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Coccidioides immitis

1. INTRODUCTION

Coccidioidomycosis is a systemic fungal infection generally considered to be endemic for localized areas of the Western Hemisphere, in the so-called "Lower Sonoran Life Zone" (the semiarid section of southwestern United States and Mexico), and Central and South America *(1–9)*. As recent reports have suggested, however, because of increased exposure to the pathogen, mainly because of expanded travel and tourism to endemic areas, incidence of coccidioidomycosis have been diagnosed in various other parts of the United States and the world *(10–19)*.

While *Coccidioides immitis* is a dimorphic fungus, it actually infiltrates the host with a multifarious range of fungal morphotypes *(20)*. Thus, although the diagnostic pathologic finding in tissue is expected be a mature endosporulating spherule, hyphal structures can also be found in pathologic specimens *(21,22)*. Further, Nosanchuk et al. *(23)* presented a case of pulmonary coccidioidomycosis in which there were no intact spherules, but the characteristic barrel-shaped arthrospores predominantly present in tissue and cultures positively identified the organism as *C. immitis*.

Infections due to *C. immitis* usually begin in the lungs usually initiated by the airborne arthroconidia, a desiccated, diasarticulated mycelial fragment measuring between 2 and 4 µ. Despite the initial pulmonary portal of entry, endotracheal- and endobronchial-acquired coccidioidomycosis have also been described *(24)*.

Although in the immunocompetent host, the majority of infections are asymptomatic, in a number of cases, miliary manifestations *(25)* as well as a subacute influenza-like transient illness characterized by fatigue, cough, chest pain, sore throat and headache *(26)*, have been observed and usually resolve spontaneously.

In immunocompromised patients, however, coccidioidomycosis can lead to serious complications because of dissemination *(27,28)*. If not treated, disseminated coccidioidomycosis is often life-threatening. Among the risk factors that predispose to dissemination, race is important. As compared with Caucasians, Asians (particularly Filipinos) and African Americans have shown an increased risk of dissemination.

With the increase of cancer chemotherapy, organ and bone-marrow transplantations, the use of corticosteroids, and the advent of the AIDS pandemic, the incidence of coccidioidomycosis resulting from reactivation of dormant infections has been on the rise. Other predisposition factors for dissemination of the disease include pregnancy, especially during the third trimester and the peripartum period *(2,29)*, Hodgkin's disease *(30)*, some genetic factors, such as race and ethnic background (Filipino, African-American, Hispanic, Native American, and oriental extraction) *(31–36)*, and specific blood groups and histocompatability types *(37,38)*. Thus, data by Louie et al. *(39)* supported the hypothesis that host genes, in particular HLA class II and the ABO blood group, influenced the susceptibility to severe coccidioidomycosis.

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Even though neonatal coccidioidomycosis has been reported *(40,41)*, infants of infected mothers are usually uninfected *(2)*. With the exception of pregnant women *(42)*, disseminated coccidioidomycosis in males seems to be more prevalent than in women *(1,43)*. Age is probably a risk factor only in infants, young children, and adults over 50 yr of age *(35,44–48)*. Diabetics may also be at high risk. Although there is no strong evidence to demonstrate a higher rate of dissemination in diabetics than in nondiabetics, the rate of pulmonary complications among diabetic patients is definetely higher *(49,50)*.

Pulmonary complications resulting from coccidioidomycosis may include pleural involvement *(18,51)*, interstitial dermatitis *(52)*, as well as adult respiratory distress syndrome (ARDS), formation of cavities and nodules, empyema *(53)*, and peritonitis *(54)*. Extrapulmonary dissemination of infection include skin lesions *(55)*, abscesses, arthritis, osteomyelitis, and meningitis *(2)*; the latter is one of the most serious complication of coccidioidomycosis. In addition, coccidioidal infection can be observed in the thyroid *(56)*, eye *(57,58)*, sella turcica *(59)*, larinx *(60–62)*, external ear *(63,64)*, liver *(65–67)*, intestinal tract *(68)*, peritoneum *(69,70)*, prosthetic grafts of the femoral artery *(71)*, placenta during pregnancy *(72)* and the female genital tract *(73–75)*, as well as various urogenital disorders *(76–79)*. Hypercalcemia associated with *C. immitis* dissemination was also described *(80,81)*. Treatment with pamidronate was reported to easily resolve this condition *(81)*.

Constrictive pericarditis in the setting of disseminated coccidioidomycosis can be fatal despite antifungal therapy and pericardectomy *(82)*.

A case describing coccidioidomycosis associated with Sweet syndrome (likely related to Th-1 lymphocyte proliferation) has been reported *(83)*.

An unusual case of a female patient manifesting genital coccidioidomycosis, Addison's disease and sigmoid loop abscess due to *C. immitis*, was described by Chowfin and Tight *(75)*.

2. IMMUNE RESPONSES TO HUMAN COCCIDIOIDOMYCOSIS

In regard to innate resistance, arthroconidia (the infectious propagale of *C. immitis*) and newly released endospores would elicit an intense cellular infiltrate comprised predominantly of polymorphonuclear cells. Ingestion of cells is followed by a respiratory burst, and although arthroconidia are susceptible to the products of oxidative burst and cationic peptides, less than 20% of the phagocytized cells are killed *(84)*.

