



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

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

### Panel's Recommendations

- Routine use of antifungal medications is not recommended for primary prophylaxis of cryptococcal infections in children (**BIII**).
- Combination therapy with amphotericin B deoxycholate (or liposomal amphotericin B) and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for central nervous system disease (**AI\***). Amphotericin B lipid complex is another alternative to amphotericin B deoxycholate (**BII\***).
- Liposomal amphotericin B is preferred over amphotericin B deoxycholate for patients with or at risk of renal insufficiency (**AI\***); amphotericin B lipid complex is an alternative (**BII\***).
- In patients who cannot tolerate flucytosine or if flucytosine is unavailable, amphotericin B deoxycholate (or liposomal amphotericin B or amphotericin B lipid complex) with or without high-dose fluconazole can be used for initial therapy (**BI\***). Fluconazole plus flucytosine is superior to fluconazole alone and an option in patients who cannot tolerate any form of amphotericin (**BII\***).
- Echinocandins are not active against cryptococcal infections and should not be used (**AIII**).
- After a minimum of 2 weeks of induction therapy, if there is clinical improvement and a negative cerebrospinal fluid culture after repeat lumbar puncture, amphotericin B and flucytosine can be discontinued and consolidation therapy with fluconazole administered for a minimum of 8 weeks (**AI\***); itraconazole is a less preferable alternative to fluconazole (**BI\***).
- Secondary prophylaxis with fluconazole (**AI\***) or itraconazole (less preferable) (**BI\***) is recommended for a minimum of 1 year.
- Discontinuing secondary prophylaxis (after receiving secondary prophylaxis for  $\geq 1$  year) can be considered for asymptomatic children aged  $\geq 6$  years with CD4 counts  $\geq 100$  cells/mm<sup>3</sup> and an undetectable viral load on  $\geq 3$  months of combination antiretroviral therapy (**CIII**). Secondary prophylaxis should be reinitiated if the CD4 count decreases to  $< 100$  cells/mm<sup>3</sup> (**AIII**). Most experts would not discontinue secondary prophylaxis for patients younger than age 6 years (**CIII**).
- Patients with severe pulmonary disease or disseminated cryptococcosis should be treated with amphotericin B with or without the addition of flucytosine, as for CNS disease (**AIII**). Those with mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy (**AIII**).
- In antiretroviral-naïve patients newly diagnosed with cryptococcal meningitis or disseminated disease, delay in initiation of potent antiretroviral therapy may be prudent until the end of the first 2 weeks of induction therapy (**CIII**).

**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

Given the low incidence of cryptococcosis in HIV-infected children, even during the era before combination antiretroviral therapy (cART), management of this disease in this age group has not been prospectively studied. Treatment recommendations largely reflect information extrapolated from many well-designed studies involving HIV-infected adults with cryptococcal meningitis.<sup>1</sup>

### Epidemiology

Most cases of cryptococcosis in HIV-infected patients are caused by *Cryptococcus neoformans*; *Cryptococcus gattii* (formerly *Cryptococcus neoformans* variety *gattii*) infection occurs primarily in tropical and subtropical areas. Cryptococcal infections occur much less frequently in HIV-infected children than in adults.<sup>2-5</sup> During the pre-cART era, most cases of cryptococcosis in HIV-infected children (overall incidence, 1%) occurred in those aged 6 through 12 years and in those with CD4 T lymphocyte (CD4) cell counts

indicating severe immunosuppression.<sup>4</sup> Access to cART has further decreased the overall incidence of cryptococcal infection<sup>6,7</sup> in HIV-infected children. Data from Pediatric AIDS Clinical Trials Group studies before and after the advent of cART indicate that the rate of invasive fungal infection, including cryptococcosis, has remained <0.1 per 100 child-years.<sup>8,9</sup>

## Clinical Manifestations

Cryptococcosis often presents with subtle and non-specific findings, such as fever and headache. Early diagnosis requires consideration of this infection in symptomatic patients whose CD4 counts indicate severe immunosuppression. In both HIV-infected adults and children, meningoencephalitis is the most common initial manifestation of cryptococcosis. The disease typically evolves over days to weeks with fever and headache. Less frequent findings include nuchal rigidity, photophobia, and focal neurologic signs, as were seen among 30 HIV-infected children with cryptococcosis reported from the United States.<sup>4</sup> In contrast to this indolent presentation, children in Zimbabwe presented with an acute form of neurologic cryptococcosis (69% with nuchal rigidity, 38% with seizure activity, and 23% with focal neurologic signs).<sup>10</sup> *C. gattii* infections occur mostly in people who are not HIV-infected (or do not have other immunocompromising conditions), and neurologic disease due to *C. gattii* in such apparently normal hosts responds more slowly to treatment and results in high risk of neurologic complications.<sup>11</sup> *C. gattii* infections in HIV-infected patients, however, are uncommon and are similar in presentation to *C. neoformans* infections in HIV-infected hosts.<sup>12</sup>

