Pulmonary Coccidioidomycosis

Irene M. Spinello, M.D.,[1] Augustine Munoz, M.D.,[1] and Royce H. Johnson, M.D.[1]

ABSTRACT

Coccidioidal infection can manifest as pulmonary or extrapulmonary disease. Pulmonary coccidioidomycosis occurs in 95% of all cases and can be divided into three main categories: primary, complicated, and residual pulmonary coccidioidomycosis.

The primary infection occurs with inhalation of airborne arthroconidia. As few as 10 arthroconidia are capable of causing an infection in animal models. Sixty percent of infected individuals will remain asymptomatic. This results in a positive skin test and, with rare exception, lifelong immunity. The other 40% will develop symptomatic disease that manifests with variable signs and symptoms, predominantly an influenza-like syndrome, pneumonia, or pleural effusion.

The category of complicated pulmonary coccidioidomycosis includes clinical entities as severe and persistent pneumonia, progressive primary coccidioidomycosis, fibrocavitary coccidioidomycosis, cavities, and empyema, a complication of a ruptured cavity. Progression of primary pulmonary disease to acute respiratory distress syndrome (ARDS) can also qualify as a complication.

The third category of residual disease comprises only two entities: pulmonary nodule and fibrosis. This review focuses on uncomplicated and complicated pulmonary coccidioidomycosis and its management as outlined earlier in addition to special considerations of coccidioidal fungemia, pulmonary coccidioidomycosis in pregnancy, and organ transplantation.

KEYWORDS: Pulmonary coccidioidomycosis, complicated pulmonary coccidioidomycosis, residual pulmonary coccidioidomycosis, progressive primary coccidioidomycosis, fibrocavitary coccidioidomycosis

Coccidioidomycosis has been present in the deserts of the Western Hemisphere since prehistory. Coccidioidomycosis was identified more than 100 years ago, first in Argentina and subsequently in California.[1,2] The original clinical descriptions were only of disseminated illness. The etiology, epidemiology, pathophysiology, and clinical characteristics of the disease were elucidated over the first 50 years of investigation. The recognition of the primary pneumonic disease awaited the work of Dickson, Gifford, and others in the 1930s.[3,4] William Winn described the pulmonary cavity shortly thereafter. The therapy of this most pathogenic of endemic fungi has been the major focus of investigation over the last 50 years.

The illness was originally thought to be protozoal. The investigations of Ophüls revealed the organism to be fungal.[5] Ophüls also worked out the dimorphic life cycle. All *Coccidioides* were originally designated as one species, *Coccidioides immitis*. More recent molecular studies by Fisher et al have shown two species, now named *c. immitis* and *c. posadasii*.[6] The former is most commonly seen in California, the latter in Texas and

[1]Department of Medicine, Kern Medical Center, Bakersfield, California.

Address for correspondence and reprint requests: Irene M. Spinello, M.D., Critical Care and Pulmonary Services, Kern Medical Center, 1830 Flower St., Bakersfield, CA 93305 (e-mail: spinelloi@kernmedctr.com).

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Latin America; both are found in Arizona. It is currently estimated that 100,000 to 150,000 individuals are infected in the United States annually.[7] The majority of these individuals are asymptomatic. Of the approximate one third with symptoms at least three out of four have mild to moderate pulmonary disease that either does not come to medical attention or is not diagnosed. Approximately 10% of the total infected population is diagnosed with pleural-pulmonary disease. Asymptomatic, symptomatic undiagnosed, and symptomatic diagnosed cases are the reservoir from which extrapulmonary disease arises. It appears the latter two categories contribute the largest percentage.