The high immunogenicity of *C. immitis* would trigger acquired immunity consisting of both humoral responses and cell-mediated immunity. Patients with progressive disease usually display a polyclonal B-cell activation with increased levels of IgG and IgE antibodies as well as circulating C1q-binding immune complexes consisting of *C. immitis* antigen and anti-*Coccidioides* IgG *(85–88)*. The IgE antibodies were shown to be directed against *C. immitis* antigens and to directly correlate with the disease involvement *(84)*.

Using T27K, a coccidioidal antigen preparation protective in mice but not previously studied in humans, Ampel et al. *(89)* carried out whole blood flow cytometry experiments with donors showing various clinical forms of coccidioidomycosis. The obtained data indicated that there was a specific human cellular immune response to T27K as a coccidioidal antigen. Further, a membranous outer wall component (SOWgp), another major cell surface-expressed antigen of *C. immitis*, was found to elicit both humoral and cellular immune responses in patients with coccidioidal infection *(90)*.

A *C. immitis* proline-rich antigen described by Peng et al. *(91)* has been found among genetically and geographically diverse *C. immitis* isolates *(80)*.

3. EVOLUTION OF THERAPIES AND TREATMENT OF COCCIDIOIDOMYCOSIS

The way therapeutic strategies and treatment of coccidioidomycosis have been determined depended to a large extent on the seriousness of infection after complete evaluation, and the immune status of the patient *(92)*. In the majority of cases, patients with uncomplicated acute pulmonary

Table 1
Treatment of Coccidioidomycosis in the Immunocompetent Host[a]

Indication	Clinical Stage	Treatment
Acute infection		
Low-risk for dissemination		None
High-risk for dissemination	Rapid progression	Amphotericin B: 1.5–2.0 g total dose, i.v.
	Slow progression	Fluconazole: 400–800 mg daily for 6–12 mo, p.o.
Thin-walled cavity	Symptomatic, enlarging	Fluconazole: 400 mg daily for 6 mo, p.o.; or resection
	High-risk	Fluconazole: 400 mg daily for 6 mo, p.o.; or resection
Ruptured cavity with empyema and pneumothorax		Amphotericin B: 1.5–2.5 g total dose, i.v.
Rapidly progressive miliary		Amphotericin B: 2.0–3.0 g total dose, i.v.
Meningeal infection	Patient awake	Fluconazole: 400–600 mg daily for 1 yr or longer, p.o.
	Patient confused	Amphotericin B: 2.0–3.0 g (systemically + intracisternally 3× weekly until cultures negative, then decreased frequency); with improvement: fluconazole (400–800 mg daily, p.o., for 1 year or longer)

[a]Data taken from Sarosi and Davies *(93)*, Einstein and Johnson *(36)*, and Johnson and Sarosi *(95)*. Some of the recommended dose regimens may reflect the personal preferences of the authors, and therefore, may remain controversial.

coccidioidomycosis or asymptomatic coccidioidal lung nodules may recover without treatment. However, immediate therapy is required in immunocompromised patients (especially those with AIDS) to prevent morbidity (e.g., destroyed joints) and mortality due to hypoxemia, dissemination, or meningitis *(2,43,93)*. Patients with severe primary pulmonary infections having a prolonged fever or prostration, persistent adenopathy, or extensive or progressive coccidioidomycotic pneumonia should also be treated, as well as the very young or the very old, patients with diabetis, and those with underlying malignancies or concurrent lung diseases *(2)*. Persistent thin-walled cavities are commonly observed in acute pulmonary infections. Treatment of such cavities is strongly advised when they begin to enlarge or when symptoms, such as productive cough and/or hemoptysis begin to develop *(93,94)*.

For years, intravenous amphotericin B has been the most efficacious drug for treating coccidioidomycosis in patients with extensive and rapidly progressive primary disease and at risk of developing dissemination, or in those already having disseminated disease (Table 1) *(36,93,95)*.

Because of the potential seriousness of its side effects, amphotericin B should always be applied with caution, especially in severely ill patients. In general, a total dose of 1.0–2.0 g of the antibiotic may be used in an attempt to prevent dissemination; the drug is given in 50-mg increments as either once-daily or three times weekly infusions administered over 1–2 h. In cases of meningeal infection, amphotericin B should be administered by direct lumbar or protracted intracisternal injection, or by using ventricular or the cisternal Ommaya reservoir *(96)*; the average tolerated dose is 0.5 mg *(36)*.

Koehler et al. *(97)* used amphotericin B lipid complex to successfully treat a case of disseminated coccidioidomycosis after intolerance and toxicity precluded therapy with other antifungal agents.

After their introduction into the clinic, the oral azole antimycotics (ketoconazole, fluconazole, and most recently itraconazole) have been used extensively to treat less severe cases of the disease. Currently, treatment with fluconazole (400–800 mg, daily) is recommended to prevent disease progression in high-risk patients with acute coccidioidomycosis, and in cases of meningeal infection *(36,93,98)*. Ketoconazole has been used orally in mild to moderate but stable infections at doses of 400 mg daily from 3 mo to several years *(36)*. The recommended dose regimens for itraconazole in patients with nonmeningeal coccidioidomycosis are 100 mg daily given for periods of up to 39 mo *(99)*.

A randomized, double-blind, clinical trial was conducted to compare the efficacies of oral fluconazole and itraconazole in the therapy of progressive, nonmeningeal coccidioidomycosis *(100)*. At the doses studied (fluconazole, 400 mg, daily; itraconazole, 200 mg, b.i.d.), neither of the drugs showed statistically superior efficacy although there was a trend toward slightly greater efficacy with itraconazole at the doses studied.

