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for PDH. Stable or rising antigen levels suggest treatment failure or relapse and should raise concerns regarding proper intake of itraconazole (capsule formulation with food), adherence to treat ment, drug absorption, itraconazole serum concentrations, and drug interactions.

Lifelong itraconazole maintenance therapy is recommended for patients with persistently suppressed immunity but not for those with immune recovery—e.g., patients with AIDS who complete at least 1 year of itraconazole and show no signs of active infection including Histoplasma antigen levels <2 ng/mL, CD4+ T-cell count recovery to at least 150/µL (preferably >250/µL), and HIV sup pression with viral load <50 copies/mL on antiretroviral therapy. Similarly, maintenance therapy may not be necessary in other immunocompromised patients if the clinical findings have cleared, antigen levels are <2 ng/mL, and immunosuppression is substan tially reduced. Fibrosing mediastinitis, which represents a chronic fibrotic reac tion to past mediastinal histoplasmosis rather than an active infec tion, does not respond to antifungal therapy. Often patients with mediastinal granuloma have chronic or progressive courses and receive treatment with itraconazole and corticosteroids to reduce disease progression. ■ ■FURTHER READING Abdallah W et al: Diagnosis of histoplasmosis using the MVista Histo plasma galactomannan antigen qualitative lateral flow-based immu noassay: A multicenter study. Open Forum Infect Dis 8:ofab454, 2021. Azar MM et al: Clinical perspectives in the diagnosis and manage PART 5 Infectious Diseases ment of histoplasmosis. Clin Chest Med 38:403, 2017. Azar MM et al: Current concepts in the epidemiology, diagnosis, and management of histoplasmosis. Semin Respir Crit Care Med 41:13, 2020. Bahr NC et al: Histoplasmosis infections worldwide: Thinking outside of the Ohio River valley. Curr Trop Med Rep 2:70, 2015. Hage CA et al: A multicenter evaluation of tests for diagnosis of histo plasmosis. Clin Infect Dis 53:448, 2011. Neil M. Ampel

Coccidioidomycosis ■ ■DEFINITION AND ETIOLOGY Coccidioidomycosis, commonly known as Valley fever (see “Epidemi ology,” below), is caused by dimorphic soil-dwelling fungi of the genus Coccidioides. Genetic analysis has demonstrated the existence of at least two species, C. immitis and C. posadasii. These species are indis tinguishable with regard to the clinical disease they cause and their appearance on routine laboratory media, although C. posadasii may grow more quickly at higher temperatures. 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 ende micity include the southern San Joaquin Valley of California (hence the sobriquet “Valley fever”)

and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the other southern counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas. Cases acquired well outside the recognized endemic

areas, including in eastern Washington state and in northeastern Utah, have also been described, and a recent climate model suggests that the endemic range may expand further east and north over time. 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 fungus is known to inhabit the native soils within the endemic regions. Because of the difficulty in isolating Coccidioides from envi ronmental sites, the precise characteristics of potentially infectious soil are not known, but alluvial alkaline deposits in regions of relative aridity with moderate temperature ranges are most closely associated with endemicity. In the United States, several outbreaks of coccidioi domycosis have been associated with soil from archeologic excava tions of Amerindian sites both within and outside of the recognized endemic region. When isolated from the soil, Coccidioides is found no more than 2–20 cm below the surface, nor is it usually isolated from cultivated soil. In addition to its saphrophytic soil phase, Coccidioides appears to have an endozoan life cycle, likely infecting burrowing rodents. This would suggest that the organisms are concentrated in these rodents and their burrows rather than extant in the soil. In endemic areas, most cases of human coccidioidomycosis occur without obvious soil or dust exposure. Climatic factors may increase the risk of infection. Periods of aridity following rainy seasons are associated with increases in the number of symptomatic infections. The number of reported cases of coccidioidomycosis has been steadily increasing over the past two decades. In 2019, a total of 20,003 cases were reported. The majority of these were either from Arizona or Cali fornia, in approximately equal numbers, with Nevada, New Mexico, and Utah reporting a small fraction of cases. The factors associated with these increases have not been elucidated but likely include an influx of older individuals without prior coccidioidal infection into endemic areas, construction activity, increased reporting, and chang ing climate. ■ ■PATHOGENESIS, PATHOLOGY, AND

