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PHARMACOLOGY AND PHARACODYNAMICS OF ANTIFUNGAL AGENTS (ME KLEPSER, SECTION EDITOR)

Coccidioidomycosis: An Update

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Abstract Coccidioidomycosis is the oldest of the major mycoses. In recent years the incidence of the disease has increased in California and Arizona, which may be partially due to the massive migration to the endemic region. The endemic region for the disease lays exclusively in the Western Hemisphere, between the 40° latitudes north and south. The disease manifests in one of four clinical syndromes: acute pulmonary, chronic pulmonary and acute or chronic disseminated coccidioidomycosis. Serologic tests identifying anticoccidioidal antibodies are the most frequently employed assays for diagnosis. Primary coccidioidomycosis is usually self-limited; therapy of primary disease is recommended when symptoms persist for more than 6 weeks, for severe acute cases and for patients with impaired cellular immunity. Chronic pulmonary coccidioidomycosis and all forms of disseminated coccidioidomycosis require antifungal therapy. The drugs of choice are either fluconazole or itraconazole.

Keywords Coccidioidomycosis · *Coccidiodesimmitis Coccidioides posadasii* · Spherule · Arthroconidia · Coccidioidomycosis serology · Azole therapy

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Introduction

Coccidioidomycosis is the oldest of the major mycoses [1]. It was first described in 1892 by Alejandro Posadas, a medical intern in Buenos Aires; he at first thought that the patient had the malignant skin disease, *Mycosis fungoides*, but examination of skin biopsy specimens revealed organisms resembling the protozoan *Coccidia*. In 1896 Caspar Gilchrist, Emmet Rixford and C.W. Stiles named the organism after both its morphologic and clinical features: *Coccidioides* ("resembling Coccidia") *immitis* ("not mild") [2, 3].

Coccidioides is considered to be the most virulent of the primary fungal pathogens of humans [4]. It is now recognized to be caused by two distinct species, *Coccidioides immitis* and *C. posadasii*. The former appears to be geographically limited to the southern portion of California and Northern Mexico while the latter occurs in all geographic endemic areas. At this time, the presentation of disease, diagnosis and treatment do not appear to differ between the two species [5••].

Ecology

The endemic region for *Coccidioides* spp. lays exclusively in the Western hemisphere, nearly all of it between the 40° latitudes north and south. This life zone corresponds with the hot deserts of the Southwestern United States and Northwestern Mexico. The climate is arid with a yearly rainfall ranging from 10 to 50 cm, with extremely hot summers, winters with few freezes and alkaline, sandy soil. In the United States this semiarid zone encompasses the southern parts of Texas, Arizona, New Mexico, and much of central and southern California.

Endemic regions have also long been identified in semi-arid areas of Mexico and endemic foci have been described in areas of Central and South America (Fig. 1). Cases of coccidioidomycosis may also arise outside endemic areas. Such cases occur because of a recent visit to an endemic area or infection through exposure to fomites from such an area [6].

Epidemiology

An estimated 150,000 new infections occur annually in areas of the southwestern United States. However, since coccidioidomycosis is not a nationally reportable disease (reportable only in Arizona and California), the exact incidence is unknown. In recent years the incidence of the disease has increased in California and in particular to Arizona, one of the fastest-growing states in the United States [6]. Since implementation of this mandatory requirement, reports of coccidioidomycosis in Arizona and California drastically increased; in 2006, Arizona reported 5,535 cases (89/100,000 population) 10,279 cases (155/100,000 population) in 2009 and 11,888 cases in 2010 (179 per 100,000 population) [7]. This increase in incidence could be due to a number of factors, including soil disturbance due to construction for Arizona's rising population and to an influx of susceptible individuals into the population secondary to the massive migration to the Sunbelt states. The regions in Arizona in which *Coccidioides* is most intensely endemic were previously sparsely populated and now contain major population centers, filled primarily with persons who have moved from areas where *Coccidioides* was not endemic [6].

