Cryptococcosis

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Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the cause. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the U.S. Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of people with advanced HIV in some high-resourced countries had disseminated cryptococcosis.[1] In a surveillance study in the late 1990s, people with HIV who developed cryptococcosis were severely immunosuppressed and had barriers to accessing routine HIV medical care.[2] Estimates indicate that every year, approximately 280,000 cases of cryptococcal infection in people with AIDS occur worldwide, and the disease accounts for 15% of AIDS-related deaths.[3] Overall, 90% of cryptococcal cases in people with HIV are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3. The incidence of the disease has declined substantially among people treated effectively with ART.[4]

Clinical Manifestations

In people with HIV, cryptococcosis commonly presents as subacute meningitis or meningoencephalitis with fever, malaise, and headache slowly developing over many weeks, with a median duration of 2 weeks.[1] Classic meningeal symptoms and signs—such as neck stiffness and photophobia—occur in only one-quarter to one-third of people. Some individuals experience encephalopathic symptoms—such as lethargy, altered mentation, personality changes, and memory loss—that are usually a result of increased intracranial pressure (ICP).[5] Among people presenting with cryptococcal meningitis shortly after initiating ART, the symptom onset can be more acute, likely related to an unmasking immune reconstitution inflammatory syndrome (IRIS).[6]

Despite manifesting principally as a central nervous system (CNS) disease, cryptococcosis may involve any bodily organ. In fact, despite widespread disseminated disease, people with HIV may manifest few symptoms. Skin lesions may show different manifestations, including umbilicated skin lesions that mimic those seen with molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and even mimic *Pneumocystis* pneumonia.

Diagnosis

In people with HIV, cryptococcosis is usually disseminated at the time of diagnosis and most commonly presents as subacute meningoencephalitis. Analysis of cerebrospinal fluid (CSF) in initial cases generally demonstrates mildly elevated protein levels, low-to-normal glucose concentrations, and a variable presence of pleocytosis consisting mostly of lymphocytes. Some people with advanced HIV may have very few CSF inflammatory cells. A Gram stain or an India ink preparation, if available, may reveal numerous yeast forms. In patients with HIV and cryptococcal meningitis, the

opening pressure for the CSF may be elevated, with pressures ≥25 cm CSF in 60% to 80% of patients.[7,8]

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In HIV-related cryptococcal meningitis, most blood cultures and CSF cultures will be positive (47% to 70% and 90% to 94%, respectively).[5] Visible *Cryptococcus* colonies on a fungal Sabouraud dextrose agar plate, or even a standard aerobic bacterial culture, generally can be detected within 7 days. *Cryptococcus* may be identified occasionally on a routine Gram stain preparation of CSF as poorly staining Gram-positive yeasts. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. India ink is relatively insensitive early in disease when <1,000 *Cryptococcus* colony-forming units (CFU)/mL are present.[9] In tissue or fluids, yeasts will stain with Grocott methenamine silver stain, and the capsule will stain with mucicarmine or alcian blue stains. Positive cultures are required to prove yeast viability because strains can be stain positive with nonviable yeasts.

Cryptococcus can infect any part of the body, but brain and lungs are frequently target organs. Cultures and/or histopathology are essential for precise diagnosis. However, in many patients with advanced HIV, the presentation is more commonly a meningeal syndrome rather than a pulmonary syndrome.

CSF CrAg is usually positive in people with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and a positive CrAg in blood only.[10] Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown CNS disorder.[10] Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.[11] All positive CrAg tests in patients with HIV require consideration for therapy.

Three methods exist for antigen detection: latex agglutination, enzyme immunoassay (EIA), and lateral flow assay (LFA). The IMMY CrAg LFA (IMMY, Norman, Oklahoma) is the only LFA test for CrAg approved by the U.S. Food and Drug Administration (FDA). It is a useful initial screening tool for diagnosing cryptococcosis in people with HIV when applied to serum or plasma,[9,12] and it also can be used with whole blood or CSF. CrAg testing of serum or plasma may be particularly useful when a lumbar puncture is delayed or refused. In a person with HIV, when serum CrAg LFA titers are ≥1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are ≥1:640, or when there is high clinical suspicion, disseminated and/or CNS involvement should be assumed, regardless of CSF antigen titer results.[13,14] Antigen titers by the LFA are approximately fourfold higher than those with latex agglutination or EIA testing; thus, a titer of 1:640 by LFA is approximately equal to a titer of 1:160 by EIA or latex agglutination. A prozone effect needs to be checked when CrAg with latex agglutination and LFA testing is negative despite observing yeasts in tissues or fluids.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (BioFire Diagnostics, Salt Lake City, Utah) was approved by the FDA. This multiplex PCR tests for 14 targets, including *C. neoformans* and *C. gattii,* and performs well in infections with a moderate-to-high fungal burden.[15-17] False negative results have been noted to occur when there is a low burden of yeasts; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.[15] In one well-described case, a woman who had two negative results with this PCR assay later had a positive result on a CrAg test done by IMMY LFA.[18] Thus, a negative CSF PCR does not completely exclude

cryptococcal meningitis, and CrAg testing of CSF and blood should always be performed simultaneously. The PCR assay appears to have diagnostic utility when a second episode of cryptococcal meningitis is suspected; the test has been noted to differentiate a relapse (PCR positive) from IRIS (PCR negative).[15]

Preventing Exposure

Cryptococcus is ubiquitous in the environment, and people with HIV cannot completely avoid exposure to *C. neoformans* or *C. gattii.* Limited epidemiological evidence suggests that exposure to dried bird droppings, including those from chickens and pet birds, may increase the risk of infection and should be avoided. It is likely that many patients are infected with mixed strains of *Cryptococcus* over a lifetime, and clinical implications remain uncertain.[19,20]

