 15 adults whose infections were refractory to previous therapy.<sup>65</sup> Posaconazole has also been effective for chronic refractory meningitis unresponsive to fluconazole.<sup>54</sup> Voriconazole was effective in treating coccidioidal meningitis and non-meningeal disseminated disease in adults who did not respond to fluconazole or were intolerant of amphotericin B.<sup>66,67,68</sup> Monotherapy with caspofungin successfully treated disseminated coccidioidomycosis in a renal transplant patient intolerant of fluconazole and other adults in whom conventional therapy failed.<sup>69,70</sup> Others have used caspofungin in combination with fluconazole.<sup>71</sup>

Adjunctive interferon-gamma (IFN- $\gamma$ )<sup>72</sup> was successfully used in a critically ill adult with respiratory failure who did not respond to amphotericin B preparations and fluconazole.<sup>73</sup> However, no controlled clinical studies or data exist for children; thus, adjunctive IFN- $\gamma$  is not recommended for use in HIV-infected children (**BIII**).

In instances in which patients with coccidioidal meningitis fail to respond to treatment with azoles, both systemic amphotericin B and direct instillation of amphotericin B into the intrathecal, ventricular, or intracisternal spaces, with or without concomitant azole treatment, have been used successfully. These regimens are recommended in such instances (**AIII**).<sup>48,52</sup> The basilar inflammation that characteristically

accompanies coccidioidal meningitis often results in obstructive hydrocephalus requiring 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.<sup>74</sup> 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 coccidioidomycosis 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 ongoing CD4 counts <250 cells/mm<sup>3</sup> or CD4 percentages <15% (**BIII**).<sup>26,47,49,75,76</sup>

### ***Discontinuing Secondary Prophylaxis***

In disseminated infection, continued 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<sup>26</sup>—because of high risk of relapse (**AII\***). In HIV-infected adults with focal coccidioidal pneumonia who have clinically responded to antifungal therapy and have sustained CD4 counts >250 cells/mm<sup>3</sup> 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. However, only a small number of patients have been evaluated, and the safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children has not been studied. Therefore, in HIV-infected children, 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**).

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## Dosing Recommendations for Prevention and Treatment of Coccidioidomycosis

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b>	N/A	N/A	Primary prophylaxis not routinely indicated in children.
<b>Secondary Prophylaxis</b>	Fluconazole 6 mg/kg body weight (maximum 400 mg) by mouth once daily	Itraconazole 2–5 mg/kg body weight (maximum 200 mg) by mouth per dose twice daily	Lifelong secondary prophylaxis with fluconazole for patients with meningitis or disseminated disease in the immunocompromised patient is recommended. Secondary prophylaxis should be considered after treatment of milder disease if CD4 count remains <250 cells/mm <sup>3</sup> or CD4 percentage <15%.
<b>Treatment</b>	<p><u>Severe Illness with Respiratory Compromise due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease:</u></p> <ul style="list-style-type: none"> <li>Amphotericin B deoxycholate 0.5–1.0 mg/kg body weight IV once daily, until clinical improvement.</li> <li>A lipid amphotericin B preparation can be substituted at a dose of 5 mg/kg body weight IV once daily (dosage of the lipid preparation can be increased to as much as 10 mg/kg body weight IV once daily for life-threatening infection).</li> <li>After the patient is stabilized, therapy with an azole (fluconazole or itraconazole) can be substituted and continued to complete a 1-year course of antifungal therapy.</li> </ul>	<p><u>Severe Illness with Respiratory Compromise Due to Diffuse Pulmonary or Disseminated Non-Meningitic Disease (If Unable to Use Amphotericin):</u></p> <ul style="list-style-type: none"> <li>Fluconazole 12mg/kg body weight (maximum 800 mg) per dose IV or by mouth once daily</li> <li>Treatment is continued for total of 1 year, followed by secondary prophylaxis.</li> </ul>	<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.</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, caspofungin, or posaconazole (or combinations). However, experience is limited and definitive pediatric dosages have not been determined.</p>
	<p><u>Meningeal Infection:</u></p> <ul style="list-style-type: none"> <li>Fluconazole 12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily followed by secondary lifelong prophylaxis.</li> </ul>	<p><u>Meningeal Infection (Unresponsive to Fluconazole):</u></p> <ul style="list-style-type: none"> <li>IV amphotericin B plus intrathecal amphotericin B followed by secondary prophylaxis. <b>Note:</b> Expert consultation recommended.</li> </ul>	<p>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 and is continued lifelong for meningeal disease.</p>
	<p><u>Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia):</u></p> <ul style="list-style-type: none"> <li>Fluconazole 6–12 mg/kg body weight (maximum 400 mg) per dose IV or by mouth once daily.</li> </ul>	<p><u>Mild-to-Moderate Non-Meningeal Infection (e.g., Focal Pneumonia):</u></p> <ul style="list-style-type: none"> <li>Itraconazole 2–5 mg/kg body weight per dose (maximum dose 200 mg) per dose IV or by mouth 3 times daily for 3 days, then 2–5 mg/kg body weight (maximum dose 200 mg) by mouth per dose twice daily thereafter.</li> <li>Duration of treatment determined by rate of clinical response.</li> </ul>	<p>Therapy with amphotericin results in a more rapid clinical response in severe, non-meningeal disease.</p>

**Key to Abbreviations:** CD4 = CD4 T lymphocyte; IV = intravenous