Data by Jiang et al. *(101)* indicated that co-administration of interleukin-12 (IL-12) expression vector with antigen 2 cDNA enhanced the induction of protective immunity against *C. immitis*.

Surgical intervention of coccidioidomycosis has also been considered as an alternative management of the disease *(102)*.

3.1. Coccidioidomycosis in Immunocompromised Hosts and AIDS Patients

Among the various opportunistic mycoses, infections caused by *C. immitis* have become a distinct possibility in patients who live in or have travelled to endemic areas of the disease *(103)*. The most important factor associated with the risk for developing clinically active coccidioidomycosis is a CD4+ peripheral blood lymphocyte count of less than 250 cells/μL *(104)*. If the infection is not treated immediately, the underlying immunodeficiencies associated with AIDS account for its high morbidity and mortality rate in those patients. Because of the sustained immune depression characteristic of AIDS, a complete eradication of the disease, even after a prolonged treatment, is virtually imposible with the currently available chemotherapeutics. Difffuse pulmonary infections and coccidioidal meningitis remain the most common and most dangerous manifestations of disseminated coccidioidomycosis in AIDS. Thus, in cases of diffuse pulmonary coccidioidomycosis, the mortality rate in HIV-infected patients within 1 mo of diagnosis may reach as high as 70%, and at this point, it is not clear whether treatment will alter disease outcome *(105)*. It is highly recommended that a lifelong therapy for such patients is initiated as soon as the $CD4^+$ lymphocyte count become less than 200 cells/μL. One major management strategy would be to control the initial infection as effectively as possible, followed by indefinite suppressive chemotherapy aimed to prevent relapse (Table 2) *(106)*. The initial therapy, especially in diffuse pulmonary disease and coccidioidal meningitis, should include treatment with amphotericin B. The recommended daily regimens vary between 0.5 and 1.0 mg/kg (usually between 40 and 60 mg daily for adults) *(106)*.

Although a decline in frequency is possible, few data are available regarding the incidence of coccidioidomycosis since the initiation of the highly active antiretroviral therapy (HAART) *(104)*.

For meningeal coccidioidal infections, amphotericin B is administered repeatedly into the cerebrospinal space and the treatment may last for months or even years. In this regard, the less toxic oral fluconazole has emerged as an attractive alternative to intrathecal therapy with amphotericin B. Also, oral therapy (400 mg daily) with fluconazole and itraconazole should be considered for other forms of disseminated disease when the patient is clinically stable *(105)*. Both fluconazole and itraconazole are recommended for long-term suppressive chemotherapy usually at daily doses of 400 mg. Zar and Fernandez *(107)* reported failure of 400-mg daily maintenance dose of oral ketoconazole to prevent recurrence of infection in an AIDS patient. For patients who do not respond to or cannot tolerate azole therapy, treatment with amphotericin B should be considered *(105)*.

Table 2
Treatment of Coccidioidomycosis in Immunocompromised Hosts[a]

		Treatment	
Indication	Clinical stage	Without AIDS	With AIDS
Acute infection			
	Rapid progression	Amphotericin B:1.5–2.0 g total dose, i.v.	Amphotericin B: 1.0–2.0 g; then, 400–800 mg for life, p.o.
	Slow progression	Fluconazole: 400 mg daily for 6–12 mo, p.o.	Fluconazole: 800 mg daily for life, p.o.
Thin-walled cavity		Fluconazole: 400–800 mg daily for 6–12 mo, p.o.	Fluconazole: 400–800 mg daily for life, p.o.
Ruptured cavity with empyema and pneumothorax		Amphotericin B: 1.5–2.0 g total dose, i.v.; then, fluconazole (400–800 mg daily for 1 year), p.o.	Amphotericin B: 2.0–3.0 g total dose, i.v.; then, fluconazole for life, p.o.
Rapidly progressive miliary		Amphotericin B: 2.0–3.0g total dose, i.v.	Amphotericin B: 2.0–3.0 g total dose, i.v.; then, fluconazole for life, p.o.
Meningeal infection	Patient awake	Fluconazole: 400–800 mg daily, p.o., likely for life	Fluconazole: 400–800 mg, p.o. for life; or amphotericin B 2.0–3.0 g (systemically + intracisternally 3× weekly); once awake and cultures negative: fluconazole (400–800 mg p.o., for life)
	Patient confused	Amphotericin B:2.0–3.0 g total dose (systemically + intracisternally 3× weekly until cultures negative; then, fluconazole (400–800 mg, for life)	

[a]Data taken from Sarosi, G. A. and Davies, S. F. *(93)* and Johnson P. and Sarosi, G. *(95)* Some of the recommended dose regimens may reflect the personal preferences of the authors, and therefore, may remain controversial.

In one of many complications with AIDS patients, it is not uncommon to have concurrent pulmonary infections with *C. immitis* and *Pneumocystis carinii (108,109)*. In such cases, the diagnosis of *C. immitis* could be delayed or missed. In cases of *P. carinii* pneumonia (PCP), AIDS patients are often treated in the early stage of the infection with combination of anti-PCP agents (trimethoprim-sulfamethoxazole [TMP-SMX]) and adjuvant corticosteroids *(110–113)*. However, the use of corticosteroids in patients with PCP concurrent with coccidioidal pneumonia may be to risky in this setting because corticosteroids have been previously associated with severe, disseminated progression of coccidioidomycosis in patients without HIV disease *(114)*. To this end, Mahaffey et al. *(115)* reported two cases of concurrent pulmonary coccidioidomycosis and PCP in which the coccidioidal infection was not immediately recognized and the patients received TMP-SMX medication combined with oral prednisone (40 mg daily); in both patients, the therapy led to clinical worsening associated with the development of a reticulonodular pulmonary infiltrate. Such distinct nodular pattern is visible on chest roentgenograms; because it is uncommon for PCP, the nodular pattern should be used as a diagnostic tool for coccidioidomycosis *(115)*.