IMMUNE RESPONSE The life cycle of Coccidioides is depicted in Fig. 219-1. On agar media and in the environment, Coccidioides organisms exist as filamentous molds or mycelia. Individual filaments (hyphae) elongate and branch, some growing upward. Portions of these aerial hyphae thicken and sep tate, and alternating cells then degenerate by autolysis, leaving barrelshaped viable spores called arthroconidia. Measuring approximately 2 μm by 5 μm, individual arthroconidia can easily dislodge from the hypha and become airborne. These may persist in the air for prolonged periods. When arthroconidia are inhaled by a susceptible host, their small size allows them to evade initial mechanical mucosal defenses and reach deep into the bronchial tree, where infection is initiated. Once within a susceptible host, the individual arthroconidia enlarge, become rounded, and develop internal septations. The resulting struc tures, called spherules, may attain sizes up to 200 μm and are unique to Coccidioides. The septations encompass uninuclear elements called endospores. Spherules may rupture and release packets of endospores that can themselves develop into new spherules, thus propagating infection locally. If returned to artificial media or the soil, the fungus reverts to its mycelial stage. Clinical observations and data from animal studies strongly sup port the critical role of a robust cellular immune response in the host’s control of coccidioidomycosis. Necrotizing granulomas containing spherules are typically identified in patients

with resolved pulmonary infection. In disseminated disease in which infection is not controlled, granulomas are generally poorly formed or do not develop at all, and a polymorphonuclear leukocyte response is frequently seen. In patients who are asymptomatic or in whom the initial pulmonary infection has resolved, delayed-type hypersensitivity to coccidioidal skin anti gens has been routinely documented and T-cell activation has been observed in peripheral blood stimulated with coccidioidal antigens. In persons who have developed protective cellular immunity, spherules exist in the lungs for prolonged periods, possibly lifelong, in a latent

Host Maturing spherule Rupturing spherule Early spherule Endospore Spherule stage ~ 5 µm Arthroconidium Environment Mycelial stage FIGURE 219-1 Life cycle of Coccidioides, including the mycelial phase in the environment and the spherule phase in the host. state. This results in the persistence of protective immunity but also places those infected at risk of recurrent active disease if that immunity should wane. ■ ■CLINICAL AND LABORATORY MANIFESTATIONS After infection, 60% of individuals are completely asymptomatic. The other 40% have symptoms that are related primarily to pulmonary infection, including fever, cough, and pleuritic chest pain. Symptoms generally occur from several days to up to 3 weeks after inhalation of arthroconidia. The risk of symptomatic illness increases with age. In addition to these local symptoms indicative of infection, there are several manifestations of primary pulmonary coccidioidomycosis that are due to an immunologic response. Most prominent among these are cutaneous reactions. A diffuse, erythematous maculopapular rash, known as toxic erythema, has been noted in some cases. In addi tion, erythema nodosum (see Fig. A1-39)—typically over the lower extremities—and erythema multiforme (see Fig. A1-24)—usually in a necklace distribution—may occur. Lesions consistent with Sweet syn drome have also been reported (Chap. 21). Cutaneous manifestations are especially common in women. Symmetrical arthralgias (“desert rheumatism”), often involving the ankles, knees, and hips, may also occur with or without cutaneous manifestations. Primary pulmonary coccidioidomycosis is often misdiagnosed as a community-acquired bacterial pneumonia. However, the diagnosis of primary pulmonary coccidioidomycosis is strongly suggested by the findings of rash or symmetrical arthralgias in a patient with an appropriate exposure history. The finding of any of the following is also strongly suggestive of coccidioidomycosis: a history of night sweats, marked fatigue, peripheral-blood eosinophilia, failure to improve with antibacterial therapy, and an upper lobe infiltrate or hilar or mediasti nal lymphadenopathy on chest imaging. In most patients, primary pulmonary coccidioidomycosis resolves without sequelae over several weeks. However, several pneumonic complications may arise. Pulmonary nodules are residua of the pri mary pneumonia. Generally single, frequently located in the upper lobes, and usually ≤4 cm in diameter, nodules are often discovered on routine chest radiograph in asymptomatic patients. Calcifica tion is uncommon. Coccidioidal pulmonary nodules can be difficult