Preventing Disease

The incidence of cryptococcal disease is low among people with HIV in the United States. However, one report indicates that among study participants with HIV in the United States with peripheral blood CD4 counts ≤100 cells/mm^3, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤50 cells/mm^3, the prevalence was 4.3%.[21] Routine surveillance testing for serum CrAg in people with newly diagnosed HIV who have no overt clinical signs of meningitis is recommended for patients whose CD4 counts are ≤200 cells/mm^3 and particularly in those with CD4 counts ≤50 cells/mm^3 **(AII).**[22] All positive tests generally should prompt CSF evaluation for CNS infection, particularly when the serum LFA titer is ≥1:160 **(AII).**[23] See section on Treatment of Asymptomatic Antigenemia.

Prospective controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in people with HIV who have CD4 counts <100 cells/mm.[24,25] However, in the United States, primary prophylaxis in the absence of a positive serum CrAg test is not recommended because of the relative infrequency of cryptococcal disease, lack of clear survival benefit associated with prophylaxis,[26] possibility of drug–drug interactions, potential development of antifungal drug resistance, and cost **(BII).**

Treating Disease

Recommendations for Treating Cryptococcosis
Treating CNS and/or Disseminated Disease
Treatment consists of three phases: induction, consolidation, and maintenance therapy. Induction Therapy (Duration: 2 Weeks, Followed by Consolidation Therapy) • Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days (AII). LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated (AII). *Preferred Regimens* • In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and IV fluid is possible: o Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (AII)

- In resource-limited health care systems, as recommended by the World Health Organization:
  - Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg PO four times a day plus fluconazole 1,200 mg PO daily for 2 weeks (AI)

Alternative Regimens

- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (BII), *or*
- Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week (BI)

Note: The flucytosine dose should be adjusted in renal impairment and ideally use TDM (see Table 6).

Additional Studied Regimens (Duration of Therapy: 2 Weeks)

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day (BI)
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily (BIII)
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily (BI)
- Fluconazole 1,200 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day (BII)

If the patient has not improved clinically or remains clinically unstable, continue or start (liposomal amphotericin B or amphotericin B deoxycholate) plus flucytosine induction therapy until the CSF culture is confirmed to be negative (BIII).

Additional Considerations

- CSF opening pressure should always be measured when an LP is performed. Repeated therapeutic LPs are essential to manage symptomatic increased ICP and have a survival benefit (AII).
- Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS (AI).
- Corticosteroids, acetazolamide, and mannitol are ineffective in reducing ICP and are not recommended (AIII).

Consolidation Therapy (Duration of Therapy: ≥8 Weeks, Followed by Maintenance Therapy)

Perform LP after 1 week and/or 2 weeks of induction therapy to document the culture is negative (AII). After 2 weeks of induction therapy, people who are clinically stable may be switched to consolidation therapy while awaiting culture results. Duration of consolidation therapy should be for at least 8 weeks after receiving CSF culture at 2 weeks is negative (AII).

Preferred Regimen

- Fluconazole 800 mg PO daily (AI)
- For clinically stable patients, continue fluconazole 800 mg until CSF cultures are known to be sterile and ART has been initiated; dose then can be reduced to 400 mg PO daily (AII).
- If CSF remains positive in a clinically stable patient after 2 weeks of induction therapy, use one of the following two options for an additional 2 weeks before reducing the dose to fluconazole 800 mg PO daily:
  - Fluconazole 1,200 mg PO daily plus flucytosine 25 mg/kg PO four times a day for an additional 2 weeks (BIII), or
  - Fluconazole 1,200 mg PO daily for an additional 2 weeks (BIII)

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated (CI)

Maintenance Therapy

Preferred Regimen

- Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy (AI)

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated (CI)
- If susceptibility studies have been performed and the fluconazole MIC is ≥16 μg/mL, the fluconazole dose may be increased to 400 mg daily (BIII).

Criteria for Stopping Maintenance Therapy (BII)

- At least 1 year from initiation of antifungal therapy, *and*
- Patient remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy

- If CD4 count declines to <100 cells/mm^3 (AIII)

Treating Non-CNS Extrapulmonary Disease, Diffuse Pulmonary Disease, or Non-CNS Symptoms With Normal CSF and Serum CrAg Titer **≥1:640** by LFA **(or ≥1:160 by EIA or** Latex Agglutination)

Administer the same treatment as for patients with cryptococcal meningitis to people with the following conditions:

- Non-CNS extrapulmonary disease (BIII)
- Diffuse pulmonary disease (BIII)
- Non-CNS symptoms, normal CSF, and serum CrAg titer ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination) (BII)

Note: All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.

Treating Non-CNS Focal Pulmonary Infiltrates (With Mild Symptoms) and Negative Serum CrAg

- Fluconazole 400 mg daily for 6 to 12 months (duration guided by symptom resolution) (BIII)

Treating Isolated Asymptomatic Cryptococcal Antigenemia (Serum CrAg Titer of LFA <**1:640** [or **<1:160 by** EIA or Latex Agglutination])

- Fluconazole 800–1,200 mg PO daily for 2 weeks, followed by fluconazole 400–800 mg PO daily for 10 weeks, then fluconazole 200 mg PO daily for a total of 6 months plus effective ART (BIII)

Note: Those with lower risk and serum CrAg titer <1:80 by LFA (<1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture (AI). All others should undergo CSF sampling to rule out CNS disease.