Disseminated cryptococcosis can be associated with cutaneous lesions, including small, translucent, umbilicated papules (indistinguishable from molluscum contagiosum), nodules, ulcers, and infiltrated plaques resembling cellulitis. Pulmonary cryptococcosis without dissemination is unusual in children. Presenting findings include unexplained recurrent fever, cough with scant sputum, intrathoracic lymphadenopathy, and focal or diffuse pulmonary infiltrates. The infection also can be asymptomatic, with pulmonary nodules revealed on routine chest radiograph.<sup>3</sup>

## Diagnosis

Detection of cryptococcal antigen in serum, cerebrospinal fluid (CSF) or other body fluids is highly effective for rapid and accurate diagnosis of cryptococcal infection.

A lumbar puncture should be done in any patient with suspected cryptococcal meningitis. CSF cell count, glucose, and protein can be virtually normal with central nervous system (CNS) cryptococcosis, but the opening pressure usually is elevated. Microscopic examination of CSF on India ink-stained wet mounts can be performed to diagnose suspected CNS disease but is largely replaced with the use of the cryptococcal antigen test. In more than 90% of patients with cryptococcal meningitis, cryptococcal antigen can be detected in CSF or serum by latex agglutination test (available from several manufacturers).

Fungal cultures from CSF, sputum, and blood can identify the organism. In some cases (meaning refractory or relapsed disease), susceptibility testing of the *C. neoformans* isolate can be beneficial. Overall, *in vitro* resistance to antifungal agents remains uncommon.<sup>13</sup>

Diffuse pulmonary disease can be diagnosed through bronchoalveolar lavage and direct examination of India ink-stained specimens, culture, and antigen detection. Focal pulmonary and skin lesions may require biopsy with culture and staining.

## Prevention Recommendations

### *Preventing Exposure*

No strategies have been proven to prevent exposure. *C. neoformans* infection is believed to be acquired through inhalation of aerosolized particles from the environment. Serologic studies of immunocompetent children in an urban setting indicate that most children have been infected by *C. neoformans* by the third year of life.<sup>14</sup>

## ***Preventing the First Episode of Disease***

Because the incidence of cryptococcal disease is so low in HIV-infected children,<sup>2-4,15</sup> routine testing of asymptomatic children for serum cryptococcal antigen is not recommended (**CIII**).

A review of randomized controlled trials using antifungal interventions for the primary prevention of cryptococcal diseases indicates that fluconazole and itraconazole can reduce cryptococcal disease in adults who have advanced HIV disease and severe immunosuppression (CD4 count <50 cells/mm<sup>3</sup>).<sup>16</sup> However, neither of these interventions clearly affected mortality.

In addition, routine use of antifungal medications is not recommended for primary prophylaxis of cryptococcal infections in children because of the low incidence of cryptococcosis in HIV-infected children, lack of survival benefits in primary prevention studies of adults,<sup>16</sup> possibility of drug interaction, potential resistance to antifungal drugs, and cost (**BIII**). Early diagnosis of HIV infection and treatment with cART (following current HIV treatment guidelines) to prevent or reverse immune suppression should further reduce risk of cryptococcal disease in HIV-infected children.

## ***Discontinuing Primary Prophylaxis***

Not applicable.