As of June 2010, the California Department of Public Health received reports of 20,931 cases of coccidioidomycosis from 2001 through 2009, reaching a peak at 3,043 reported cases in 2006. The annual incidence rate per 100,000 population increased by 91.1 % from 4/100,000 in 2001 to 8/100,000 in 2006, and decreased by 33.4 % subsequently to approximately 5/100,000 in 2009 [8•].

Statistics on the prevalence and incidence of coccidioidomycosis in Latin America are either fragmentary or simply not available. In Mexico most clinical case reports originate in the northern region of the country. Since coccidioidomycosis is not a reportable disease in Mexico, its true incidence unknown. Skin test surveys indicate that *Coccidioides* spp. infections are as prevalent there as in the endemic areas of the United States. Coccidioidin skin test regional surveys for prevalence of infection have shown rates ranging from 10 % [9] to 93 % [10].

Historically, Argentina is of the greatest interest because the first known case was reported by Posadas from that

Fig. 1 Geographic distribution of Coccidioidomycosis

country [11]. Few coccidioidin skin test surveys have been carried out in Argentina, and thus the magnitude of infections in the endemic areas is unknown. A couple of coccidioidin surveys have shown a prevalence of infection ranging from 14.8 % to 16 % [12, 13].

In Brazil the number of published cases of the disease in humans has increased considerably in recent years. Also, there are reports of isolation of the fungus from tissues of armadillos (*Dasypus novemcinctus*) dogs, and from soil samples collected in armadillo burrows. Currently, this systemic mycosis is considered endemic in northeastern Brazil [6].

Risk Factors for Infection and Disease

Because *Coccidioides* spp. infects humans by the respiratory route, exposure to dust is one critical factor determining the risk of infection [9]. The main risk factors for acquiring infection from *Coccidioides* spp. are activities that bring one into contact with dust from undisturbed soil in the endemic areas. *Coccidioides* spp. is distributed unevenly in the soil, usually found 10 to 30 cm below the surface of the soil [6].

It has long been speculated that environmentally mediated mechanisms cause significant seasonal and inter-annual fluctuations in the incidence of coccidioidomycosis infection. One proposed mechanism suggests that precipitation modifies the suitability of the environment for fungal growth. Consistent with this hypothesis are several relationships identified between case rates and precedent precipitation in Arizona. In addition to influencing the presence of *Coccidioides* spp. in the soil, the absence of precipitation may cause the fungus to sporulate and aerosolize more readily. Together, these mechanisms constitute the "grow and blow" hypothesis: precipitation facilitates the growth of the fungus, while subsequent dry conditions result in sporulation and enable the spores to become airborne, ultimately resulting in human exposure. Wind or other disturbance is required to fragment the hyphae and disperse the spores for inhalation by a host. On average, peaks in exposure to the fungal spores occur during the drier and dustier months of the year [14, 15•].

Dust storms in the endemic area are often followed by outbreaks of coccidioidomycosis. One particularly severe dust storm in 1977 carried dust from the San Joaquin Valley up to the San Francisco Bay area and resulted in hundreds of cases of non-endemic coccidioidomycosis in areas north of the San Joaquin Valley [16]. Above this ambient risk occupational and recreational dust exposure as well as natural phenomena has occasionally caused outbreaks. Outbreaks of coccidioidomycosis have been described under several different circumstances: military maneuvers, construction work [17], earthquakes [18], model airplane competitions, and hunting (armadillo) expeditions [19].

Coccidioidomycosis has long been and continues to be a threat to military personnel who reside or train in areas where *Coccidioides* spp. is endemic as the armed forces have traditionally deployed large numbers of personnel to endemic areas [20].

Males are more often infected, which is likely related to occupational dust exposures; however, males also appear to be at a higher risk for dissemination, suggesting a hormonal or genetic component [21]. During 2006–2008 in Arizona 54 % percent of patients with coccidioidomycosis were male (84/100,000 population), and 46 % were female (72/100,000 population) [22].