Treatment in Pregnancy

Preferred Therapy During First Trimester

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII), *or*
- Lipid formulation amphotericin B 3–4 mg/kg IV daily (AIII)
- Addition of flucytosine should be considered only when the benefits outweigh the risks, with delay until after the first trimester when feasible (AIII).

Notes: Optimal dosing of liposomal amphotericin B in pregnancy is unknown. Use of ideal body weight rather than total body weight may minimize risk of adverse effects to the fetus while maintaining efficacy (BII). In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect, unless benefit is felt to outweigh risk (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrAg = cryptococcal antigen; CSF = cerebrospinal fluid; EIA = enzyme immunoassay; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; MIC = minimum inhibitory concentration; PO = orally; TDM = therapeutic drug monitoring

Treatment of Central Nervous System and/or Disseminated Disease

Treatment of CNS and disseminated disease consists of three phases: induction, consolidation, and maintenance.

Induction Therapy

For induction treatment of cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously (IV), in combination with oral flucytosine, is recommended for 2 weeks in a resource-available health care system **(AII),** and in resource-limited health care systems, a single dose of liposomal amphotericin B (10 mg/kg) is recommended, followed by 2 weeks of flucytosine and fluconazole **(AI).** Historically, amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily had been the preferred formulation of the drug.[27] In resource-available health care systems, however, lipid formulations of amphotericin B have become the standard polyene formulations because they are effective for cryptococcosis and have lower toxicity. A study that compared amphotericin B deoxycholate (0.7 mg/kg daily) and liposomal amphotericin B (AmBisome) at two doses (3 mg/kg daily and 6 mg/kg daily) showed similar outcomes for all three regimens; however, lower nephrotoxicity was observed among those receiving the 3 mg/kg daily liposomal amphotericin B regimen.[28] The noncomparative CLEAR study demonstrated a 58% response rate in people with HIV and cryptococcosis who were treated with amphotericin B lipid complex (Abelcet) at a mean dose of 4.4 mg/kg daily.[29]

Several large clinical trials that used shorter courses of amphotericin B have been reported from Africa.[30,31] A multicenter clinical trial that evaluated two different induction regimens in 721 African adults with HIV found that an initial regimen of 1 week of amphotericin B deoxycholate at 1 mg/kg/day and flucytosine 25 mg/kg four times daily, followed by 1 week of oral fluconazole 1,200 mg/day was non-inferior (95% confidence interval [CI], -12.5 to 5.35 at 10 weeks) to the standard regimen of 2 weeks of amphotericin B deoxycholate 1 mg/kg/day and flucytosine 25 mg/kg four times daily when outcomes at 10 weeks were studied.[30] At 1 year, follow-up of 236 participants from this treatment trial continued to show noninferiority of the 1-week amphotericin B deoxycholate regimen compared with the 2-week regimen.[32]

A phase 3 open-label, randomized, controlled noninferiority trial of single-dose liposomal amphotericin B was conducted at five sites in Africa in 814 patients.[33] Results of this study showed that outcomes of people receiving a single dose of liposomal amphotericin B, 10 mg/kg, combined with 14 days of oral flucytosine, 25 mg/kg four times daily, and oral fluconazole, 1,200 mg/day, were not inferior to a control group that received therapy with amphotericin B deoxycholate, 1 mg/kg/day, and flucytosine, 25 mg/kg four times daily for 7 days, followed by oral fluconazole, 1,200 mg/day for another 7 days.[33] At 10 weeks, deaths were reported in 101 participants (24.8%; 95% CI, 20.7–29.3) in the liposomal amphotericin B group and 117 participants (28.7%; 95% CI, 24.4–33.4) in the control group (difference, −3.9 percentage points); the upper boundary of the one-sided

95% CI was 1.2 percentage points (within the noninferiority margin; P <0.001 for noninferiority). Grade 3 or 4 toxicity was reduced in the single-dose liposomal amphotericin B group compared with the amphotericin B deoxycholate group (50% vs. 62.3%, P <0.001).[33] It is important to note that patients in both groups were monitored closely in a hospital for a minimum of 7 days. Lumbar punctures were performed on Day 7 and Day 14 and daily if ICP was >25 cm of CSF or if the patient demonstrated symptoms and signs consistent with elevated ICP.

Currently, several different treatment regimens for **induction therapy** of cryptococcal meningitis are recommended:

- Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days **(AII).** Lumbar puncture should be performed on Day 7 and Day 14 of treatment to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily lumbar punctures should be performed until the pressure and symptoms are decreased to the normal range **(AII).**

Preferred Regimens

In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and intravenous fluids is possible:

- Liposomal amphotericin B (IV 3–4 mg/kg daily) plus flucytosine (25 mg/kg orally [PO] four times daily) for 2 weeks is the regimen preferred and recommended by the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections Adults and Adolescent With HIV (the Panel) **(AII).**[28,34]

In resource-limited health care settings:

- A single dose of liposomal amphotericin B (IV 10 mg/kg on Day 1) combined with oral flucytosine (25 mg/kg four times daily) and fluconazole (1,200 mg/day) for 2 weeks is the preferred regimen recommended by the World Health Organization **(AI).**[33]

Alternative Regimens

- If amphotericin B lipid complex is the only available lipid amphotericin B formulation available, a dosage of 5 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily should be administered for 2 weeks **(BII).** However, there is much less experience with amphotericin B lipid complex than with the liposomal amphotericin B formulation.
- If amphotericin B deoxycholate is the only available formulation of amphotericin B, this can be used at a dosage of 1 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily for 1 week, followed by fluconazole 1,200 mg/day PO for an additional week **(BI).**[30]

When using flucytosine, therapeutic drug monitoring should be performed, if available, particularly in patients who have renal impairment. Serum peak concentrations of flucytosine should be obtained 2 hours post dose after three to five doses have been administered. Peak serum concentrations should be between 25 mg/L and 100 mg/L.[17] Renal function should be monitored closely and the flucytosine dose adjusted accordingly for those with renal impairment (see Table 6). For those without access to timely flucytosine concentrations, which is a common occurrence, frequent blood counts and renal functions are needed to detect bone marrow toxicity, especially when renal impairment is present.