## **Treatment Recommendations**

### ***Treating Disease***

**Note:** These recommendations are largely based on high-quality evidence from studies in adults.

#### **CNS Disease**

The most common and well-studied presentation of cryptococcal infection in HIV-infected patients is CNS disease. In light of studies in adults,<sup>17-19</sup> combination therapy with amphotericin B deoxycholate (or liposomal amphotericin B) and flucytosine for 2 weeks (induction therapy) followed by fluconazole for a minimum of 8 weeks (consolidation therapy) is recommended for children (**AI\***). Amphotericin B lipid complex is an alternative to amphotericin B deoxycholate (**BII\***).<sup>20</sup> CSF was sterilized significantly more rapidly in adults with CNS cryptococcal disease who received initial therapy with amphotericin B deoxycholate (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) than in those who received amphotericin B deoxycholate alone, amphotericin B deoxycholate plus fluconazole, or triple-antifungal therapy.<sup>21,22</sup> In one study of adults, liposomal amphotericin B (AmBisome<sup>®</sup>) dosed at 4 mg/kg/day resulted in significantly earlier CSF culture conversion than did amphotericin B deoxycholate at 0.7 mg/kg/day.<sup>23</sup> However, a randomized, double-blind clinical trial before the routine availability of cART that compared amphotericin B (0.7 mg/kg/day), liposomal amphotericin B (3 mg/kg/day), and liposomal amphotericin B (6 mg/kg/day) showed no difference in efficacy among the three arms, but significantly fewer adverse events with liposomal amphotericin B (3 mg/kg body weight/day).<sup>24</sup> Cost considerations aside (liposomal amphotericin is significantly more expensive than amphotericin B deoxycholate), based on the reported experience in adults, liposomal amphotericin B would be preferable to amphotericin B deoxycholate in patients with cryptococcal meningitis who have or are at risk of renal failure (**AI\***). Amphotericin B lipid complex is another option (**BII\***).<sup>20</sup> Monitoring for and managing increased intracranial pressure (ICP) is crucial to optimal management of CNS cryptococcosis (see below).

In patients who cannot tolerate flucytosine (or if flucytosine is not available), amphotericin B deoxycholate (or its liposomal preparation) with or without fluconazole can be used for initial therapy (**BI\***). In a randomized Phase II trial in HIV-infected adolescents and adults, amphotericin B deoxycholate plus high-dose fluconazole (800 mg daily) was found to be well tolerated and with a trend toward better outcome at days 42 and 70, compared with amphotericin B deoxycholate alone.<sup>25</sup> Studies are needed to further validate the use of this combination. In another study 80 HIV-seropositive, antiretroviral (ARV)-naive adults presenting with

cryptococcal meningitis were randomized to 4 treatment arms of 2-week duration: group 1, amphotericin B (0.7–1 mg/kg) and flucytosine (25 mg/kg 4 times daily); group 2, amphotericin B (0.7–1 mg/kg) and fluconazole (800 mg daily); group 3, amphotericin B (0.7–1 mg/kg) and fluconazole (600 mg twice daily); and group 4, amphotericin B (0.7–1 mg/kg) and voriconazole (300 mg twice daily). The primary end point was the rate of clearance of infection from CSF or early fungicidal activity, as determined by results of serial, quantitative CSF cryptococcal cultures. There were no statistically significant differences in the rate of clearance of cryptococcal colony-forming units (CFU) in CSF samples among the 4 treatment groups.<sup>26</sup> Fluconazole plus flucytosine is superior to fluconazole alone<sup>27,28</sup> and provides an alternative to amphotericin B deoxycholate for acute therapy of invasive disease (**BII\***) that should be used only if amphotericin B-based therapy is not tolerated. Although fluconazole monotherapy was an effective alternative to amphotericin B in adults with AIDS-associated cryptococcal meningitis,<sup>29</sup> concerns in this study about differences in early death, delayed CSF sterilization, and drug resistance<sup>30,31</sup> make fluconazole monotherapy less favorable for initial therapy of CNS disease. Because of rapidly developing resistance, flucytosine alone should never be used to treat cryptococcosis. Echinocandins are not active against cryptococcal infections and should not be used (**AIII**).

After a minimum of 2 weeks of induction therapy with evidence of clinical improvement and a negative CSF culture after repeat lumbar puncture, amphotericin B deoxycholate (or its liposomal preparation) and flucytosine can be discontinued and consolidation therapy for a minimum of 8 weeks initiated with fluconazole (**AI\***).<sup>32</sup> Itraconazole is a less preferable alternative to fluconazole for the consolidation phase of CNS therapy (**BI\***). Fluconazole is preferred because studies comparing the two agents demonstrate higher rates of CSF sterilization during consolidation therapy<sup>18</sup> and less frequent relapse<sup>32</sup> during maintenance therapy in fluconazole recipients. After completion of consolidation therapy, secondary prophylaxis (maintenance therapy or suppressive therapy) should be initiated (see below).