EPIDEMIOLOGY

The main risk factors for symptomatic infection can be grouped into endemic, occupational, and host-related. Endemic factors include residence in or travel to endemic areas. Occupational factors include activities that have soil exposure.[8] Coccidioidomycosis is more common among agricultural workers, excavators, military personnel, and archaeologists.[9]

There are certain groups of patients that are more prone to develop severe pulmonary and/or disseminated coccidioidomycosis than others. They include immunocompromised patients, including patients who have acquired immunodeficiency syndrome (AIDS)[10]; transplant recipients, especially those who received *Coccidioides*-infected organs[11]; patients treated with tumor necrosis factor-α (TNF-α) antagonists; pregnant women, especially in the third trimester and early postpartum; and cancer patients.[12] Certain ethnic groups are also at high risk of suffering disseminated disease. Persons of Filipino or African American descent have a 10- to 175-fold higher risk for dissemination.[13] Persons with blood group B are also at risk for more severe disease.[14] In a non-outbreak setting, older age, smoking, and diabetes mellitus are associated with severe pulmonary coccidioidomycosis.[15]

CLINICAL FEATURES

Primary Pulmonary Coccidioidomycosis

Patients with primary pulmonary coccidioidomycosis present commonly as community-acquired pneumonia, which is not easily distinguishable from those presenting with other etiologic agents. Other patients will present with at least some of the classic "valley fever" manifestations of fever, chills, headache, nonproductive cough, chest pain, erythema nodosum, erythema multiforme, and polyarthralgias. This constellation of findings is not as likely to be seen in other pneumonias. There are radiographic findings that are more suggestive of coccidioidal pneumonia such as hilar and paratracheal adenopathy, unilateral or bilateral, occurring with the primary illness in up to 10% or more of the cases and rarely in other primary pneumonias.

The x-ray findings of primary pulmonary disease include variable nonspecific infiltrates, hilar adenopathy, and pleural effusions. Findings such as cavities and nodules demonstrate progression into the complicated or residual stage of pulmonary coccidioidomycosis.[16]

Pleural Effusion

The pleura is a common site of involvement in the primary infection, with 50 to 70% of patients reporting some type of chest pain. Pleural effusions are noted on chest x-ray, with 20% reported as having blunted angles and as many as 10% reporting effusions.[16]

Effusions are predominantly left sided, but right-sided and bilateral effusions have also been noted. The fluid is an exudate with a straw-colored appearance and a pleocytosis of less than 10,000 cells. There is a lymphocytic predominance and rarely eosinophilia. The glucose is similar to serum glucose and the protein is usually greater than 4 g/dL. Pleural fluid microscopy rarely reveals the organism, but cultures will be positive on occasion. Pleural biopsy usually shows the coccidioidal granuloma on microscopy, and the culture is frequently positive. Chest x-ray will often show an ipsilateral parenchymal infiltrate. The pathogenesis of the effusion is thought to be direct extension from the neighboring parenchymal focus or less commonly hematogenous seeding.[17,18]

Persistent and Chronic Progressive Coccidioidal Pneumonia

After presenting with acute pneumonia some patients fail to recover; they continue with fever, weight loss, and sputum production. Alternatively, others will slowly improve over a period of months. The development of this persistent infection occurs in ~1% of patients. X-ray findings include changes such as fibrosis and cavitation (fibrocavitary).[17] X-ray abnormalities include persistent infiltrations or fibrocavitary changes. Coexistent hilar adenopathy and pleural changes may also be noticed in these individuals.

Cavitary Lesions

In the course of the pneumonia a persistent parenchymal cavity can develop. In the classic presentation this is a thin-walled lesion without an air-fluid level (Fig. 1). Ninety percent are single, 70% are located peripherally in the upper lobes, and most are usually 2 to 4 cm in size. Less commonly, they may also present as giant cavities (> 6 cm). Cavities may cross fissure borders.

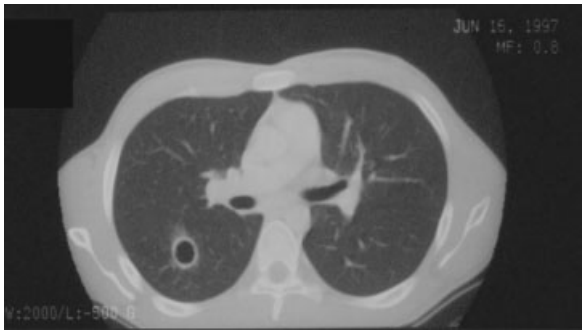

Figure 1 Typical computed tomographic scan presentation of coccidial cavity.