The addition of flucytosine to the amphotericin B regimen during acute treatment is associated with more rapid sterilization of CSF and survival benefit.[34-36] For instance, a randomized clinical trial of 299 patients showed that the combination of amphotericin B deoxycholate at a dose of 1 mg/kg daily plus flucytosine was associated with improved survival compared to the same dose of amphotericin B without adjunctive flucytosine.[37] Adjunctive fluconazole 800 to 1,200 mg per day plus amphotericin B has been used in the absence of flucytosine, but flucytosine has a survival advantage over fluconazole and is preferred **(BI).**[30] Amphotericin B deoxycholate with flucytosine **(BI)** or with fluconazole at a dose of 800 to 1,200 mg per day **(BI)** or liposomal amphotericin B with fluconazole at a dose of 800 to 1,200 mg per day **(BIII)** may be reasonable alternatives in some circumstances.

Fluconazole, administered at 1,200 mg daily **(CIII)** or with flucytosine **(BII),** is a potential all-oral alternative to amphotericin B regimens.[30,38] Based on studies assessing early fungicidal activity, fluconazole alone (1,200 mg/day) is inferior to amphotericin B for induction therapy.[39,40] Therefore, fluconazole is preferably used with flucytosine. Fluconazole alone is recommended only for patients who cannot tolerate other agents or who do not respond to standard treatment, or when other antifungals are not available.

Consolidation Therapy

A lumbar puncture and repeat CSF culture should be performed after 1 week and/or 2 weeks of induction therapy in all patients **(AII).** After 2 weeks of induction therapy, clinically stable patients may be switched to consolidation therapy while awaiting CSF culture results. Successful induction therapy is defined as substantial clinical improvement and a negative CSF culture from the end-of-induction lumbar puncture. India ink and CSF CrAg may remain positive at Week 2 of therapy and are not indicative of failure. Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and **is not recommended (AII).**[41,42] If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of lumbar opening pressure and CSF culture, should be performed.

Consolidation therapy should be initiated with fluconazole 800 mg daily for at least 8 weeks after receiving a clinically successful 2 weeks of induction therapy **(AII).** The recommendation to use 800 mg rather than 400 mg fluconazole for consolidation therapy is based on several findings. Early clinical trials that used 400 mg fluconazole for consolidation noted breakthrough infection during consolidation.[27] Fluconazole 400 mg per day provides concentrations in the CSF that are only fungistatic, and other studies showed that the early antifungal activity of fluconazole in CSF of people with cryptococcal meningitis increases linearly with increasing doses of the drug.[37,39] A phase 2 trial of treatment with either 400 mg or 800 mg fluconazole found that relapses were more frequent in people receiving 400 mg fluconazole.[43] In clinically stable people, the dose of fluconazole for consolidation therapy should be 800 mg per day until CSF cultures are known to be sterile and ART is initiated, at which point the dose can be decreased to 400 mg per day **(AII).**[44]

For people who have completed first-line recommended or other regimen(s) as 2-week induction therapy but have not improved clinically or remain clinically unstable, continuation or starting of amphotericin B plus flucytosine is recommended until the CSF fungal cultures are confirmed to be negative **(BIII).** For outpatients who are not ill enough to be hospitalized but still have positive CSF cultures after completing 2 weeks of induction therapy, flucytosine can continue to be administered for an additional 2 weeks with fluconazole at a dose of 1,200 mg daily or fluconazole monotherapy can be administered at 1,200 mg daily **(BIII).** A lumbar puncture should be performed after 4 weeks of induction therapy to confirm that the cultures have become negative; if still positive, another 2-

week liposomal amphotericin B plus flucytosine induction course may be considered. For all people with CSF cultures positive at Week 2, the duration of consolidation therapy should be for 8 weeks from the time the CSF cultures are confirmed as negative.[27,35,45]

Itraconazole 200 mg twice per day can be used as an alternative therapy for consolidation if fluconazole is not available or is not tolerated by an individual patient **(CI),** but it is clearly inferior to fluconazole.[45] Limited data are available for use of the newer triazoles—voriconazole, posaconazole, and isavuconazole—for either consolidation or maintenance therapy for patients with cryptococcosis. Most of the reported data have been on the use of these extended-spectrum triazole antifungals for treatment of refractory cases, with success rates of approximately 50%.[46-48] Currently, the role of posaconazole, voriconazole, and isavuconazole in the initial management of cryptococcosis has not been established, and these agents **are not initially recommended** for consolidation or maintenance therapy **(AIII).** Echinocandins have no clinical activity against *Cryptococcus* spp. and **are not recommended** for the clinical management of cryptococcosis **(AII).**

Maintenance Therapy

Fluconazole 200 mg per day is used for maintenance treatment and continued until at least 1 year from initiation of antifungal therapy and assuming there is some immune reconstitution on ART and the patient is asymptomatic at the end of 1 year **(AI)** (see the Preventing Recurrence section below).[49]