### **Pulmonary and Extra Pulmonary Cryptococcosis (CNS Disease Ruled Out)**

No controlled clinical studies describe the outcome of non-CNS cryptococcosis in HIV-infected patients. CNS disease should be ruled out in all patients, after which the choice of antifungal medication and length of initial therapy can be decided in light of the clinical severity of illness. Patients with severe pulmonary disease or disseminated cryptococcosis should be treated with a form of amphotericin B with or without the addition of flucytosine, as for CNS disease (**AIII**). Usually combination therapy should be provided until symptoms resolve. Those with mild-to-moderate pulmonary illness or other localized disease can be managed with fluconazole monotherapy (**AIII**). Regardless of the antifungal agent selected for initial therapy, secondary prophylaxis with fluconazole or itraconazole should be provided as for CNS disease (**AIII**) (see notes below on secondary prophylaxis).

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

#### **Monitoring for Raised Intracranial Pressure**

At the time of diagnosis and on subsequent lumbar punctures, all patients with cryptococcal meningitis should have their lumbar opening pressure measured. Studies in adults clearly show the role of increased ICP in deaths associated with CNS cryptococcosis.<sup>18,33</sup> Patients with severe headache, confusion, blurred vision, papilledema, or other neurologic signs or symptoms of increased ICP should be managed using measures to decrease ICP. One approach recommended for adults is to measure pressure continually or repeatedly during the lumbar puncture procedure and to remove CSF until the pressure is approximately half the opening pressure but still no lower than normal.<sup>34</sup> This may be repeated as often as every day until symptoms and signs consistently improve. Similar data describing experience with therapeutic lumbar punctures in children with cryptococcal meningitis are not available. Not specific to cryptococcal meningitis, a cutoff opening pressure of 28 cm of water has been proposed in children, above which the pressure should be considered elevated.<sup>35</sup> CSF shunting through a lumbar drain or ventriculostomy can be considered for patients who continue to have symptomatic increased ICP despite multiple lumbar taps (**BIII**). Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis and most

experts would not recommend their use in children (**CIII**). Acetazolamide is hazardous as therapy for increased ICP management in adults without signs of immune reconstitution inflammatory syndrome (IRIS) and has not been evaluated in children with cryptococcal meningitis; acetazolamide is **not** recommended for adults and most experts would similarly not use it in children (**BIII**).

### Monitoring Treatment Response

In addition to monitoring clinical response, mycological response in patients with CNS cryptococcosis typically is assessed by a repeat lumbar puncture and CSF examination at 2 weeks of treatment, with continuation of induction therapy until CSF culture is negative.

Monitoring serial serum cryptococcal antigen titers is not useful for following treatment efficacy because changes in serum cryptococcal antigen titers do not correlate well with outcome during treatment for acute meningitis or during suppressive therapy.<sup>36,37</sup> Serial measurement of CSF cryptococcal antigen is more useful; in one study, an unchanged or increased titer of antigen in CSF correlated with clinical and microbiologic treatment failure, and a rise in CSF antigen titer during suppressive therapy was associated with relapse of cryptococcal meningitis.<sup>36</sup> However, monitoring of CSF cryptococcal antigen levels requires repeated lumbar punctures and is not routinely recommended for monitoring response.

### Monitoring for Adverse Events

Adverse effects of amphotericin B ([Table 5](#)) are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, but they are less frequent in children than in adults. Close monitoring for drug toxicities is needed especially when amphotericin B is used with flucytosine.

Flucytosine has the potential for marked toxicity, especially affecting the bone marrow (meaning anemia, leukopenia, and thrombocytopenia), liver, gastrointestinal (GI) tract, kidney, and skin. In patients receiving flucytosine, flucytosine blood levels should be monitored to prevent bone marrow suppression and GI toxicity; after 3–5 days of therapy, the target 2-hour post-dose serum level of flucytosine is 40–60 µg/mL. Flucytosine should be avoided in children with severe renal impairment.

Fluconazole and the other azoles have relatively low rates of toxicity, but their potential drug interactions can limit their use. Because of their ability to inhibit the CYP450-dependent hepatic enzymes, the potential for drug interactions, particularly with ARV drugs, should be carefully evaluated before initiation of therapy. Liver function tests should be monitored during treatment.

### Immune Reconstitution Inflammatory Response Syndrome (IRIS)

While cases of IRIS in HIV-infected children have been described,<sup>38</sup> most of the available information comes from adult literature.