to distinguish radiographically from pulmonary malignancies. Like malignancies, coccidioidal nodules often enhance on positron emis sion tomography. However, unlike malignancies, routine computed tomography (CT) imaging often demonstrates multiple nodules and there may be microsatellite lesions, scattered smaller nodules sur rounding the larger one. These findings are not specific, and biopsy may be required to distinguish between these two entities.

Pulmonary cavities occur when a nodule extrudes its contents into the bronchial tree, resulting in a thin-walled shell. Frequently asymp tomatic, these cavities may on occasion be associated with persistent cough, hemoptysis, and pleuritic chest pain. They may also become secondarily infected

with bacterial oral flora, environmental fungi such as Aspergillus species, or even with Coccidioides growing from the cavity wall. Rarely, a cavity may rupture into the pleural space, causing pyopneumothorax. In such cases, patients present with acute dyspnea, and the chest radiograph reveals a collapsed lung with a pleu ral air-fluid level. Chronic or persistent pulmonary coccidioidomycosis manifests with prolonged fever, cough, and weight loss and is radio graphically associated with pulmonary scarring, fibrosis, and cavities. It is most common in patients who already have chronic lung disease due to other etiologies. In some cases, primary pneumonia presents as a diffuse reticulo nodular pulmonary process in association with dyspnea and fever. This manifestation of pulmonary coccidioidomycosis may occur in settings of intense environmental exposure or in those with profoundly sup pressed cellular immunity, such as persons with untreated HIV-1 infec tion and markedly depressed peripheral blood CD4 cell count. In the latter case, this picture is associated with unrestrained fungal growth and is frequently associated with fungemia. CHAPTER 219 Clinical dissemination occurs in approximately 1% of infected indi viduals and is defined as finding the fungus outside the thoracic cavity. Dissemination is more likely to occur in male patients, particularly those of African and perhaps Filipino ancestry, and in persons with depressed cellular immunity, including patients with HIV-1 infection and peripheral blood CD4 counts of <250/μL, those receiving chronic glucocorticoid therapy, those with allogeneic solid-organ transplants, and those being treated with tumor necrosis factor-α antagonists or other biological response modifiers. Women who acquire new coc cidioidal infection during the second or third trimester of pregnancy or postpartum also are at significant risk for disseminated disease. Com mon sites for dissemination include the skin, bones, joints, soft tissues, and meninges. Dissemination may follow symptomatic or asymptom atic pulmonary infection and may involve only one site or multiple anatomic foci. When it occurs, clinical dissemination is usually evident within the first 6 months after primary pulmonary infection and is generally associated with a lack of cellular immunity to Coccidioides. Coccidioidomycosis Of the disseminated syndromes, coccidioidal meningitis is the most dire and is uniformly fatal if untreated. Patients usually present with a persistent dull headache, often accompanied by lethargy, and confusion. Nuchal rigidity, if present, is not severe. Examination of cerebrospinal fluid (CSF) demonstrates lymphocytic pleocytosis with profound hypoglycorrhachia and elevated protein levels. CSF eosino philia is occasionally observed. The diagnosis is usually established by finding coccidioidal complement-fixing antibody (see below) in the CSF in association with the CSF inflammatory pattern described above. The fungus is isolated from the CSF in fewer than one-third of cases. Magnetic resonance imaging with gadolinium frequently demonstrates enhancement in the basilar meninges. With or without appropriate therapy, patients may develop hydrocephalus, usually com municating, which presents clinically as a marked decline in mental status, often with gait disturbances. An elevated opening CSF pressure on lumbar puncture and dilated ventricles on brain imaging are hall marks of this condition. ■ ■DIAGNOSIS Serology is the most common method to establish the diagnosis of coccidioidomycosis. Several techniques are available, including the traditional tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion TP and CF (IDTP and IDCF), and enzyme