Treatment of Non–Central Nervous System Cryptococcosis and Asymptomatic Antigenemia

Non-CNS extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated the same as CNS disease **(BIII).** For those with mild symptoms and only focal pulmonary infiltrates with negative serum CrAg, treatment with fluconazole 400 mg per day for 6 to 12 months combined with effective ART is recommended **(BIII).** Duration of therapy should be guided by symptom resolution.[22]

All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.[13,23,50] If the CSF is normal but the serum CrAg titer is ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination), even in the absence of meningitis, the risk for mortality and/or progression to meningitis increases with fluconazole monotherapy alone, and these patients should be treated the same as patients with cryptococcal meningitis **(BII).**[23]

Whether to sample the CSF to rule out CNS disease in people with isolated, fully asymptomatic cryptococcal antigenemia is dependent on underlying risk, such as advanced immunosuppression and absence of antiretroviral therapy, and the serum CrAg LFA titer. Those at lower risk and with serum CrAg titer <1:80 by LFA (or <1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture, as empiric treatment for meningitis does not improve outcomes **(AI).**[51] All others should undergo CSF sampling to rule out CNS disease. Those with normal CSF, fully asymptomatic cryptococcal antigenemia, and serum CrAg titers <1:640 by LFA (or <1:160 by EIA or latex agglutination) should be treated with fluconazole 800 to 1,200 mg per day for 2 weeks, followed by 400 to 800 mg per day for 10 weeks, followed by 200 mg daily, for a total of 6 months combined with effective ART **(BIII).**[22]

Special Considerations Regarding ART Initiation

Unlike with other opportunistic infections (OIs), ART initiation generally is deferred for 4 to 6 weeks after antifungal agents are started for treatment of CNS cryptococcosis **(AI).** A randomized clinical trial conducted at three sites in Africa compared patients with cryptococcal meningitis who started ART within 1 to 2 weeks (median 9 days) after the diagnosis of meningitis with patients for whom ART was delayed for 4 to 6 weeks (median 36 days) after diagnosis.[52] This clinical trial used amphotericin B deoxycholate 0.7 to 1.0 mg/kg once daily plus fluconazole 800 mg once daily during the induction phase of antifungal treatment. A significantly greater increase in 6-month mortality occurred in the early ART group than in the delayed ART group (45% vs. 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of the study ($P = 0.007$). The difference in mortality between the early ART group and the delayed ART group was even greater among individuals with CSF white cell count <5 cells/μL ($P = 0.008$). The excess deaths in the early ART group may have been attributable to paradoxical IRIS, although the timing and incidence of IRIS reportedly did not differ between the two groups.[53] In a trial conducted in China, 102 participants with cryptococcal meningitis were randomized to start ART within either 2 to 5 weeks or >5 weeks after starting antifungal therapy; the majority received amphotericin with flucytosine induction therapy. The primary analysis did not demonstrate a statistically significant difference in mortality; however, a smaller secondary analysis of 78 patients demonstrated excess risk of death in the early ART group compared with the deferred group within the window of 5 to 10 weeks after initiation of antifungal treatment.[54] It is not clear that the secondary analysis had adequate statistical power for the comparison, making the overall interpretation of this study complicated. In a recently published retrospective observational cohort study of participants enrolled from high-resourced health care systems in Europe and North America, investigators used marginal structural modeling with category censoring, inverse proportional weighting, and adjustment for bias to simulate a randomized trial of earlier versus later initiation of ART.[53] A total of 630 people with HIV were identified with cryptococcal meningitis from more than 30 cohorts between 1994 and 2012. Participants were eligible for the analyses if at meningitis diagnosis they were older than 16 years and had a CD4 count, a viral load measurement and follow-up laboratory test results, study visits, and outcomes data. Among these, 432 (69%) were considered ineligible due to insufficient outcome data (256; 41%) or missing baseline CD4 or HIV viral load (176; 28%). Among the 190 eligible patients, 145 started ART during treatment for cryptococcal meningitis.[55] The primary analysis for the simulated trial compared initiation of ART within 14 days of cryptococcal meningitis diagnosis versus starting ART within 14 to 56 days of diagnosis. There were 13 deaths in the early ART group and 20 deaths in the delayed ART group, with an adjusted hazard ratio (aHR) of 1.40 (0.66–2.95) for early versus later initiation of ART. The authors concluded that there was little evidence that earlier ART was associated with higher mortality. The incidence of IRIS was not reported.[55,56]

The issue of when to start ART in the setting of cryptococcal meningitis remains controversial. The randomized trials, most of which are more than a decade old, were largely done in low- and middle-income countries where access to currently recommended antifungal treatment, monitoring, and support may have been less optimal, and they demonstrated overall mortality rates substantially higher than had been reported in higher resourced settings. While the observational cohort study in higher resourced settings is limited by its observational, retrospective nature and cannot fully address unrecognized biases, it is unlikely that a suitably powered prospective randomized trial can be done in high-resourced settings now, given the precipitous decline in incidence of cryptococcal meningitis in people with HIV treated with more effective antifungal therapy and more effective and better tolerated ART regimens than were available in some of the earlier trials. Therefore, most experts aim to start ART within 4 weeks of antifungal therapy; however, individual patient factors may allow for

earlier or later initiation of ART. In general, ensuring that the patient's CSF cultures are sterile before starting ART will reduce the risk of IRIS.[57] If ART must be started sooner, the patient should be monitored closely for paradoxical IRIS with a low threshold to intervene (see "Monitoring of Response to Therapy and Adverse Events," below).[55] For non-CNS cryptococcosis, for which the risk of symptomatic IRIS appears to be lower, the optimal time to begin ART after antifungal therapy is less clear. However, in patients with non-CNS cryptococcosis, it is prudent to delay initiation of ART for 2 weeks after starting antifungal therapy **(BIII).**

All of the triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. These interactions and recommendations for dosage adjustments, where feasible, are listed in the Drug–Drug Interaction tables in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV.