Numerous studies document an increased predilection for severe coccidioidal infections, coccidioidomycosis-related hospitalizations, and extrapulmonary dissemination in persons of African descent [23]. The 1977 dust storm in California provided a natural means of confirming this increased risk. The incidence of disseminated coccidioidomycosis in the non-Caucasian population was disproportionate to its overall representation. During this wind-borne outbreak of coccidioidomycosis in the non-endemic disease region of Sacramento County, California, the rate per 100,000 of disseminated coccidioidomycosis among African American men compared with Caucasian men was 23.8 versus 2.5 (ratio 9.1:1). This difference could not be explained by differential exposure [16]. The apparent variation in susceptibility among ethnic groups suggests that genetic factors influence the development of disseminated coccidioidomycosis [6].

Underlying medical diseases that affect T cell function are known to increase the risk of disseminated disease including human immunodeficiency virus (HIV), cancer (particularly Hodgkin's disease), and disease processes requiring transplantation and subsequent immunosuppressive agents [21]. Coccidioidomycosis is a recognized opportunistic infection among persons infected with HIV. The first reports of coccidioidomycosis associated with acquired immunodeficiency syndrome (AIDS) occurred just a few years after the initial reports of AIDS. Early in the HIV epidemic, most cases presented as overwhelming diffuse pulmonary disease with a high mortality rate [24]. Fortunately the incidence of severe symptomatic coccidioidomycosis has declined dramatically since the advent of highly active antiretroviral therapy. Although these cases are still seen, they are typically in patients with previously undiagnosed HIV infection and extremely low peripheral blood CD4 cell counts [25].

Coccidioidomycosis is the most common endemic mycosis to cause disease in solid-organ transplant patients in North America. Underlying renal and liver disease, T

lymphocyte suppression from antirejection medication and activation of immunomodulating viruses, such as cytomegalovirus, increase the risk for coccidioidomycosis among these patients [26].

Fungal infections have become an increasing problem for older persons in the United States. Older subjects today are more likely to be considered for transplantation, receive aggressive regimens of chemotherapy, or take immunosuppressive drugs for rheumatologic or autoimmune diseases. Increasing age and decreasing cell-mediated immunity as a result of transplantation, chemotherapy, or other immunosuppressive medications (e.g., tumor necrosis factor–α inhibitors) are the main predisposing factors [27].

Pregnant women have long been considered to be at increased risk of developing severe or disseminated coccidioidomycosis, presumably because of a general depression in cell-mediated immunity or because of changes in the levels of hormones that stimulate the growth of the fungus [28]. Rates of spherule maturation and endospore release are accelerated, in a dose-dependent fashion, with the most striking effects seen at levels encountered in advanced pregnancy. This suggests that direct stimulation of *Coccidioides* spp. by human sex hormones may help to account for sex-related and pregnancy-related predisposition to dissemination of coccidioidomycosis [29].

Clinical Forms

The clinical manifestations of coccidioidomycosis have a broad spectrum, ranging from an absence of symptoms to severe life-threatening infection. The disease manifests in one of four clinical syndromes: primary coccidioidomycosis ("Valley Fever"), chronic pulmonary coccidioidomycosis and acute or chronic disseminated coccidioidomycosis.

Primary Coccidioidomycosis ("Valley Fever")

Primary coccidioidomycosis is the most common form of presentation of coccidioidomycosis. Approximately 60 % of the infected individuals acquire an asymptomatic self-limited infection without clinical or radiological manifestations. The remaining 40 % present a syndrome characterized by pulmonary and systemic manifestations that usually appear one to three weeks after exposure to the fungus.