immunoassay (EIA) to detect IgM and IgG antibodies. TP and IgM antibodies are found in serum soon after infection and persist for weeks to months. They are not useful for gauging severity of disease. The CF and IgG antibodies occur later in the course of the disease and persist longer than TP and IgM antibodies. Rising CF titers are a reflec tion of fungal growth and are associated with clinical progression, and the presence of CF antibody in CSF is indicative of coccidioidal men ingitis. Antibodies disappear over time in persons whose clinical illness resolves and the presence of

coccidioidal antibodies in the serum does not indicate immunity or control of coccidioidomycosis.

Because of its commercial availability, relatively rapid turnaround time, and higher sensitivity than other tests, EIAs for IgM and IgG are recommended for the initial diagnosis of coccidioidomycosis. Both tests, but particularly the IgM EIA, are occasionally falsely positive, and results should be interpreted cautiously when used for screening pur poses in asymptomatic individuals. If either the IgM or IgG EIA serol ogy is positive, immunodiffusion tests (IDTP and IDCF) or traditional TP and CF assays should be performed for confirmation. If the IDCF or traditional CF assays are qualitatively positive, a CF titer should be requested. The optical density obtained from the EIA IgG does not correlate with the serologic titer of either the IDCF or traditional CF assay and should not be used as a surrogate for a titer. The CF titer is an important prognostic tool. High titers, for example, those ≥1:32, sug gest unrestrained fungal growth, predict disease activity, and suggest the possibility of extrathoracic dissemination. Coccidioides grows within 3–7 days at 37°C on a variety of artificial media, including blood agar. Therefore, it is always useful to obtain samples of sputum or other respiratory fluids and tissue for culture in suspected cases of coccidioidomycosis. The clinical laboratory should always be alerted to the possibility of this diagnosis, since Coccidioides poses a significant laboratory hazard if it is inadvertently inhaled. The organism can also be identified directly. While treatment of samples with potassium hydroxide is rarely fruitful, examination of sputum or other respiratory fluids after Papanicolaou, Gomori methenamine silver, or calcofluor white staining may reveal spherules in a significant proportion of patients with pulmonary coccidioidomycosis. For fixed tissues (e.g., those obtained from biopsy specimens), spherules with surrounding inflammation can be demonstrated with hematoxylineosin or Gomori methenamine silver staining. PART 5 Infectious Diseases A commercially available test for coccidioidal antigenuria and anti genemia has been developed and appears to be useful in immunosup pressed patients with severe or disseminated disease. It is also useful when the CSF is assayed in cases of suspected coccidioidal meningitis. False-positive results may occur in cases of histoplasmosis or blastomy cosis. Some laboratories offer genomic detection by polymerase chain reaction; this assay does not appear to be more sensitive than culture but can be more rapid. TREATMENT Coccidioidomycosis Currently, two classes of antifungal agents are useful for the treat ment of coccidioidomycosis (Table 219-1). While once prescribed routinely, amphotericin B in all its formulations is now reserved for only the most severe cases of dissemination and for intrathecal or intraventricular administration in patients with coccidioidal men ingitis in whom other antifungal therapy has failed. The original formulation of amphotericin B, which is dispersed with deoxycholate, is usually administered intravenously in doses of 0.7–1.0 mg/kg

either daily or three times per week. The newer lipid-based for mulations are associated with less renal toxicity, but there are no studies indicating whether they lead to better improvement than the deoxycholate formulation in coccidioidomycosis. The lipid disper sions are administered intravenously at doses of 3–5 mg/kg daily or three times per week. Triazole antifungals are currently the principal drugs used to treat most cases of coccidioidomycosis. Clinical trials have demon strated the usefulness of both fluconazole and itraconazole as initial