IRIS related to cryptococcosis can present within weeks (such as meningitis) or months (such as lymphadenitis) after start of cART. Symptoms of meningitis are similar to those described for meningitis presenting as the initial manifestation of cryptococcosis. In one study, about 30% of all HIV-infected adults hospitalized for infection with *C. neoformans* who received cART were re-admitted with symptoms attributed to an inflammatory response.<sup>39</sup> Of the 18 patients with *C. neoformans*-related IRIS in the cited study, 17 had culture-negative meningitis, and most cases occurred during the first 30 days after initiation of cART. The most common presentation of late cryptococcal IRIS is lymphadenitis, particularly mediastinal lymphadenitis.<sup>40,41</sup>

IRIS is a clinical diagnosis. While there are no specific laboratory tests to diagnose IRIS, presence of negative cultures in a patient with clinical signs suggestive of tissue inflammation in the face of rapidly improving cellular immunity would be suggestive of IRIS over treatment failure. The optimal management of cryptococcal IRIS has not been defined. Antifungal therapy should be initiated in patients not already

receiving it, raised intracranial pressure managed if present and antiretroviral therapy (ART) should be continued. Although many cases resolve spontaneously, some experts also have used anti-inflammatory therapy (e.g., short-course corticosteroids) in patients with severely symptomatic IRIS (**CIII**).<sup>40,42</sup>

Adult HIV-infected treatment-naive patients with cryptococcal meningitis who go on to develop IRIS after starting cART are more likely to have higher HIV RNA levels at baseline<sup>43</sup> and exhibit less initial CSF inflammation at the time of cryptococcal meningitis diagnosis, compared with those who do not develop IRIS.<sup>44</sup> In patients with advanced immunosuppression and non-tuberculous opportunistic infections (OIs), the presence of a fungal infection, lower CD4 counts and higher HIV RNA levels at baseline, and higher CD4 counts and lower HIV RNA levels on treatment were found associated with IRIS.<sup>43</sup> For patients not on cART at the time of diagnosis of cryptococcal meningitis, the timing of cART in relation to antifungal treatment remains controversial. One randomized trial of adult HIV-infected patients with OIs (excluding tuberculosis) primarily from the United States that included 35 patients with cryptococcal meningitis suggested that early cART treatment (within the first 14 days of diagnosis) was safe and resulted in less AIDS progression/death compared to deferred cART.<sup>45</sup> However a randomized clinical trial in Zimbabwe was reported to show higher mortality in patients receiving cART starting within 72 hours of diagnosis compared to those waiting at least 10 weeks to initiate ART.<sup>46</sup> Patients in this study were treated with high dose fluconazole. Differences in management of cryptococcal meningitis, raised ICP, and cART treatment options may account for some of the differences between these two studies. In ARV-naive patients newly diagnosed with cryptococcal meningitis or disseminated disease, delay in potent ART may be prudent until the end of the first 2 weeks of induction therapy (**CIII**); further delays in initiating cART, especially in resource-poor settings, should be individualized.

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

Treatment failure is defined as worsening or lack of improvement in signs and symptoms after 2 weeks of appropriate therapy, including management of ICP; or relapse after an initial clinical response. Differentiating IRIS from treatment failure is important because treatment approaches and outcomes differ; persistent positive cultures indicate treatment failure. Optimal management of patients with treatment failure is unknown. If cultures remain positive, evaluation of antifungal susceptibilities can be considered, although *C. neoformans* resistance to fluconazole is rare in the United States. Patients in whom initial azole-based therapy fails should be switched to amphotericin B-based therapy,<sup>30</sup> ideally in combination with flucytosine; the possibility of drug interactions resulting in sub-therapeutic azole levels (meaning concurrent rifampin use or other drugs metabolized by the liver) should be explored.<sup>30</sup> Use of liposomal amphotericin B should be considered, because one study suggests improved efficacy in CSF sterilization with liposomal preparations than with standard amphotericin B.<sup>23</sup> Some data from HIV-infected adults indicate higher dosages (meaning 400–800 mg/day) of fluconazole in combination with flucytosine also can be considered for salvage therapy.<sup>19,47</sup> Clinical experience with new antifungal agents in managing cryptococcosis is limited. A few patients with cryptococcal infections refractory or intolerant to standard antifungal therapy have been treated with posaconazole or voriconazole with variable success.<sup>48,49</sup>