Their clinical course is variable, with 27 to 50% of the lesions resolving spontaneously over 1 to 4 years.[19] Smaller lesions (< 2.5 cm) seem to have a better outcome, whereas cavities > 5 cm will most likely persist.[20]

The majority of patients with cavitary disease are asymptomatic and are discovered radiographically. Clinically they can present with at least some of the following symptoms; hemoptysis, cough, fever, and localized chest wall pain, as well as night sweats and weight loss.[21] Cavities can develop various complications, including fungus balls with *C. immitis* or other fungi (e.g., *Aspergillus*). Bacterial superinfection may occur as well. Rupture of the cavity into the pleural space with subsequent development of empyema occurs in less than 3% of all cases and is the most serious complication. One third of these patients have negative skin tests or serology or both. Generally held indications for surgery include a rapidly expanding (> 4 cm) cavity close to the visceral pleura, serious or persistent hemoptysis, symptomatic fungus ball, or a bronchopleural fistula. Some consideration can also be given to a long-standing cavity with chronically positive sputum cultures.[22]

Pulmonary Nodule

Another potential outcome of the primary infection is for the pneumonic process to consolidate into a solitary nodule (coccidioma), occurring in 5 to 7% of these infections.[21] This is considered a benign process and usually requires no antifungal treatment. Nodules may be followed by chest x-rays on a periodic basis looking for necrotic deterioration. If the nodule cavitates, then sputum and coccidioidal serology should be collected to assess disease activity. Nodules must be differentiated from malignancy, which may also become necrotic. De novo nodules may require fine needle biopsy and rarely resection to rule out malignancy. Resected nodules do not usually require antifungal therapy if there are no satellite lesions.[19,20,23]

Coccidioidomycosis and Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) with severe hypoxemia is an uncommon complication of pulmonary coccidioidomycosis and carries a very high mortality rate, approaching 100% in some reports.[24,25] In addition to the use of lung-protective ventilation, there is case evidence that the use of systemic corticosteroids may be of benefit in decreasing the interstitial inflammation and improvement and restoration of lung function.[26] The series by Sajit et al of 16 patients with pulmonary coccidioidomycosis and ARDS treated with corticosteroids demonstrated the survival benefit as well as an absence of deleterious effects from steroid use in severe pulmonary coccidioidomycosis.[27] We have observed that the improvement in hypoxia may require steroid treatment lasting 7 days or longer. As a result, we recommend using systemic corticosteroids (employing the same regimen as given in severe *Pneumocystis* pneumonia) in all patients with pulmonary coccidioidomycosis whose pulmonary function deteriorates to qualify for ARDS.[28]

Miliary Disease

Miliary coccidioidal infection represents widespread organ involvement via a hematogenous or lymphatic route. This is usually detected as small millet-seed-sized nodules on the chest x-ray. These granulomata can be detected in any organ throughout the body. This presentation can be part of the acute primary illness or may represent part of the late-stage chronic progressive infection. In immunosuppressed patients, the illness may be fulminant and leads to respiratory failure and death; in the immunocompetent hosts the outcome is often not as grave if diagnosed early and treated aggressively. Fig. 2 presents a very rare combination of a cavitary and miliary disease. A key point is not to confuse the disease with miliary tuberculosis. This will often require a biopsy to confirm the diagnosis.[19,21,23,24]

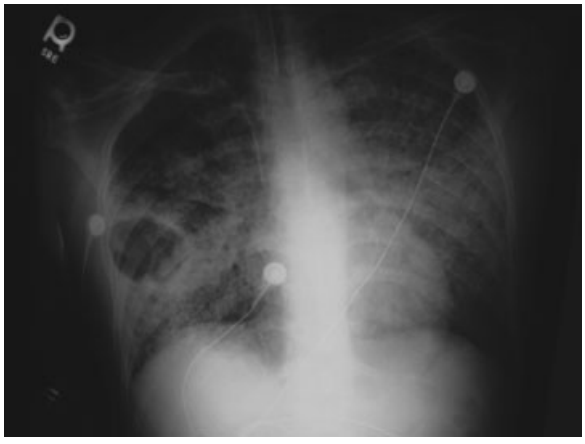

Figure 2 Unusual combination of miliary and cavitary disease.

