Coccidioidomycosis

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Epidemiology

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

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

Clinical Manifestations

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

Focal pneumonia is most common in people with CD4 counts ≥250 cells/mm^3. Focal pneumonia can be difficult to distinguish from bacterial or viral community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] However, symptoms such as hilar or mediastinal adenopathy, upper lobe infiltrates, nodules, peripheral blood eosinophilia, or rash—all of which are uncommon in bacterial pneumonia—may point towards coccidioidomycosis, particularly in patients who reside in, previously resided in, or have traveled to a known endemic area.

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

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

Elevated coccidioidal antibody titers even without symptoms can indicate risk of subsequent symptomatic diseases in people with HIV and advanced immunosuppression when CD4 count decreases to 10 cells/mm^3 or less.[10]

Diagnosis

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

Unlike other endemic fungi, *Coccidioides* species grow relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a nonpigmented mold may be observed in as few as 3 to 7 days. *Coccidioides* growth on an agar plate is a significant laboratory biosafety hazard because of the risk of inhalation of dislodged arthroconidia. When a specimen is sent for culture, laboratory personnel should be alerted to the possibility of suspected coccidioidomycosis; in the laboratory, the culture plate lid should be kept secured with tape.[11] Identification of the fungus should be performed only in a biosafety level 3 or 2+ containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test and a compatible clinical syndrome. However, it may take several weeks for antibodies to develop in normal hosts and probably longer in immunocompromised hosts. Negative serology cannot be used to rule out disease, and therefore, tissue biopsy may be necessary. Repeat testing every 1 to 2 weeks should be considered if the patient is ill and the diagnosis has not been established.

On the other hand, patients with past coccidioidal infection and without disease activity usually revert to negative serological tests over 1 to 2 years. Thus, screening with an enzyme immunoassay (EIA) for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody is recommended to detect the possibility of active disease. The EIA has a rapid turnaround time and is available in many clinical laboratories. These tests are very sensitive but occasionally have been associated with false positive results, particularly for IgM.[12] If either EIA test is positive, antibody assays by immunodiffusion (ID) and by complement fixation (CF) should be obtained to confirm the result and be used for further follow-up **(AI).** In cases of EIA positivity with negative ID, the clinical context needs to be carefully considered, as well as the value of further diagnostic workup. CF has been particularly useful in cerebrospinal fluid. A lateral flow assay has become available, but it is far less sensitive than EIA.[13]

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[14] serum,[15] and other body fluids, such as CSF,[16,17] in samples from individuals with active coccidioidomycosis.[18] The assay is most useful in diagnosing disseminated coccidioidomycosis. Detection of coccidioidal antigen in CSF has been reported to have a very high sensitivity and specificity for diagnosing coccidioidal meningitis, but assessing therapeutic responses with this method is more difficult.[19]

In addition, real-time polymerase chain reaction (RT-PCR) testing, if available, can be used on unfixed clinical specimens and on formalin-fixed tissue to aid in the diagnosis of

coccidioidomycosis. A *Coccidioides* RT-PCR assay is commercially available, but it has neither been U.S. Food and Drug Administration–approved nor tested in people with HIV.[20]

Preventing Exposure

People with HIV living in or visiting areas in which *Coccidioides* spp. are endemic cannot avoid exposure to the fungus. They should, however, avoid extensive exposure to disturbed native soil, such as at building excavation sites, without wearing proper N95 masks. Furthermore, in endemic areas, they should stay inside during dust storms **(BIII),** although the exact risk remains controversial.[21-23] However, no evidence indicates that gardening in cultivated soil in a coccidioidal endemic region increases the risk of acquiring coccidioidomycosis.

Preventing Disease

Preventing Coccidioidomycosis
Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas (BIII). Primary antifungal prophylaxis or pre-emptive therapy is not recommended for individuals with HIV and low CD4 counts who live in endemic areas and who have negative serologic tests for *Coccidioides* (AIII). Indications for Primary Prophylaxis/Pre-Emptive Therapy (AIII): • Previously tested negative and with a new positive IgM or IgG test for *Coccidioides*, *and* • No signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis, *and* • CD4 count <250 cells/mm^3 Preferred Therapy • Fluconazole 400 mg PO once daily (AIII) Discontinuation of Primary Prophylaxis/Pre-Emptive Therapy • CD4 count ≥250 cells/mm^3 with virologic suppression on ART (BIII)

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IgG = immunoglobulin G; IgM = immunoglobulin M; PO = orally