3.2. Cutaneous Manifestations

Cutaneous manifestations have been observed in nearly half of all symptomatic infections involving *C. immitis (1,94,116–118)*. In addition, virtually all cases of dissemination involved the development of morphologically highly variable skin lesions *(119)*. There are three distinct cutaneous pattern of coccidioidal skin manifestations: toxic erythema, erythema nodosum, and erythema multiforme.

Primary cutaneous coccidioidomycosis, a skin infection acquired percutaneously, has been very rarely observed (1–2% of total cases) *(1)*. Its entry route is similar to other subcutaneous mycoses and results in a primary complex resembling that of tuberculosis (lymphangitis and adenitis). In patients who are predisposed or are immunodeficient, a granulomatous lesion is established that is similar in appearance to verrucous tuberculosis, or the infection may follow the route of the regional lymph nodes as in lymphangitine sporotrichosis *(120–122)*.

Facial lesions are commonly observed and may carry the risk of a greater CNS involvement *(123)*. In an earlier report, Newland and Komisar *(124)* presented a case in which a slowly enlarging supraclavicar mass with cutaneous extension was the only evidence of disseminated coccidioidal infection; therapy with parenteral amphotericin B proved to be effective. Lavalle et al. *(125)* described mycological and clinical cure of a large coccidioidal forehead lesion 2 mo after amphotericin B therapy was instituted.

One strategy that could be pursued in treatment of disseminated coccidioidomycosis involving the skin is to achieve clinical stabilization with either amphotericin B or some of the newer azole antimycotics, followed by a longer term of suppressive therapy if needed to reduce the likelihood of relapse *(1,126)*. To this end, Bonifaz et al. *(122)* reported a successful treatment of a patient with primary cutaneous coccidioidomycosis with itraconazole, given at a daily dose of 200 mg (b.i.d.) for 5 mo.

Reevaluating the potential seriousness of primary cutaneous coccidioidomycosis if left untreated, Winn *(55)* indicated the need for early recognition of this condition, and the prompt use of suppressive intravenous amphotericin B therapy until local tissue resistance and systemic immunity have contained the infection within the initial cutaneous site, leading to complete healing of the primary lesion and its associated lymphodenopathy.

3.3. Coccidioidomycosis in Pregancy and Early Infancy

Pregnant women are at high risk for coccidioidal infections *(127,128)*. The dissemination rate is 40–100 times that of the general population and reaches its peak during the second and third trimesters. After the first cases of disseminated coccidioidomycosis in pregnant women were reported back in the 1940s *(129–131)*, it has become a major cause of mortality ranging between 20% and 60% *(30,132)*. The increased risk of dissemination is likely consequence of the relative immunosuppression observed in women during pregnancy, as well as the agonistic effect of 17-β-estradiol and progesterone in the serum of pregnant women on coccidial growth *(133,134)*. Reactivation or exacerbation of a chronic low-grade infection during pregnancy has been reported in patients previously treated for disseminated disease; in both reported cases, the patients have been insulin-dependent diabetics *(135,136)*.

In 1998, Arsura et al. *(137)* made the observation (later supported by others *[138]*) that pregnant women who developed erythema nodosum were less likely to have disseminated coccidioidomycosis. Erythema nodosum, which represents a delayed hypersensitivity reaction (cell-mediated immunity) in the subcutaneous fat in response to various bacterial, viral, fungal, and chemical antigens *(139)*, would typically appear in association with a positive intradermal skin reaction to a purified protein derivative (e.g., coccidioidin) in patients infected by their respective etiological agents *(138,139)*.

Disseminated coccidioidomycosis in early infancy has been relatively rare *(140–150)*, with aspiration of infectious vaginal secretions during birth being the major mode of transmission *(149,151)*. So far, in cases of neonatal coccidioidomycosis there has been no evidence presented of transplacen-

tal infection because extensive coccidioidal placentitis was found without transmission of infection to the fetus; the placenta is thought to be impermeable to the coccidioidal spherule because of its large size (40–70 μm) *(140,152,153)*. However, intrauterine transmission of coccidioidomycosis has been reported *(154)*. In another case, the acquisition of infection was also thought to have occurred by maternal-fetal transmission *(155)*.

Golden et al. *(156)* described a case of *C. immitis* disseminated chorioretinis in a 7-wk-old infant. Therapy involved gradually increasing dosages of intravenous amphotericin B until a daily maintenance dose of 1.0 mg/kg was reached. An additional 50-mg/kg course of amphotericin B was administered over 3.5-mo period; follow-up examinations at 4.5 and 6.5 mo revealed no further change in the retinal lesion *(156)*.

In over 100 cases of coccidioidomycosis in pregnant women reported so far *(127)*, over half of them have been cases of disseminated infections, which were treated with intravenous amphotericin B with favorable maternal and neonatal outcomes *(135,157–162)*. Recommended dose regimens begin with a test dose of 1.0 mg, followed by sequential dose increases of 5–10 mg every other day to reach a total dose of 50 mg every other day (maximum dose of 0.5–1.5 mg/kg every other day) *(127)*. In case of emergency, following the 1.0-mg test dose, a 25-mg dose can be administered with subsequent rapid increases to the desired dosage *(127)*. During chemotherapy, the effects of amphotericin B should be monitored by weekly tests on electrolytes, hematocrit, and renal function (blood urea nitrogen and creatinine). Decreased creatinine levels indicate an early nephrotoxicity *(163)*.