Monitoring and Management of Response to Therapy and Adverse Events

Elevation of ICP can cause clinical deterioration despite a microbiologic response; complications are more likely to occur if the CSF lumbar opening pressure is ≥25 cm CSF in the lateral decubitus position.[7,27] In a large clinical trial in people with AIDS and cryptococcal meningitis, increased ICP was associated with 92% of deaths during the first 2 weeks of antifungal therapy and 71% of deaths during Weeks 3 to 10.[7] In another clinical trial, people with HIV who received at least one therapeutic lumbar puncture within 7 days after diagnosis (median time of 3 days) had a 69% relative reduction in the risk of death through 11 days, regardless of initial opening pressure.[58] Although it is uncertain which patients with high lumbar opening pressures will experience clinical deterioration, those with symptoms and signs of increased ICP require immediate clinical intervention to reduce ICP.

Control of elevated ICP is critical to reducing acute mortality. Lumbar opening pressure should be measured in all people with cryptococcal meningitis at the time of diagnosis. However, in routine practice, CSF opening pressure frequently is not measured. Among people in whom CSF opening pressure was not measured initially, a repeat lumbar puncture should be performed with measurement of opening pressure. For people with ongoing headaches, a repeat lumbar puncture should be performed with urgency, and among those without headaches, a repeat lumber puncture should be considered strongly within 48 hours of the initial procedure.[58] Measures to decrease ICP should be used for all people with cryptococcal meningitis who have confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs indicative of increased ICP. Drainage of CSF via lumbar puncture is recommended for initial management **(AII).** One approach is to remove a volume of CSF that reduces the opening pressure by at least 50% or normalizes the pressure to <20 cm CSF.[58,59] In the absence of a manometer, removal of 20 to 25 mL of CSF is recommended **(AIII).** Among patients with ongoing symptoms, therapeutic lumbar punctures should be repeated at least daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm CSF **(AII).** Because a survival benefit is associated with therapeutic lumbar puncture regardless of baseline CSF opening pressure, strong consideration should be given to repeating a therapeutic lumbar puncture within 72 hours of the initial procedure in those who are relatively asymptomatic or who had a baseline CSF opening pressure of <25 cm CSF, because ICP can be a dynamic process that changes over time **(BII).**[58] If the initial opening pressure was not measured, a second lumbar puncture is recommended **(AII).**

CSF shunting through a lumbar drain or ventriculostomy should be considered for people who cannot tolerate repeated lumbar punctures or for those in whom signs and symptoms of increased ICP persist

after multiple lumbar punctures **(BIII).** Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (AIII).** Acetazolamide **should not be used** as therapy for increased ICP management because it may exacerbate hyperchloremic acidosis from amphotericin B and does not result in a meaningful decrease in ICP **(AI).**[60] A randomized study that compared a 6-week course of a tapering dose of dexamethasone with placebo among 451 Asian and African patients with cryptococcal meningitis found that dexamethasone did not improve survival through 10 weeks, was noted to not be as effective at killing of *Cryptococcus,* and was associated with more adverse events.[61] These data support the recommendation that **corticosteroids should not be used** during induction therapy for ICP control for HIV-associated cryptococcal meningitis unless they are being used for treatment of IRIS **(AI).**

People treated with amphotericin B formulations should be monitored for nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1,000 mL of normal saline reduces the risk of nephrotoxicity during amphotericin B treatment. For people with severe infusion-related adverse reactions, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered 30 minutes before the infusion to reduce the severity of amphotericin B infusion reactions **(CIII);** meperidine (25–50 mg titrated during infusion) is effective for treating amphotericin B–associated rigors and should be given before each dose daily and after the first incidence of rigors to prevent future rigors **(BII).** Routine use of potassium chloride (40 mEq per day) and magnesium (8 mEq per day) supplementation should be considered because the risk of hypokalemia and hypomagnesemia becomes near universal after 1 week of therapy, regardless of the amphotericin B formulation used **(AII).**[62]

Flucytosine is associated with concentration-dependent bone marrow toxicity. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities. In people receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine concentrations. Peak serum flucytosine concentrations should be obtained 2 hours after an oral dose; the therapeutic range is between 25 and 100 mg/L. If therapeutic drug monitoring is not possible or kidney dysfunction is not present, frequent complete blood counts with differential (i.e., at least biweekly) can be used to detect cytopenias **(BII).**[30]

Common side effects of higher dose fluconazole therapy can include dry skin (17% of patients) and alopecia (16% of patients).[63] Increased liver transaminases or alkaline phosphatase are relatively rare in fluconazole dosages of 400 to 800 mg, with only 1 to 2% of patients having values >5 times the upper limit of normal.[52] For people who have difficulty tolerating higher fluconazole doses, the consolidation therapy fluconazole dose can be reduced to 400 mg per day after ART initiation. **(BII).**[44]