Coccidioidal Fungemia

Susceptible hosts, especially those with HIV/AIDS, are at risk for more severe respiratory infections and/or disseminated disease. Coccidioidal fungemia (CoF) is an ominous manifestation of disseminated coccidioidomycosis. In the largest reported series of CoF,[29] 23 of the 29 patients with HIV with CoF presented with CD4 + T-lymphocyte counts less than 200 cells/μL. CD4 + T-lymphocyte counts ranged from less than 1 to 200 cells/μL (median = 12). Early and effective antiretroviral therapy may help prevent low CD4 lymphocyte counts and reduce the risk for CoF.

In the foregoing study 22 patients died during the CoF admission. The mean survival was less than 2 weeks, and 24 patients died within 1 month of fungemia. Respiratory failure and hemodynamic instability were present either independently or concomitantly in all patients with a fatal outcome. Hemodynamic and oxygenation parameters were consistent with the systemic inflammatory response syndrome (SIRS) and ARDS. These features are similar to those with sepsis caused by either gram-positive or gram-negative bacteria.[30] CoF appears to be associated with a fatality rate that equals or exceeds that of bacteremia or other fungemias, particularly in patients with HIV.[29,30]

Coccidioidal Infection in Transplant Patients

After solid organ transplantation (SOT), coccidioidomycosis may occur as a primary infection or through reactivation of latent infection. Infections in SOT recipients have been reported, with an incidence of ~4 to 9% in highly endemic areas, most occurring in the first year after transplantation.[11,31–37] The clinical presentation and radiographic features are variable.

Antirejection therapy is the most significant factor associated with the increased risk of coccidioidomycosis.[31] The risk after transplantation is also increased if there is a prior history of coccidioidomycosis or if there is a positive serologic assay in the period just before transplantation. In highly endemic areas, some centers test for *C. immitis* and prophylactically treat patients who have a positive result or prior history of coccidioidomycosis before transplantation.[35] Transmission through the donated organ also occurs, and reports of such transmission frequently describe fulminant infection occurring early in the posttransplantation period.[11,34,36]

Coccidioidomycosis and Pregnancy

In pregnant patients ~90% of disease presents as a respiratory illness, the remainder as a disseminated syndrome.[38] The third trimester of pregnancy is a time of highest risk for dissemination. Immunologic and hormonal changes during pregnancy and the postpartum period may account for the increased frequency and severity of disease during pregnancy.

Maternal mortality correlates with late recognition of the disease and delay in initiation of effective antifungal therapy. Historically, 65% of mothers survived. But this number decreased to 45% when patients were diagnosed in their third trimester. The current survival rates are considerably improved due to effective antifungal therapy.[39] Pregnant individuals with coccidioidomycosis require substantially different treatment standards than nonpregnant patients. The predominant reason for this is that azoles are contraindicated in pregnancy. Fluconazole exposure is teratogenic in the first trimester and could possibly predispose to prematurity in the second trimester.[25] Whether azoles can be used in late pregnancy with safety is unclear. Amphotericin B is the drug of choice, especially in the early stages of pregnancy. In the absence of comparative trials for *Coccidioides* infections in pregnant patients, the cumulative clinical experience with the lipid-based amphotericin preparations is now adequate to consider them suitable replacements for amphotericin B deoxycholate.[40] There are new agents that have activity against *Coccidioides*, including posaconazole, voriconazole, and caspofungin, but the evidence of their efficacy and safety is limited to case reports only.[41] Posaconazole's safety is similar to that of fluconazole. Voriconazole (category D) certainly has the most unfavorable profile due to documented fetal harm and teratogenicity and should be avoided in pregnancy.

DIAGNOSTIC EVALUATION

Once a patient presents with a clinical syndrome in which coccidioidomycosis is in the differential, specific diagnostic testing will virtually always be required to confirm or refute *Coccidioides* as an etiologic agent. Although radiographic features such as thin wall cavity, miliary disease, or hilar adenopathy may help distinguish coccidioidomycosis from other etiologies, radiographs are seldom in and of themselves diagnostic. Proof of coccidioidomycosis relies on histopathologic, mycological, and serological evaluation.

Histological evaluation relies on submission of adequate biopsy specimens from either or both pleural and pulmonary tissues. Specimens from bronchoscopic, pleural, or surgical biopsy tissues may be diagnostic. Pathological diagnosis requires the demonstration of endosporulating spherules (Fig. 3), usually within noncaseating granulomas. Nonendosporulating spherules are not diagnostic but may be suggestive. Granulomatous infiltration includes coccidioidomycosis as a differential consideration.