3.4. Coccidioidomycosis in Transplant Recipients

Although primary coccidioidal infections are acquired in endemic areas, in immunocompromised hosts reactivation of the disease can develop months or even years later *(156,164)*. Among organ-transplant recipients, disseminated disease is common and has substantial morbidity *(165)*. In cases when organ transplantations are needed, the question has been raised whether they should be even considered in endemic areas for coccidioidomycosis *(166,167)*. Because endogenous reactivation is a distinct possibility, caution should be used with patients with a history of symptomatic coccidioidomycosis before transplant surgery is deliberated, especially in cases where extrapulmonary infections have been involved *(168)*. To this end, Hall et al. *(169)* proposed that before any transplantation surgery is performed, certain markers relevant to this problem should be examined. First will be the measurement of coccidioidal serum antibodies in patients with any endemic exposure. Patients having had previous history of coccidioidal pulmonary infections or with reactive coccidioidal serologies may benefit from receiving antifungal chemotherapy following the surgery. In addition, serologic surveillance and antifungal therapy should be considered during periods of increased immunosuppression, which may occur during the treatment of rejection episodes *(169)*.

Amphotericin B and antifungal azoles remained the mainstay of therapy.

3.4.1. Cardiac Transplant Recipients

In cardiac-transplant recipients, coccidioidal infections, although seldom, have been reported *(166,169–172)*. Similarly, coccidioidomycosis of the myocardium has been very rarely observed *(173)*. However, in patients on immunosuppressive therapy (either a two-drug regimen of prednisone-azathioprine or prednisone-cyclosporin A, or the triple-drug regimen of cyclosporin A-prednisone-azathioprine), the likelihood of primary or recurrent mycoses with higher rate of dissemination and mortality should not be underestimated. Therefore, screening for exposure to *C. immitis* before cardiac transplantation is performed is important.

Hall et al. *(174)* conducted a retrospective analysis of 199 patients who underwent transplantation in Arizona during a 6-yr period. The data showed that although in endemic area, the incidents of coccidioidomycosis among heart-transplant recipients accounted for only 4.5% of the population. In cases of either past medical history or positive serology, 200 mg of oral ketoconazole was applied

twice daily beginning immediately after transplantation and maintained indefinitely. Vartivarian et al. *(171)* described a case of reactivated disseminated coccidioidomycosis in a orthotopic cardiac-transplant recipient, presented with invasion of the cardiac graft. The patient, who received immunosuppressive medication but not antifungal therapy, died. At the time of transplanation, it was not known that coccidioidomycosis was apparently acquired during a brief visit to an endemic area several years prior to the surgery.

In all earlier reports (before the introduction of the newer triazole antimycotics), the postoperative antifungal chemotherapy in the presence of prior clinical history of primary coccidioidal pneumonia or detectable coccidioidal serum antibodies at the time of surgery, consisted mainly of ketoconazole (200 mg daily), or amphotericin B (100 mg given to a child over a 4-mo period); no relapses have been observed at follow-up monitoring *(169)*. Even so, the more effective fluconazole and itraconazole should be considered first for controlling recurrence of infection.

3.4.2. Renal Transplant Recipients

Although systemic fungal infections have been frequently diagnosed in renal allograft recipients subjected to immunosuppressive therapy *(175,176)*, cases of disseminated coccidioidomycosis, because of the endemic nature of the disease, have been rare *(177–182)*. However, if not treated, as in other transplant recipients, such infections usually have high mortality rate. According to Cohen et al. *(177)*, predisposing factors for disseminated coccidioidomycosis in renal-transplant recipients living in Arizona, included gender (males have been found to be at higher risk than females), and blood group (either B or AB, or a combination of both). Dissemination was manifested with pneumonia (59%), arthritis (24%), meningitis (12%), and pyelonephritis (6%). However, these conclusions should be viewed with caution since the study involved a limited number of patients and was conducted in only one localized endemic area. Amphotericin B (total dose of 1.5–2.7 g) was used to treat the pulmonary dissemination; the results were disappointing because relapse occured in all patients treated. Ketoconazole was also used as an alternative *(177)*.

Chandler et al. *(183)* described a case of disseminated coccidioidomycosis with choroiditis in which an apparent healed focus of pulmonary infection was reactivated after treatment with corticosteroids and immunosupressive therapy after renal transplantation. The following treatment with systemic polymyxin, methicillin, amphotericin B, and gentamicin sulfate proved unsuccessful and the patient died.

3.4.3. Liver Transplant Recipients

Disseminated fungal infections in recipients of liver allografts have a particularly poor prognosis *(184–189)*. Disseminated *C. immitis* infection was first diagnosed in a liver transplant recipient in 1990 *(190)*. The reported case was unusual because the infection was not clinically suspected until the spherules of the pathogen were fortuitously detected in a percutaneous liver biopsy. Therapy with amphotericin B proved unsuccessful and the patient died.