Immune Reconstitution Inflammatory Syndrome

An estimated 10 to 30% of people with HIV who have cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART and both unmasking (before start of antifungal therapy) or paradoxical (after start of antifungal therapy) IRIS may occur.[64,65] People with HIV who have cryptococcal IRIS are more likely to be ART naive and those whose CSF has less inflammation on presentation seem to be at higher risk of cryptococcal IRIS.[66] The risk of IRIS can be minimized by achieving CSF culture sterility before starting ART, using fluconazole 800 mg per day as consolidation therapy, and deferring ART initiation for 4 to 6 weeks from the start of antifungal therapy **(AII).**[52,67] Distinguishing paradoxical IRIS from treatment failure with culture-positive relapse is difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite

microbiological evidence of effective antifungal therapy with sterile CSF cultures,[66,68] whereas treatment failure is associated with continued positive cultures. The primary microbiological criterion for treatment failure is a CSF culture that yields *Cryptococcus*, not the visual appearance of yeasts during treatment; the culture may take days to weeks to become positive. A negative PCR test (e.g., BioFire FilmArray Meningitis/Encephalitis Panel) has a high predictive value for sterile CSF cultures and can be diagnostically useful for distinguishing paradoxical IRIS with a negative CSF PCR from culture-positive relapse with a positive CSF PCR.[15]

The appropriate management strategy for IRIS **is to continue both ART and antifungal therapy** and reduce elevated ICP if present **(AII).** While diagnostic tests are pending, escalating antifungal therapy (i.e., restarting amphotericin B therapy or increasing the fluconazole dose to 1,200 mg per day) is recommended **(BIII).** In people with severe symptoms of IRIS, some experts recommend a brief course of tapering doses of corticosteroids. Dosages have varied but commonly start at 1.0 mg/kg per day of prednisone; precise data-driven management strategies have not been developed. Serum C–reactive protein (CRP) is generally elevated at the time IRIS develops;[69] CRP will decrease with corticosteroid therapy if IRIS is present and can be used to empirically monitor IRIS resolution. Once clinical improvement is evident, it is recommended that fluconazole at consolidation therapy doses should be continued or restarted upon hospital discharge **(BIII).**

The risk of IRIS appears to be much lower and the syndrome seems to be less severe with other forms of cryptococcosis—such as lymphadenitis, cutaneous abscesses, and bony lesions—than with cryptococcal meningitis.[70] Management of IRIS with other forms of cryptococcosis is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII),** and only considering the use of corticosteroids if clinical symptoms are severe **(CIII).**

Managing Treatment Failure

Treatment failure is defined as (1) a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy that has included management of increased ICP, or (2) relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Primary fluconazole resistance in *Cryptococcus* isolates has been reported in the United States but is uncommon.[71] Therefore, susceptibility testing is not recommended routinely for initial management of cryptococcosis. However, if treatment failure or relapse occurs, *Cryptococcus* isolates should undergo antifungal susceptibility testing. Robust clinical data are lacking, but strains of *Cryptococcus* with fluconazole minimum inhibitory concentrations (MIC) ≥16 µg/mL are considered not fully susceptible.[72,73]

Optimal therapy for patients with treatment failure has not been established. If treatment failure occurs after induction with alternative regimens, preferred regimens should be started. Furthermore, those initially treated with an amphotericin B formulation should remain on this agent until clinical response occurs. In this setting, liposomal amphotericin B (3–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than the deoxycholate formulation[28,74,75] and should be considered when initial treatment with other regimens fails **(AII).**

In the setting of treatment failure or relapse, verifying CSF culture sterility at the completion of re-induction therapy is critical **(AIII).** After CSF sterility is achieved, outpatient consolidation therapy should consist of fluconazole at a higher dose of 1,200 mg per day and optimization of ART. For *Cryptococcus* with decreased azole-susceptibility (i.e., ≥16 µg/mL MIC for fluconazole), adjunctive

weekly amphotericin B administration during consolidation therapy may be considered **(BIII).**[73] Higher doses of fluconazole (i.e., 1,200 mg per day) in combination with flucytosine 25 mg/kg four times per day also may be considered **(BI).** The newer triazoles—posaconazole, voriconazole, and isavuconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy,[46-48] but they offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates only high-level fluconazole resistance. Most clinical failures are not due to antifungal drug resistance but rather result from inadequate induction therapy, nonadherence, drug-drug interactions that decrease the serum concentrations of fluconazole (e.g., with rifampin), or the development of paradoxical IRIS. Failures also may occur with high fungal burden disease and/or severe immunosuppression of host.

Preventing Recurrence

When to Start Maintenance Therapy

People who have completed 10 weeks of induction and consolidation therapy for cryptococcal meningitis or disseminated cryptococcosis should be treated with chronic maintenance or suppressive therapy with fluconazole 200 mg per day for at least 1 year **(AI).** Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease and should generally not be considered **(CI).**[45 73] For people in whom susceptibility studies have been performed and the fluconazole MIC is ≥16 µg/mL, the fluconazole dose may be increased to 400 mg per day **(BIII).** Failure to administer this secondary prophylaxis for an entire year is the most common reason for subsequent relapse of cryptococcal disease.[76]

When to Stop Maintenance Therapy

Data evaluating relapse after successful antifungal therapy for cryptococcosis and discontinuation of maintenance therapy while on ART are limited. In a European study, recurrences of cryptococcosis were not found among 39 participants on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 count was 297 cells/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[77] A prospective randomized study of 60 people in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after reaching a CD4 count >100 cells/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[78] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated OIs, it is reasonable to discontinue maintenance therapy after at least 1 year from initiation of antifungal therapy in people whose CD4 counts are ≥100 cells/mm^3 with undetectable viral loads on ART **(BII).**[79] Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm^3 **(AIII).**