Primary antifungal prophylaxis (i.e., prophylaxis for individuals with negative results on serological tests for *Coccidioides*) does not appear to benefit people with HIV who have low CD4 counts and live in regions in which *Coccidioides* spp. are endemic,[5] and it **is not recommended (AIII).** Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas **(BIII).** Testing is advised also for individuals who have previously traveled to or lived in endemic areas. Both IgM and IgG antibody testing using either an EIA or ID technique are recommended **(BIII).** In people who have CD4 counts <250 cells/mm^3 and who previously tested negative for *Coccidioides*, a new positive serological test suggests possible active disease[10] and should prompt further clinical evaluation. If no signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis are identified, pre-emptive antifungal therapy with fluconazole 400 mg daily is recommended without definitive trials for those with a new positive serological test and CD4 counts <250 cells/mm^3 **(AIII).** This regimen should be continued until the CD4 count is ≥250 cells/mm^3 and virologic suppression is documented **(BIII).** For those with CD4 counts already ≥250 cells/mm^3 and with viral suppression on

antiretrovirals (ARVs), close clinical follow-up without antifungal therapy is recommended **(BIII).** For asymptomatic patients who have not lived in or traveled to endemic regions, routine testing does not appear useful and **should not be performed (AIII).**

Treating Disease

Treating Coccidioidomycosis

Mild-to-Moderate Pulmonary Infections

Indications for Treatment

- Clinically mild infection, such as focal pneumonia

Preferred Therapy

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

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

- Voriconazole loading dose of 400 mg PO twice daily on Day 1, followed by 200 mg PO twice daily (BIII), *or*
- Posaconazole delayed-release tablet 300 mg PO twice daily on Day 1, followed by 300 mg once daily (BIII), *or*
- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily (BIII)

Severe Pulmonary or Extrapulmonary Infection (Except Meningitis)

Preferred Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII), *or*
- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), particularly for those with underlying renal dysfunction

Use until clinical improvement, then switch to triazole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) (BIII).

Alternative Therapy

- Some specialists recommend combining amphotericin B deoxycholate or lipid formulation amphotericin B (see above dosing) with a triazole (fluconazole or itraconazole 400 mg daily) as initial therapy and continue the triazole once amphotericin B is stopped (CIII).

Meningeal Infections (Consultation With a Specialist Is Advised [AIII])

Preferred Therapy

- Fluconazole 800–1,200 mg PO once daily (AII)

Alternative Therapy

- Itraconazole 200 mg PO two to three times daily (BII), *or*
- Voriconazole 200–400 mg PO twice daily (BIII), *or*
- Posaconazole delayed-release tablet 300 mg PO twice on Day 1, followed by 300 mg PO once daily (CIII), *or*
- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily (CIII), *or*

- Intrathecal amphotericin B deoxycholate (AIII) when triazole antifungals are not effective. Use in consultation with a specialist and ensure administration by a clinician experienced in this drug delivery technique.

Treatment in Pregnancy

Preferred Therapy During the First Trimester

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII)
- Note: In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect unless benefit is thought to outweigh risk (BIII).
- After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered (AIII).

Discontinuing Therapy

Focal Coccidioidal Pneumonia (AII)

- Discontinuation can be considered after the following:
  - Clinical response to 3–6 months of antifungal therapy, *and*
  - CD4 count ≥250 cells/mm^3, *and*
  - Virologic suppression on ART, *and*
- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis

- Relapse can occur in 25% to 33% of people without HIV and in people with HIV who have CD4 count ≥250 cells/mm^3.
- Discontinuation may be considered after ≥12 months of therapy based on clinical and serological response, and the decision should be made in consultation with experts (BIII).
- For diffuse pulmonary disease, continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Coccidioidal Meningitis

- Relapse has been reported in 80% of patients after stopping triazoles; suppressive therapy at treatment doses should be lifelong. Discontinuation of therapy is not recommended (AII).

Other Considerations

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy. Use of corticosteroids is not recommended.
- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines list these interactions and recommend dosage adjustments where feasible.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; CSF = cerebrospinal fluid; DDI = drug–drug interaction; IV = intravenous; PO = orally

Treatment of mild-to-moderate pulmonary coccidioidal infection: Therapy with an oral triazole antifungal agent is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII).** Fluconazole should be given as 400 mg daily **(AII);** itraconazole should be given in divided doses of 200 mg three times daily for 3 days, followed by 200 mg twice daily **(AII).**[24,25]

Itraconazole is preferred for those who have bone or joint disease **(AI).**[26] Serum itraconazole concentrations should be measured after the drug reaches steady state at 2 weeks to ensure adequate absorption. Target random serum concentrations (the sum of the parent itraconazole and hydroxyl itraconazole metabolite levels), measured by high-performance liquid chromatography, should be between 1.0 to 2.0 μg/mL.[27]