3.4.4. Bone-Marrow Transplant Recipients

Riley et al. *(191)* reported three cases of coccidioidomycosis (one pulmonary and two disseminated) in allogeneic bone-marrow transplant recipients. All three patients had been in an area endemic for *C. immitis* prior to the bone-marrow transplantation. The treatment consisted mainly of intravenous amphotericin B. Both patients with disseminated infection died; the patient with localized pulmonary disease survived. One major impediment in managing coccidioidomycosis in bone marrow transplant recipients is the difficulty in diagnosing the infection. In treating such cases, one recommendation made was to reduce immunosuppressive medication as much as possible in order to allow for increased doses of amphotericin B *(191)*. The question of whether itraconazole, high doses of fluconazole, or liposomal amphothericin B would be most efficacious in these patients is still not resolved *(191)*.

3.5. Ocular Coccidioidomycosis

Although relatively rare, ocular coccidioidomycosis has been diagnosed not only in patients with progressive disseminated illness, but also in patients with very little or no systemic involvement *(192)*. Usually it is confined to the anterior segment and adnexa *(193)*. In general, the ocular dissemination of coccidioidomycosis is presented as either: (1) extraorbital disease, involving the optic nerve and cranial nerve lesions; (2) extraocular disease, manifested as nonspecific phlyctenular conjunctivitis, episcleritis, scleritis, and fungal granulomata of the lids and orbit; or (3) intraocular disease, manifested as anterior uveitis (iris and ciliary body) or posterior uveitis (choroid), or both, as well as occasional retinal and vitreous manifestations *(192,194)*.

It has been reported *(195–198)* that initial therapy with topical and systemic corticosteroids led to improvement in the ocular lesions. However, further evidence has suggested that continuation of such therapy may, in fact, exacerbate the ocular inflammation or as the corticosteroids were being tapered to cause progressive destruction of the eye *(183,196–198)*.

Since its introduction into the clinic in 1955 and in subsequent years, amphotericin B has been used extensively in the therapy of ocular coccidioidomycosis *(192,199)*. The antibiotic can be used topically to treat external ocular infection as aqueous suspension at concentrations of 1–5 mg/mL, instilled one drop every 30 min; however, severe local irritations may frequently occur with its topical use *(200)*. When injected intravenously, amphotericin B has shown poor intraocular penetration unless used in large doses, which, in turn, would increase its hepato- and nephrotoxicity. In the therapy of corneal ulcers and endophthalmitis, the antibiotic may be used by conjunctival and subconjunctival routes in doses ranging from 0.75–5.0 mg in a 1.0-mL aqueous suspension *(200,201)*. In the latter route, the injection is painful and may cause yellowing of the conjunctiva with a nodular formation *(202)*.

In treating a case of macular coccidioidomycosis, Lamer et al. *(203)* used amphotericin B in daily doses ranging from 20–50 mg given for 1 mo; by the end of the period, the lesion was cicatricial. It is important to mention that macular dissemination in coccidioidomycosis differs from that in histoplamosis both funduscopically and angiographically *(203,204)*.

Miconazole has also been utilized to treat ocular coccidioidomycosis. Blumenkranz and Stevens *(199)* found that at doses of 400–1000 mg, given three times daily for a period of 1 mo, miconazole was ineffective in preventing the development of new lesions. In fact, new retinal lesions had developed, which were later reversed with the institution of amphotericin B therapy. Overall, in the reported study, miconazole was inferior to amphotericin B in the treatment of intraocular fungal infection *(199)*.

3.6. Acute Respiratory Failure

Acute respiratory failure in coccidioidomycosis is a rather serious complication occuring usually in the setting of a disseminated illness *(181,205–221)*. In the majority of cases, there was one or more predisposing factors for disseminated illness.

In 1972, Knapp et al. *(222)* described a patient with primary pulmonary coccidioidomycosis who developed acute respiratory failure. Recently, two more such cases caused by primary pulmonary coccidioidomycosis have been described *(223)*. The acute failure is believed to be the consequence of an intense exposure to arthrospore-laden dust and massive inoculation with the pathogen. The proliferating fungus and the associated immune-mediated response would have caused the resulting lung injury *(224,225)*. Both patients survived after treatment with intravenous amphotericin B (total doses, 2.8 and 2.0 g, respectively); oral ketoconazole was also administered to one of the patients *(223)*.

3.7. Coccidioidal Peritonitis and Gastrointestinal Dissemination

Peritonitis is a rare complication of disseminated pulmonary coccidioidomycosis *(213,226–228)*, which is likely to occur by hematogenous dissemination at the time of the primary pulmonary infection *(228)*. Jamidar et al. *(70)* described an HIV-positive patient with a very rare AIDS-defining

peritoneal coccidioidomycosis. The patient, who presented with ascites, low serum-ascites albumin gradient, and laparoscopy showing peritoneal implants that grew *C. immitis*, was discharged after 2 wk of amphotericin B therapy with greatly reduced amount of ascites; 6 mo later, the patient remained afibrile with no clinically detectable ascites.

So far, excluding autopsy series, only 15 cases of coccidioidal peritonitis have been reported *(68,226,228–230)*, and only one of these occured in an AIDS patient who had a history of alcohol-induced cirrhosis, portal hypertension, and secondary hypersplenism *(70)*.

Amphotericin B was used widely for treatment of coccidioidal peritonitis even when there was no evidence for additional sites of dissemination. On the negative side, a lack of peritoneal clearance in a patient with fungal peritonitis given systemically amphotericin B has been reported *(231)*. However, the dose regimen of amphotericin B still remains largely empiric and is dependent on the overall clinical response, sequential serologies, and the immunological status of patients *(68,232)*.