TABLE 219-1 Clinical Presentations of Coccidioidomycosis, Their Frequency, and Recommended Initial Therapy for the Immunocompetent Host CLINICAL PRESENTATION FREQUENCY, % RECOMMENDED THERAPY Asymptomatic infection

None Primary pneumonia (focal)

In most cases, nonea Diffuse pneumonia <1 Amphotericin B followed by prolonged oral triazole therapy Pulmonary sequelae

Nodule None Cavity In most cases, noneb Chronic pneumonia Prolonged triazole therapy Disseminated disease ≤1 Skin, bone, joint, soft Prolonged triazole therapyc tissue disease Meningitis Lifelong triazole therapyd aTreatment is indicated for hosts with depressed cellular immunity as well as for those with prolonged symptoms and signs of increased severity, including night sweats for >3 weeks, weight loss of >10%, a complement-fixation titer of >1:16, and extensive pulmonary involvement on chest radiography. bTreatment (usually with the oral triazoles fluconazole and itraconazole) is recommended for persistent symptoms. cIn severe cases, some clinicians would use amphotericin B as initial therapy. dIntraventricular or intrathecal amphotericin B is recommended in cases of triazole failure. Hydrocephalus may occur, requiring a cerebrospinal fluid shunt. Note: See text for dosages and durations. agents. Fluconazole has been the triazole of choice for the treat ment of coccidioidomycosis in the past because of availability, cost, predictable oral absorption, and perceived lack of severe adverse events. However, there are no studies demonstrating its superiority over other triazole antifungals, and evidence indicates that itra conazole is more effective against bone and joint disease and may be more effective for other forms of coccidioidomycosis. For both drugs, a minimal oral adult dosage of 400 mg/d should be used. The maximum dose of itraconazole is 200 mg three times daily, but higher doses of fluconazole may be given and 800 mg is frequently prescribed for coccidioidal meningitis. The newer triazole anti fungals, voriconazole and posaconazole, are useful for all types of clinical disease, including meningitis, and should be considered in cases where fluconazole or itraconazole therapy has failed. To date, isavuconazole has been used in limited circumstances in coccidioi domycosis but also appears to be effective, including for meningitis. High-dose triazole therapy may be teratogenic during the first trimester of pregnancy, and triazole therapy should be avoided in pregnant women during this period. There are several new antifungal agents that are promising for the treatment of coccidioidomycosis in the future. These include olorofim, oteseconazole, ibrexafungerp, fosmanogepix, and oral liquid nanocrystal amphotericin B. At this time, only olorofim has been studied in human coccidioidomycosis, and none are currently approved for use in coccidioidomycosis. However, olorofim has been studied in human coccidioidomycosis and has received U.S. Food and Drug Administration breakthrough therapy designation for difficult-to-treat Coccidioides meningitis. Most patients with focal primary pulmonary coccidioidomycosis do not require antifungal therapy. Patients for whom antifungal therapy should be considered include those with underlying cellular immunodeficiencies and those with prolonged symptoms and signs of extensive disease. Specific criteria include symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of

> 10%, a serum CF antibody titer of >1:16, and extensive pulmo nary involvement apparent on chest radiography. When antifungal therapy is used, either fluconazole or itraconazole at 400 mg daily anywhere from 6 weeks to 6 months is considered appropriate. Diffuse pulmonary coccidioidomycosis represents a special situation. Because most patients with this form of disease are

Revision #1
Created 2026-01-06 16:32:39 UTC by Omar Ayman
Updated 2026-01-06 16:32:39 UTC by Omar Ayman