Data to support clinical efficacy for treatment with posaconazole,[28,29] voriconazole,[30] or isavuconazole[31] are limited, but these agents are recommended for patients who do not respond to fluconazole or itraconazole **(BIII).** Voriconazole is given as a loading dose of 400 mg twice on Day 1, followed thereafter by 200 mg twice daily. Trough serum voriconazole concentrations should be measured to ensure efficacy and avoid toxicity; a concentration of 1 to 5 μg/mL is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used,[29] but the current delayed-release tablet formulation of posaconazole at a dosage of 300 mg twice on the first day and then 300 mg once daily is better tolerated by people and provides more reliable serum concentrations and is therefore recommended **(BIII).** A syndrome of mineralocorticoid excess manifesting as hypertension with hypokalemia was reported in some patients taking posaconazole.[32] Monitoring of blood pressure and serum potassium levels is appropriate in patients taking posaconazole.

Data supporting isavuconazole treatment in people with HIV are limited; however, in a cohort of 82 patients that included three people with HIV and CD4 ≥200 cells/mm^3, improvement occurred in 70% of patients.[31] Isavuconazole is given as isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) every 8 hours for six doses then isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) once daily. Target serum isavuconazole levels are not always measured, but concentrations of 1 to 4.6 μg/mL are preferred, with adverse events increasingly common in concentrations exceeding 4.6 μg/mL.[33]

All triazole antifungals have the potential for complex and possibly bidirectional interactions with certain ARV agents and other anti-infective agents. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines and Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections list such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Treatment of severe pulmonary coccidioidal infection or extrapulmonary infection:
Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or who are severely ill with extrathoracic disseminated disease **(AII).**[25] Most experience has been with the deoxycholate formulation using a dose of amphotericin B of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are only retrospective reports from studies that used lipid formulations of amphotericin B for the treatment of coccidioidomycosis.[34] Lipid formulations are likely to be as effective as the deoxycholate formulation and should be favored initial therapy, particularly in patients with underlying renal dysfunction **(AIII).** For lipid formulations, a daily dose of amphotericin B of 3 to 5 mg/kg IV is appropriate. Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII).**

Some specialists recommend combining amphotericin B with a triazole antifungal (400 mg of fluconazole or itraconazole daily) at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII).**[25] No experience has been reported with single-dose liposomal amphotericin at 10 mg/kg combined with azoles as used in cryptococcosis.[35]

Treatment of patients with coccidioidal meningitis: Treatment of coccidioidal meningitis requires consultation with a specialist in the treatment of coccidioidal meningitis **(AIII).**[36] Intravenous amphotericin B alone is ineffective as treatment for coccidioidal meningitis. Treatment with a triazole antifungal is recommended instead with the early addition of the polyene. Fluconazole (800 to 1,200 mg daily) is the preferred regimen **(AII),**[24,37] but itraconazole 400 to 600 mg daily also has been successfully used **(BII).**[38] Therapy with voriconazole **(BIII),**[39-41] posaconazole **(CIII),**[29,42] and isavuconazole **(CIII)**[43] has been limited and described in individual case reports but has been successful and is generally used with expert opinions. Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B deoxycholate is recommended **(AIII).**[44] When required, intrathecal therapy should be administered by someone very experienced in this drug delivery technique.

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

Monitoring the CF antibody titer is useful to assess response to therapy, which should be measured every 12 weeks. More than a twofold rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. Immune reconstitution inflammatory syndrome (IRIS) has been reported infrequently in people with HIV and coccidioidomycosis.[45-47] In general, delaying initiation of ART while treating coccidioidomycosis **may not be necessary (BIII).** However, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm^3) with disseminated disease, clinical decline may occur with initiation of ART.[48] It might be prudent to delay ART for 4 to 6 weeks after initiating antifungal therapy in severely immunosuppressed patients who have disseminated or central nervous system (CNS) disease **(CIII).** On the other hand, ART delay may not always prevent IRIS, as reported in at least one patient with disseminated disease and who received treatment with fluconazole for 28 days but still had worsening symptoms within a week after starting ART.[49] Thus, close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed people who have HIV and disseminated coccidioidomycosis.

Managing Treatment Failure

Therapeutic random itraconazole concentrations of 1.0 μg/mL to 2.0 μg/mL should be the goal in patients with severe coccidioidomycosis who do not respond to treatment with itraconazole. In the case of confirmed treatment failure with adequate serum concentrations of the azole, treatment should be changed to IV amphotericin B, either deoxycholate or a lipid formulation for patients who are severely ill **(AIII).** For those who are not severely ill, posaconazole **(BIII),** voriconazole **(BIII),** or isavuconazole **(BIII)** are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir- or cobicistat-boosted regimens (see the Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines). Posaconazole and voriconazole have known drug–drug interactions with ARVs.[50] In certain situations, surgical intervention may be indicated and is a bedside decision.[24]

Therapy After Immune Reconstitution

People with HIV and peripheral blood CD4 counts ≥250 cells/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[51] Moreover, a prospective study has demonstrated that coccidioidomycosis is less severe in those with lower HIV RNA and higher CD4 counts.[3] Given these facts, in people with HIV who have undetectable HIV RNA on potent ART and

who have CD4 count ≥250 cells/mm^3, coccidioidomycosis should be managed no differently than it is in patients in the general population **(AII).**

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

Preventing Relapse

Relapse of coccidioidomycosis occurs in 25% to 33% of individuals without HIV who have diffuse pulmonary coccidioidomycosis or non-meningeal disseminated coccidioidomycosis[52,53] and may occur in people with HIV who have CD4 counts ≥250 cells/mm^3 and are virologically suppressed on ARVs.[1,54] Patients with diffuse or focal coccidioidal pneumonia should have serial chest radiographs and coccidioidal serology tests every 3 to 6 months during coccidioidomycosis therapy and for 2 to 3 years after therapy discontinuation **(BIII).** Relapses have been reported in ≥80% of patients with meningitis in whom triazoles have been discontinued.[55] Therefore, therapy for coccidioidal meningitis with treatment doses of the azole should be continued for life even in those with immune reconstitution **(AII).**

Special Considerations During Pregnancy

During pregnancy, coccidioidomycosis should be considered in the differential diagnosis of a consistent clinical presentation and the presence of epidemiological risk such as living in an endemic region or having an appropriate travel history. Reactivation during pregnancy in individuals with prior coccidioidomycosis but without active disease is uncommon, though the risk may be somewhat higher with a history of disseminated coccidioidomycosis.[56] When coccidioidomycosis is acquired later in pregnancy (e.g., during the second or third trimester) the infection is more likely to be more severe and potentially disseminated, with the greatest severity occurring during the immediate postpartum period.[56] There is no evidence that maternal coccidioidomycosis increases risk for pregnancy loss or premature delivery. Perinatal infection is uncommon and most likely acquired during delivery.[56]

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII).** Extensive clinical use of amphotericin B has not been associated with teratogenicity. There remain significant gaps in determining optimal dosing regimens in pregnancy; 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.[57] 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.[58]

For coccidioidal meningitis in the first trimester, for which the only alternative treatment to triazole antifungals is intrathecal amphotericin B, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the patient, the infectious diseases consultant, and the obstetrician.[56]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit is felt to outweigh the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered **(AIII).**[24] Congenital malformations, including craniofacial and limb abnormalities similar to those observed in animals exposed to fluconazole, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[56,59] Furthermore animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole resulting in increased risk of craniofacial defects.[60]

Most studies on the effects of fluconazole in pregnancy have involved low doses and short-term exposure. A meta-analysis of literature 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.[61] Maternal fluconazole use was correlated with an increased prevalence of heart defects in infants for both a low dose (≤150 mg) (odds ratio [OR] 1.95; 95% confidence interval [CI], 1.18–3.21; *P*=0.01) and any dose (OR 1.79; 95% CI, 1.18–2.71; *P*=0.01). No association was found between fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects at either low- or high-dose exposure to fluconazole. One registry-based cohort study of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot,[62] and a large population-based case-control study specifically noted an increase in transposition of the great arteries (OR 7.56; 95% CI, 1.22–35.45).[63] 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).[64] 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).[65]

A systematic review and meta-analysis of 6 cohort or case-control studies that analyzed more than 16,000 exposures and reported fetal outcomes after exposure to fluconazole used in the first trimester of pregnancy found a marginal association with increased risk of congenital malformations (OR 1.09; 95% CI, 0.99–1.2, *P* = 0.088), including heart defects, as well as spontaneous abortion; exposure to more than 150 mg was associated with an overall increase in congenital malformations.[61]

A nationwide cohort study in Denmark found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561; hazard ratio [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).[66] 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 OR for ≤150 mg fluconazole 2.23; 95% CI, 1.96–2.54; adjusted OR for >150 mg fluconazole 3.20; 95% CI, 2.73–3.75).[64] 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.[67] The meta-analysis noted above also found no association between fluconazole exposure and risk of

abortion or stillbirth. 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.

Although case reports of birth defects in infants exposed to itraconazole have occurred, 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 non-exposure.[68] Although limb and congenital heart defects were the most common defects seen, they were within the rates of these 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. No difference was found in rates of in spontaneous abortion or stillbirth based on itraconazole exposure. In sum, itraconazole should be used in pregnancy depending on a cost-benefit analysis.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animal studies; 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 **(AIII).**

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