C. immitis is commonly believed not to spread into the gastrointestinal tract with the possible exception of some widely disseminated terminal stages of the disease. However, Weisman et al. *(68)* reported a unique case of gastrointestinal dissemination where histologic and culture evidence were presented to demonstrate invasion of the pathogen into chylous ascites, the mesentery, as well as into the entire length of the small bowel. As with the case of coccidioidal peritonitis, the gastrointestinal infiltration was likely the result of an initial hematogenous dissemination. The initial treatment of the patient consisted of intravenous amphotericin B (total dose, 4.25 g); in spite of the observed progressive clinical improvement, there has been recurrence of the disease. Following persistent renal toxicity, the amphotericin B medication was ceased and oral ketoconazole was instituted for 1 mo at 400 mg daily, folowed by increased dosage for an additional month. Both drugs failed, and stools continued to be positive for *C. immitis*. Next, itraconazole therapy was initiated. Repeated endoscopy 3 mo after initiation of itraconazole showed nearly total resolution of the intraluminal duodenal disease, and stablization in the patient's clinical condition with minimal persistent ascites *(68)*.

3.8. Coccidioidal Infections of Bones and Joints

Coccidioidomycosis involving the bones and joints is a very common occurence during dissemination *(233)*. As sometimes referred to as "desert rheumatism," it is reportedly present in 10–50% of cases involving extrathoracic infection *(234–237)*. The most affected sites of bone involvement included the ends of the long bones and bony prominences, as well as the spine and pelvis. However, diagnosis and treatment may pose difficult problems. Data from a retrospective study involving 24 patients with 44 separate skeletal lesions caused by *C. immitis* showed that a successful outcome was more likely in those patients treated by a combination of chemotherapy and surgical intervention, rather than chemotherapy alone *(238–244)*. Patients with a complement fixation serum antibody titer ratio of 1:128 or less were more likely to fail chemotherapy alone ($p < 0.01$) *(244)*. There were earlier studies done before the availability of the newer generation of triazole antimycotics, with treatment regimens consisting of intravenous amphotericin B (total dose, 3.0–4.9 g *[245]*) or oral ketoconazole (400–800 mg daily for a minimum of several months) *(246)*. Both drugs have been shown to produce detectable levels in the joints *(246,247)*. Synovial infection were more likely to improve as a result of ketoconazole medication than osteomyelitis *(246)*.

Buckley and Burkus *(248)* presented a case of coccidioidal osteomyelitis of a tarsal bone that was successfully treated with local surgical debridement followed by a long-term treatment with ketoconazole.

Magnetic resonnance imaging (MRI) studies of 15 patients with diagnosed vertebral column coccidioidomycosis were retrospectively reviewed to determine the MR features of coccidioidal spondylitis *(249)*.

A case of musculoskeletal coccidioidomycosis involving the wrist has also been described *(250)*. In a rare finding, disseminated coccidioidomycosis of the medial cuneiform was also reported *(27)*. as well as coccidioidomycosis in the hand mimicking a metacarpal enchondroma *(251)*.

3.9. Genitourinary Coccidioidomycosis

Genitourinary involvement is commonly observed in disseminated coccidioidomycosis. Autopsy results have shown renal involvement in as many as 60% of patients suffering from disseminated infection *(213,227)*. Although less frequent, other sites of coccidioidal involvement include the kidney, adrenal, prostate, scrotal content, psoas, and the retroperitoneum *(213,217)*.

3.9.1. Coccidioidomycosis of the Prostate

A number of clinically diagnosed cases of coccidioidal dissemination in the prostate have been described *(227,252–261)*. Earlier treatment included intravenous amphotericin B or ketoconazole *(252,254,257,258)*. Surgical procedures (transuretral resection *[254,257,258])* have also been part of the therapy. The clinical outcome was dependent on the presence or absence of other sites of dissemination. When dissemination confined within the prostate gland had good prognosis for recovery, in general, the presence of extragenital dissemination was associated with high mortality rate *(259)*.

3.9.2. Infection of Intrascrotal Contents With or Without Prostatic Involvement

Coccidioidal infection of the scrotal contents have been reported on a numerous occasions *(253,255,262–271)*. The most common manifestations have been the development of a scrotal mass representing either granuloma or an abscess in the epididymus, and the presence of a sinus tract. In the mostly early reports, treatment was usually surgical, with only one patient treated with a combination of surgery and intravenous amphotericin B *(270)*.

3.9.3. Bladder Involvement

Bladder involvement is a very rare manifestation of systemic coccidioidomycosis *(79)*. In one such case, Weinberg at al. *(272)* found the mycelial phase of the fungus in the bladder. The patient was treated with ketoconazole and showed no clinical symptoms one year after the therapy. In another case report, Kuntze et al. *(79)* treated one patient with 2.0 g of amphotericin B followed by 200 mg of oral ketoconazole every morning for 1 yr; at the 4-yr follow-up examination, the patient was still asymptomatic.

3.9.4. Other Coccidioidal Genitourinary Involvement

Infection of the female reproductive organ is also a rare manifestation of systemic coccidioidomycosis *(79,273)*. It may be presented as pelvic inflammatory disease, pelvic mass, infertility, abdominal pain, hypermenorrhea, or vaginal discharge. The disease is usually associated with coccidioidal peritonitis. In earlier reported cases, the recommended therapy has been combination of surgical excision and systemic therapy *(274,275)*.