### ***Preventing Recurrence (Secondary Prophylaxis)***

Patients who have completed initial therapy for cryptococcosis should receive secondary prophylaxis (maintenance therapy or suppressive therapy) (**AI\***). Fluconazole (**AI\***) is superior and preferable to itraconazole (**BI\***) for preventing relapse of cryptococcal disease.<sup>32,50,51</sup>

### ***Discontinuing Secondary Prophylaxis (Maintenance or Suppressive Therapy)***

Until recently, lifelong secondary prophylaxis typically was recommended. The safety of discontinuing secondary prophylaxis for cryptococcosis after immune reconstitution with cART has not been studied in children, and decisions in that regard should be made on a case-by-case basis. Adults who have successfully completed a course of initial therapy (including  $\geq 12$  months of secondary prophylaxis), remain asymptomatic with regard to signs and symptoms of cryptococcosis, and have a sustained ( $\geq 6$  months) increase in their CD4 counts to  $\geq 100$  cells/mm<sup>3</sup> with an undetectable viral load on ART for  $> 3$  months after cART are at apparent low risk of recurrence of cryptococcosis.<sup>52-54</sup> In light of these observations and inference from data

regarding discontinuing secondary prophylaxis for other OIs in adults with advanced HIV infection, discontinuing secondary prophylaxis for cryptococcosis (after receiving secondary prophylaxis for at least 1 year) can be considered for asymptomatic children aged  $\geq 6$  years, with increase in their CD4 counts to  $\geq 100$  cells/mm<sup>3</sup> and an undetectable viral load on cART for  $\geq 3$  months (CIII). Secondary prophylaxis should be re-initiated if the CD4 count decreases to  $< 100$  cells/mm<sup>3</sup> (AIII). Most experts would not discontinue secondary prophylaxis for patients younger than age 6 years (CIII).

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### Dosing Recommendations for Prevention and Treatment of Cryptococcosis (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b>	Not recommended	Not recommended	N/A
<b>Secondary Prophylaxis<sup>a</sup></b>	Fluconazole 6 mg/kg body weight (maximum 200 mg) by mouth once daily	Itraconazole oral solution 5 mg/kg body weight (maximum 200 mg) by mouth once daily	<p><u>Secondary Prophylaxis Indicated:</u></p> <ul style="list-style-type: none"> <li>• Documented disease</li> </ul> <p><u>Criteria For Discontinuing Secondary Prophylaxis</u></p> <p><i>If <b>All</b> of the Following Criteria are Fulfilled:</i></p> <ul style="list-style-type: none"> <li>• Age ≥6 years</li> <li>• Asymptomatic on ≥12 months of secondary prophylaxis</li> <li>• CD4 count ≥100 cells/mm<sup>3</sup> with undetectable HIV viral load on cART for &gt;3 months</li> </ul> <p><u>Criteria for Restarting Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• CD4 count &lt;100/mm<sup>3</sup></li> </ul>
<b>Treatment</b>	<p><u>CNS Disease</u></p> <p><i>Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy):</i></p> <ul style="list-style-type: none"> <li>• Amphotericin B deoxycholate 1.0 mg/kg body weight (or liposomal amphotericin B 6 mg/kg body weight) IV once daily <b>PLUS</b> flucytosine 25 mg/kg body weight per dose by mouth given 4 times daily</li> </ul>	<p><u>CNS Disease</u></p> <p><i>Acute Therapy (Minimum 2-Week Induction Followed by Consolidation Therapy)</i></p> <p><i>If Flucytosine Not Tolerated or Unavailable:</i></p> <ul style="list-style-type: none"> <li>• <b>A.</b> Liposomal amphotericin B, 6 mg/kg body weight IV once daily, <b>or</b> Amphotericin B Lipid Complex, 5 mg/kg body weight IV once daily, <b>or</b> Amphotericin B deoxycholate, 1.0–1.5 mg/kg body weight IV once daily <b>alone or B. in combination</b> with high-dose fluconazole (12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight [max 800 mg] IV). <b>Note:</b> Data-driven pediatric dosing guidelines are unavailable for fluconazole with use of such combination therapy.</li> </ul>	<p>In patients with meningitis, CSF culture should be negative prior to initiating consolidation therapy.</p> <p>Overall, <i>in vitro</i> resistance to antifungal agents used to treat cryptococcosis remains uncommon. Newer azoles (voriconazole, posaconazole, ravuconazole) are all very active <i>in vitro</i> against <i>C. neoformans</i>, but published clinical experience on their use for cryptococcosis is limited.</p>