Culture of bronchial washings, pleural fluid, or biopsy tissue may yield characteristic mycelial growth on mycological or bacteriologic media (Fig. 4). The growth

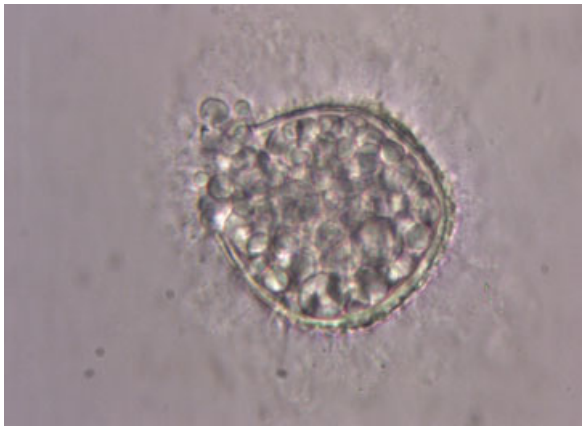

Figure 3 Spherule—KOH × 600 magnification.

of *Coccidioides* in a routine laboratory is fraught with hazard and should be undertaken only by experienced laboratories, using appropriate precautions. All suspected cultures should be confirmed using DNA probe technology.

Serology is the most commonly used diagnostic tool; ~90% of primary pulmonary disease will manifest a positive serology on repeat testing over an 8-week observation. Approximately one third of individuals with cavitary disease will have a negative serological evaluation. Culture may be more useful in this circumstance.

Patients with fulminant disease and immunocompromising illness may not have serological evidence of disease at presentation. In these patients, alternative approaches are typically required to make the diagnosis. A variety of serological tests are available. The tube precipitation and latex agglutination test for immunoglobulin (Ig)M antibodies have largely been abandoned. The most commonly available tests include the enzyme immunoassay (EIA) IgM and IgG tests. The former is the most sensitive in early disease but has many false-positive results. The latter seemingly lacks sensitivity. Immunodiffusion (ID) IgM and IgG tests are available. The ID IgM is less sensitive than the EIA IgM but is more specific. The ID IgM has good sensitivity, is usually preferred, and may be very sensitive in the most experienced hands. IgG antibody may also be measured and quantitated by the complement fixation (CF) antibody test in reference laboratories. This test is specific for diagnosis. The CF titer also has some prognostic significance; a higher titer indicates a more severe infection. The reader is cautioned that testing results vary considerably between laboratories. It is recommended that specimens be sent to a laboratory with experience in diagnosing coccidioidomycosis.

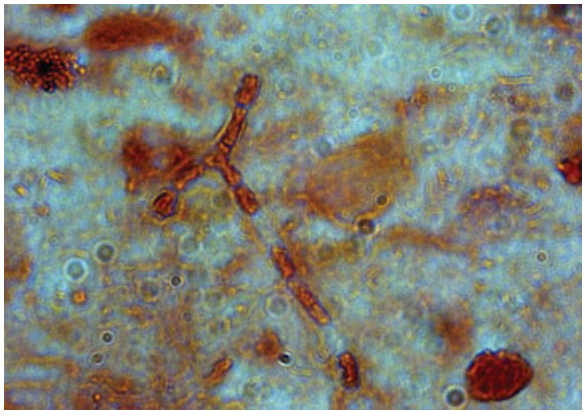

Figure 4 Hyphae in bronchial washings—Gram's stain × 1000 magnification.

TREATMENT

Table 1[42,43] presents a summary of treatment guidelines for severe pneumonia based on recommendations from the Infectious Diseases Society of America.[23] Treatment options for coccidioidomycosis depend on the severity of the disease, whether there is dissemination, and the site of dissemination. The treatment generally consists of amphotericin B deoxycholate or azoles.

Amphotericin B

Amphotericin B deoxycholate was the first successful therapy for moderate to severe coccidioidomycosis. It was developed by William Winn, M.D., Hans E. Einstein, M.D., and colleagues in the 1950s. It remained the gold standard for serious disease for almost 50 years. Its preeminence has been challenged by amphotericin B lipid preparations and possibly by advanced azoles. There are no comparative human trials of amphotericin B deoxycholate and amphotericin B lipid preparations in coccidioidomycosis. No amphotericin has been compared clinically to an azole in coccidioidomycosis. Because of demonstrable decreased renal toxicity of the lipid preparations and apparent better patient tolerance most experienced clinicians now use either liposomal amphotericin B (L-AMB) or amphotericin B lipid complex (ABLC).[44]

Amphotericin B deoxycholate or the preferred lipid preparations are currently reserved for severe pulmonary infection, both primary and hematogenous. Coccidioidal sepsis is also an indication. Our current practice is to initiate amphotericin B for any pneumonia with a $PaO_2 < 70$ mm Hg. Although controlled data are lacking, the experience with fluconazole in such patients has been less than satisfactory (i.e., progression to requiring mechanical ventilation). There are anecdotal data of posaconazole used as salvage therapy after amphotericin B failure.[45]

Primary Azole Therapy

The approach to treatment of primary pleural pulmonary disease remains controversial. It is clear from the historical

Table 1 Treatment Guidelines for Severe Coccidioidal Pneumonia

Drug	Dose		Comments
Amphotericin B deoxycholate	0.5–0.7 mg/kg/d IV	Inexpensive, most nephrotoxic High doses are occasionally recommended by some	Decreased frequency to thrice weekly is commonly made as treatment success is appreciated. Reduction in dose or frequency is often the consequence of noted decline in glomerular filtration rate. This may be acceptable if the patient is improving, but should not be performed in severely ill patients. Monitoring of creatinine, K^+, Mg^{2+}, HCO_3^-, and Na^+ should be done on a frequent basis. CBC with differential and LFT must also be monitored for potential toxicity
Amphotericin B liposomal	3–5 mg/kg	More expensive and less nephrotoxic than amphotericin B deoxycholate	
Amphotericin Blipid complex	5 mg/kg	More expensive and less nephrotoxic than amphotericin B deoxycholate	
Fluconazole	400–1200 mg/d	Generic, relatively inexpensive, well tolerated Mild to moderate pleural pulmonary infections are most commonly treated with fluconazole in doses of 400 to 800 mg/d. The higher doses are used in larger persons and more severe disease. Dosage adjustment for renal dysfunction and potential drug interactions is required. Hepatic toxicity has been overstated but must be monitored by serum transaminases on a periodic basis.	
Itraconazole	400–800 mg/d	More expensive and toxic than fluconazole, problematic bioavailability Itraconazole is an alternative and is likely equally effective in doses of 400 to 600 mg/d in divided doses. Monitoring is as for fluconazole but because of bioavailability problems itraconazole levels should be monitored. These should include native itraconazole and its hydroxy metabolite, which is equally active.[42] Additionally, volume status and potassium monitoring are more important with itraconazole than with fluconazole. Itraconazole may induce congestive heart failure in susceptible individuals. Itraconazole is supplied both as a capsule and as a liquid with cyclodextrin. The latter may have better absorption and is to be taken on an empty stomach. The capsule has better patient acceptance (taste) but must be taken with food (fat) and acid (cola).	
Posaconazole	400 mg q12h	Very expensive, limited clinical data, good animal data	
Voriconazole	4 mg/kg q12h	Very expensive, limited clinical data, significant potential of photodermatitis with risk of cutaneous malignancy.[43]	

CBC, complete blood count; LFT, liver function test.

record that the majority of the uncomplicated pleural pulmonary diseases will resolve without treatment, especially in low-risk individuals. There has never been a treatment trial in such individuals. Because of this, many experts recommend a "wait and see" approach to mild disease.[23] The majority of treatments used for all forms of coccidioidomycosis are not approved by the US Food and Drug Administration (FDA) for this

indication. Doses used are often greater than are supported by submitted FDA-approved safety data.

Ketoconazole, fluconazole, and itraconazole have all been used to treat mild to moderate primary and complicated pleural pulmonary disease as well as some forms of disseminated disease.[45–47] Severe or prolonged symptomatic primary disease or risk factors for dissemination mandate consideration for treatment. It is the practice in Kern County to treat most if not all diagnosed cases.

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