3.10. Coccidioidal Infection of Arterial Prosthesis

Schwartz et al. *(276)* reported a case of disseminated coccidioidomycosis involving bilateral infection of femoral artherial prosthetic grafts and miliary pulmonary disease. Although the occurence of vasculitis complicating coccidioidal meningitis has been previously reported *(277)*, what made this case highly unusual is that for the first time arterial involvement (whether native or prostetic) of *C. immitis* was described in sites remote from the CNS. In the ensuing systemic chemotherapy (coupled with repeated percutaneous aspiration of the perivascular fluid collections), the patient failed to respond to ketoconazole and was intolerant to amphotericin B. However, treatment with oral fluconazole (200–400 mg daily for 9 mo) led to clinical resolution; a life-long maintenance therapy with fluconazole (400-mg daily dose) was also instituted *(276)*.

3.11. Coccidioidal Infections of CNS

Coccidiodal meningitis is a severe infection that even with antifungal treatment can result in death *(278,279)*. It can cause severe mechanical complications including hydrocephalus *(280)* and increased intracranial pressure *(281)*.

Although the hyphal (soil) form of *C. immitis* has been found rarely in humans, several reports have described cases in which hyphae were discovered in brain tissue and the spinal cord *(21,22)*. It appeared that the presence of CNS plastic devices might be associated with morphological reversion of *C. immitis* to its saprophytic form.

A rare case of coccidioidal meningitis complicated with massive dural and cerebral venous thrombosis and tissue arthroconidia has been reported *(282)*.

As compared to amphotericin B, the advent of antifungal azoles did not bring improvement in therapy, leaving amphotericin B as the treatment of choice. Thus, ketoconazole either alone or in combination with intrathecal miconazole has been used in children with coccidioidal meningitis and was effective only in some cases *(283,284)*. Itraconazole's poor bioavailability with oral administration (the need of an acidic stomach for adequate absorption) and its limited penetration into CNS *(285)* coupled with the lack of intravenous formulation have significantly curtailed its usefulness in coccidioidal meninigitis, especially in severely ill patients.

In order to achieve success, intra-cerebrospinal fluid (CSF) therapy with amphotericin B because of toxicity problems requires much more careful clinical management. As an alternative, the intrathecal administration of amphotericin B has been recommended *(286)*. However, relapses of meningitis after cessation of intrathecal amphotericin B have been reported, even after years of quiescence.

Oral fluconazole has also been used for therapy of coccidioidal meningitis. In adults, the recommended dose is 400–600 mg, daily *(287)*; in children, the usual dosage of fluconazole is 3–12 mg/kg, daily *(281)*. In general, fluconazole has been less potent than itrathecal amphotericin B in eradicating coccidioidal meningitis, in that meningitis recurred in most cases when fluconazole treatment was ceased *(288–290)*.

Cases of vasculitis complicating coccidioidal meningitis have increasingly being described *(291,292)*. Histologically, two types of vascular inflammation have so far been recognized. The first type represents a transmural inflammatory process of the intracranial blood vessels that is observed in the early course of the disease. Encroachment of the vessel lumen may result in thrombosis. Two cases of disseminated coccidioidomycosis complicated by fatal subarachnoid hemorrhage were reported by Erly et al. *(292)*. The second type of vascular inflammation occurs within a chronic disease and is associated with intimal thickering and luminal occlusion but with little inflammation *(291)*.

Currently, there are no established therapies for coccidioidal vasculitis *(291)*. The use of corticosteroids is still controversial, whereas agents that block the pathologic process (omega-3 oils and pentoxyfylline) may be of interest.

4. PROPHYLAXIS OF COCCIDIOIDOMYCOSIS

Patients who have completed initial treatment for an acute episode of coccidioidomycosis should receive lifelong suppressive therapy (secondary prophylaxis or chronic maintenance therapy) consisting of either 400 mg daily of oral fluconazole or 200 mg of oral itraconazole twice daily *(293)*. Alternative therapy with amphotericin B (1.0 mg/kg, i.v., once weekly) has also been recommended.

The recommended prophylaxis in HIV-positive infants and children to prevent recurrence of coccidioidomycosis consists of daily oral fluconazole at 6.0 mg/kg. As alternative therapy, either amphotericin B (1.0 mg/kg, i.v., once weekly) or itraconazole (2.0–5.0 mg, p.o., every 12–48 h) have been recommended *(293)*.

5. VACCINE STUDIES IN HUMANS

Although vaccine studies thus far have largely yielded disappointing results, supportive evidence exist to demonstrate the feasibility and need of developing a vaccine for coccidioidomycosis *(84)*. Most persons who had recovered from benign or asymptomatic infection developed a solid state of immunity to exogenous re-infection. Another factor is the presence of a well-defined target population of persons who are genetically predisposed to developing disseminated disease as well as per-

sons who have a high probability of exposure based on their occupation. Also, because the saprobic phase of *C. immitis* is geographically limited, delineating the areas of potential infection would be possible.

Early experiments in animal models have established that killed spherules induced protection against death (but not infection) following pulmonary challenge with *C. immitis* arthroconidia *(294–297)*. However, the following studies in healthy, skin-test-negative volunteers to evaluate the efficacy of this approach in humans while showing vaccine toleration rendered unacceptable levels of toxicity with doses of 10 mg or more; recipients of doses of 2.7 mg of the vaccine (given intramuscularly in one to three injections) showed localized tenderness or induration at the site of injection *(298–301)*. A larger randomized, double-blind, multicenter study conducted between 1980 and 1985 and involving 2867 healthy, skin-test-negative volunteers who received three intramuscular injections of 1.75 mg of killed spherules or sterile saline, respectively, showed no clinical benefits in the vaccinated group *(84,302)*.

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