## Dosing Recommendations for Prevention and Treatment of Cryptococcosis (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Treatment, continued</b>	<p><i>Consolidation Therapy (Followed by Secondary Prophylaxis):</i></p> <ul style="list-style-type: none"> <li>Fluconazole 12 mg/kg body weight on day 1, then 10–12 mg/kg body weight (max 800 mg) once daily IV or by mouth for a minimum of 8 weeks</li> </ul> <p><u>Localized Disease, Including Isolated Pulmonary Disease (CNS Not Involved)<sup>b</sup>:</u></p> <ul style="list-style-type: none"> <li>Fluconazole 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily</li> </ul> <p><u>Disseminated Disease (CNS Not Involved) or Severe, Pulmonary Disease<sup>b</sup>:</u></p> <ul style="list-style-type: none"> <li>Amphotericin B 0.7–1.0 mg/kg body weight, or</li> <li>Liposomal amphotericin, 3–5 mg/kg body weight, or</li> <li>Amphotericin B lipid complex 5 mg/kg body weight IV once daily (± flucytosine)</li> </ul>	<p><i>If Amphotericin B-Based Therapy Not Tolerated:</i></p> <ul style="list-style-type: none"> <li>Fluconazole, 12 mg/kg body weight on day 1 and then 10–12 mg/kg body weight (maximum 800 mg) IV or by mouth once daily <b>PLUS</b> flucytosine, 25 mg/kg body weight per dose by mouth given 4 times daily</li> </ul> <p><i>Consolidation Therapy (followed by secondary prophylaxis):</i></p> <ul style="list-style-type: none"> <li>Itraconazole 5–10 mg/kg body weight by mouth given once daily, or 2.5–5 mg/kg body weight given twice daily (maximum 200 mg/dose) for a minimum of 8 weeks. A loading dose (2.5–5 mg/kg body weight per dose 3 times daily) is given for the first 3 days (maximum 200 mg/dose; 600 mg/day). See comment on itraconazole under <a href="#">Other Options/Issues</a>.</li> </ul> <p><u>Localized Disease Including Isolated Pulmonary Disease (CNS Not Involved)<sup>b</sup>:</u></p> <ul style="list-style-type: none"> <li>Amphotericin B, 0.7–1.0 mg/kg body weight, or</li> <li>Amphotericin liposomal 3–5 mg/kg body weight, or</li> <li>Amphotericin lipid complex, 5 mg/kg body weight IV once daily</li> </ul> <p><u>Disseminated disease (CNS not involved) or severe, pulmonary disease<sup>b</sup>:</u></p> <ul style="list-style-type: none"> <li>Fluconazole, 12 mg/kg body weight on day 1 and then 6–12 mg/kg body weight (maximum 600 mg) IV or by mouth once daily</li> </ul>	<p>Liposomal amphotericin and amphotericin B lipid complex are especially useful for children with renal insufficiency or infusion-related toxicity to amphotericin B deoxycholate.</p> <p>Liposomal amphotericin and amphotericin B lipid complex are <b>significantly more expensive than amphotericin B deoxycholate</b>.</p> <p>Liquid preparation of itraconazole (if tolerated) is preferable to tablet formulation because of better bioavailability, but it is more expensive. Bioavailability of the solution is better than the capsule, but there were no upfront differences in dosing range based on preparation used. Ultimate dosing adjustments should be guided by itraconazole levels.</p> <p>Serum itraconazole concentrations should be monitored to optimize drug dosing.</p> <p>Amphotericin B may increase toxicity of flucytosine by increasing cellular uptake, or impair its renal excretion, or both.</p> <p>Flucytosine dose should be adjusted to keep 2-hour post-dose drug levels at 40–60 µg/mL</p> <p>Oral acetazolamide <b>should not</b> be used for reduction of ICP in cryptococcal meningitis.</p> <p>Corticosteroids and mannitol have been shown to be ineffective in managing ICP in adults with cryptococcal meningitis.</p> <p>Secondary prophylaxis is recommended following completion of initial therapy (induction plus consolidation)—drugs and dosing listed above.</p>

<sup>a</sup> Secondary prophylaxis is also referred to as maintenance therapy or suppressive therapy.

<sup>b</sup> Duration of therapy for non-CNS disease depends on site and severity of infection and clinical response

**Key to Acronyms:** cART = combination antiretroviral therapy; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous