TABLE 236-1 RECOMMENDATIONS FOR THE TREATMENT OF HISTOPLASMOSIS

Type of Histoplasmosis	Treatment Recommendations	Comments
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Patients with mild cases usually recover without therapy, but itraconazole should be considered if the patient's condition has not improved after 1 month.
Chronic/cavitary pulmonary	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until cerebrospinal fluid or CT abnormalities clear.

Abbreviation: AmB, amphotericin B.

patients with acute pulmonary histoplasmosis causing diffuse infiltrates, especially with hypoxemia. In most cases of pulmonary histoplasmosis, treatment is not recommended because the degree of exposure is not heavy; the infection is asymptomatic or symptoms are mild, subacute, and not progressive; and the illness resolves without therapy.

The preferred treatments for histoplasmosis include the lipid formulations of amphotericin B (AmB) in more severe cases and itraconazole in others. Liposomal AmB has been more effective than the deoxycholate formulation for treatment of PDH in patients with AIDS. The deoxycholate formulation is an alternative to lipid formulations for patients at low risk for nephrotoxicity. Posaconazole, voriconazole, and fluconazole are alternatives for patients who cannot take itraconazole.

In severe cases requiring hospitalization, a lipid formulation of AmB is followed by itraconazole. In patients with meningitis, a lipid formulation of AmB should be given for 4–6 weeks before the switch to itraconazole. In immunosuppressed patients, the degree of immunosuppression should be reduced if possible, although immune reconstitution inflammatory syndrome (IRIS) may ensue. Antiretroviral treatment improves the outcome of PDH in patients with AIDS and is recommended; however, whether antiretroviral treatment should be delayed to avoid IRIS is unknown.

Blood levels of itraconazole should be monitored to ensure adequate drug exposure, with target concentrations of the parent drug and its hydroxy metabolites of 1–5 μg/mL as measured by high-performance liquid chromatography and 2–10 μg/mL as measured by microbiologic assay. Drug interactions should be carefully assessed: itraconazole not only is cleared by cytochrome P450 metabolism but also inhibits cytochrome P450. This profile causes interactions with many other medications.

The duration of treatment for acute pulmonary histoplasmosis is 6–12 weeks, while that for PDH and chronic pulmonary histoplasmosis is ≥1 year. Antigen levels in urine and serum should be monitored during and for at least 1 year after therapy for PDH. Stable or rising antigen levels suggest treatment failure or relapse.

Previously, lifelong itraconazole maintenance therapy was recommended for patients with AIDS once histoplasmosis was diagnosed. Today, however, maintenance therapy is not required for patients who respond well to antiretroviral therapy, with CD4+ T cell counts of at least 150/μL (preferably >250/μL); who complete at least 1 year of itraconazole therapy; and who exhibit neither clinical evidence of active histoplasmosis nor an antigenuria level of >4 ng/mL. Maintenance therapy also appears to be unnecessary in patients receiving immunosuppressive treatment if the degree of immunosuppression can be reduced through an approach similar to that used for patients with AIDS.

Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy. While treatment is often prescribed for patients with pulmonary histoplasmosis who have not recovered within 1 month and for those with persistent mediastinal lymphadenopathy, the effectiveness of antifungal therapy in these situations is unknown.

237 Coccidioidomycosis

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DEFINITION AND ETIOLOGY

Coccidioidomycosis, commonly known as Valley fever (see "Epidemiology," below), is caused by dimorphic soil-dwelling fungi of the genus *Coccidioides*. Genetic analysis has demonstrated the existence of two species, *C. immitis* and *C. posadasii*. These species are indistinguishable with regard to the clinical disease they cause and their appearance on routine laboratory media. Thus, the organisms will be referred to simply as *Coccidioides* for the remainder of this chapter.

EPIDEMIOLOGY

Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. In the United States, areas of high endemicity include the southern portion of the San Joaquin Valley of California and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the southern coastal counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas, including the Rio Grande Valley. Outside the United States, coccidioidomycosis is endemic to northern Mexico as well as to localized regions of Central America. In South America, there are endemic foci in Colombia, Venezuela, northeastern Brazil, Paraguay, Bolivia, and north-central Argentina.

The risk of infection is increased by direct exposure to soil harboring *Coccidioides*. Because of difficulty in isolating *Coccidioides* from the soil, the precise characteristics of potentially infectious soil are not known. In the United States, several outbreaks of coccidioidomycosis have been associated with soil from archaeologic excavations of Amerindian sites both within and outside of the recognized endemic region. These cases often involved alluvial soils in regions of relative aridity with moderate temperature ranges. *Coccidioides* was isolated at depths of 2–20 cm below the surface. The recent identification of three cases of coccidioidomycosis in eastern Washington State may suggest that the endemic region is expanding.

In endemic areas, many cases of *Coccidioides* infection occur without obvious soil or dust exposure. Climatic factors appear to increase the infection rate in these regions. In particular, periods of aridity following rainy seasons have been associated with marked increases in the number of symptomatic cases. Overall, the incidence within the United States has increased substantially over the past decade, with nearly 43 cases per 100,000 residents of the endemic region in