Special Considerations During Pregnancy

During pregnancy, the diagnosis of cryptococcal infections is the same as for other people with HIV. Treatment should be initiated promptly after a diagnosis is confirmed, with attention to management of increased ICP. During the postpartum period, anti-inflammatory responses in pregnancy (enhancement of Th2 and suppression of Th1 cytokines) are reversed and may lead to overt clinical manifestations of a previously asymptomatic cryptococcal infection resembling IRIS.[80-82] Close collaboration between obstetric and infectious disease experts is recommended. For most patients with cryptococcal infection, experts recommend deferring ART initiation for 4 to 6 weeks after

antifungal agents are started to reduce the risk of IRIS; in pregnancy, however, starting ART as expeditiously as possible is associated with lower risk of perinatal transmission of HIV. For CNS cryptococcal infection during pregnancy, decisions about the timing of ART initiation should be made in consultation with the patient, the infectious diseases consultant, and the obstetrician. If ART is started sooner than generally recommended, close monitoring for IRIS should be implemented with a low threshold for treatment for IRIS. During pregnancy, the risk of IRIS associated with non-CNS cryptococcosis appears to be lower, and a delay in ART initiation of no longer than 2 weeks after starting antifungal therapy is recommended.

Extensive clinical experience with amphotericin B deoxycholate has not been associated with teratogenicity, and this remains a preferred therapy for cryptococcosis in the first trimester of pregnancy **(AIII).** Although there is less experience in pregnancy with lipid formulations of amphotericin B, these products have been associated with less nephrotoxicity and electrolyte abnormalities than amphotericin B deoxycholate and are an alternative as a preferred therapy for the initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis during pregnancy **(AIII).** Optimal dosing of liposomal amphotericin B in pregnancy is unknown. A recent review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy **(BII).**[83] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[84]

During pregnancy, flucytosine use should be considered only when the benefits outweigh the risks to the mother and fetus and should be delayed until after the first trimester when feasible **(AIII).** In animal studies, flucytosine is teratogenic and may be associated with cleft palate and other bone abnormalities. Flucytosine use in pregnancy is limited to case reports and small series, although normal outcomes have been described.[85-87]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit outweighs the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. Congenital malformations similar to those observed in animals exposed to the drug—including craniofacial and limb abnormalities—have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg per day throughout or beyond the first trimester of pregnancy.[88] Furthermore, animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole, resulting in increased risk of craniofacial defects.[89]

Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short-term exposure. A recent meta-analysis describing birth defects in infants exposed to fluconazole during the first trimester evaluated nine cohort, case-control or randomized controlled studies, including 53,407 pregnancies with fluconazole exposure and 3,319,353 without fluconazole exposure.[90] Maternal exposure to fluconazole was correlated with an increased prevalence of heart defects in infants for both low dose (≤150 mg) (odds ratio [OR] 1.95; 95% CI, 1.18–3.21; $P = 0.01$) or any dose (OR 1.79; 95% CI, 1.18–2.71; $P = 0.01$). No association was found between either low- or high-dose fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects.[91] One registry-based cohort study[92] of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot, and a large population-based case-control study[93] specifically noted an increase in transposition of the great arteries (OR 7.56, 95% CI, 1.22–35.45). The latter study also suggested an increase in cleft lip with cleft palate (OR 5.53; 95% CI, 1.68–18.24). In three nested case-control studies using data from the Quebec Prescription Drug

Insurance database, there was an increased prevalence of cardiac septal closure anomalies for maternal fluconazole doses greater than 150 mg during pregnancy (OR 1.81; 95% CI, 1.04–3.14).[94] A recent population-based cohort study (included in the meta-analysis) of 1,969,954 pregnancies, including 37,650 pregnancies exposed to fluconazole, found an increased risk of musculoskeletal malformations following exposure to fluconazole during the first trimester of pregnancy (risk of 52.1 per 10,000 pregnancies exposed to fluconazole versus 37.3 per 10,000 pregnancies exposed to topical azoles).[95]

A nationwide cohort study in Denmark[96] found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561, HR, 1.48; 95% CI, 1.23–1.77) or those with topical azole exposure only (n = 5,646, HR 1.62; 95% CI, 1.26–2.07). Similarly, the nested case-control studies in Canada (n = 320, 868 pregnancies) found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies, and that risk was greater with higher dose of fluconazole exposure (adjusted odds ratio [aOR] with ≤150 mg 2.23, 95% CI, 1.96–2.54; aOR with >150 mg 3.20; 95% CI, 2.73–3.75).[94] However, a cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[97] The meta-analysis noted above also found no association between fluconazole exposure and risk of abortion or stillbirth.[90] Most of the studies regarding effects of fluconazole during pregnancy have involved low doses of the drug and short-term exposure.

On the basis of reported birth defects, the use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks **(CIII).** Amphotericin B should be continued throughout the first trimester if possible **(AIII).** After the first trimester, switching to oral fluconazole may be considered if appropriate clinically for consolidation or maintenance therapy **(CIII).**

Although there have been case reports of birth defects in infants exposed to itraconazole, a recent systematic review and meta-analysis of four cohort studies involving 971,450 pregnant women with 1,311 exposures, found no significant difference in the overall risk of birth defects between those with maternal exposure to itraconazole and those not exposed.[98] While limb and congenital heart defects were the most common defects seen, they were within the rates of the defects published by EUROCAT (the European network of population-based registries for epidemiological surveillance of congenital anomalies). However, the rate of eye defects was higher than that published by EUROCAT. There was no difference in the rates of spontaneous abortion or stillbirth from itraconazole exposure.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animals; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(CIII).**

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