The vast majority of patients (~95 %) with symptomatic primary coccidioidomycosis generally present symptoms of acute flu-like respiratory disease (fever, night sweats, arthralgia, cough and pleuritic pain); this usually benign syndrome is commonly known as "Valley Fever" [30, 31]. Cough and fever are the most common symptoms, occurring in 75 % of patients, and the skin is affected in approximately 50 % of patients. A non-pruritic, fine papular rash ("toxic erythema") may precede the respiratory illness. Erythema nodosum and erythema multiforme (as well as arthralgia) are delayed-type hypersensitivity immune reactions to the infection and occur several days to weeks after the onset of illness. Blood eosinophilia is reported in 5 % to 18 % of cases with white-cell differential counts up to 20 % eosinophils [32].

Pulmonary coccidioidomycosis is often clinically and radiographically indistinguishable from other forms of acute pneumonia, such as bacterial community-acquired pneumonia (CAP); features suggestive of coccidioidal infection rather than bacterial CAP include rash, hilar adenopathy and duration of symptoms lasting over 2 weeks. Since primary pulmonary coccidioidomycosis generally resolves spontaneously, a patient with undiagnosed coccidioidomycosis who receives antibacterial therapy may appear to respond to treatment; however, a substantial portion of patients with coccidioidal pneumonia may have a prolonged course and may benefit from specific antifungal treatment. For this reason, coccidioidomycosis should be strongly considered in the differential diagnosis of all patients with CAP who reside in, or who have recently visited, a disease-endemic area [33].

Most patients with primary disease recover spontaneously and are thought to retain lifelong immunity to exogenous reinfection [34].

Chronic Pulmonary Coccidioidomycosis

Chronic and disseminated disease is estimated to occur in up to 5 % of infected individuals, with comparatively more cases occurring in older individuals and in males. Approximately 5 % of primary pulmonary cases develop residual pulmonary lesions, mostly solitary nodules and/or thin-walled cavities that are asymptomatic in most patients. In immunocompromised patients the acute pulmonary form might not resolve and progress to chronic pneumonia with the formation of a pulmonary cavitation [30].

Due to its chronic progression, progressive pulmonary coccidioidomycosis constitutes an important differential diagnosis with pulmonary tuberculosis (TB). Both diseases share some common risk factors, including overlapping areas of endemicity and increased occurrence among immunosuppressed patients. Furthermore, presenting syndromes may be similar, with lingering constitutional symptoms, respiratory symptoms, subacute meningitis, or reactivation of primary infection years after initial exposure. Co-infection should be suspected in coccidioidomycosis-endemic regions among patients with TB who fail to improve clinically or radiologically despite adequate therapy. In endemic areas for both diseases, the pertinent studies for

diagnosing both ailments should be performed in every patient with compatible clinical features. It is important to remember that the diagnosis of one of them, does not exclude the possible existence of the other [35–37].

Disseminated Coccidioidomycosis

In less than 1 % of the patients with primary pulmonary coccidioidomycosis the infection disseminates beyond the lungs; the presence of mediastinal or paratracheal lymphadenomegaly in chest imaging should suggest dissemination.

Disseminated coccidioidomycosis, thought to be the result of fungemia that occurs after the initial respiratory infection, can be either acute or chronic.

Dissemination is found more often in males, people of African or Filipino descent, pregnant women and in patients with deficient cell-mediated immunity. Transplant recipients who contract coccidioidomycosis have rates of extrapulmonary infection that may reach as high as 75 %. Although such dissemination most commonly involves the skin, the bones or joints, and the central nervous system, coccidioidomycosis has also been identified in many other tissues and organs [38].

Acute disseminated disease involves several organs or systems, with extremely high mortality. The lungs are diffusely affected as a result of hematogenous dissemination (refer to as miliary coccidioidomycosis) which can lead to acute respiratory distress syndrome [38].

Chronic disseminated coccidioidomycosis is usually progressive in a protracted form, disseminating to various organs, with periods of remission and recurrence, despite antifungal treatment. The most common affected sites are the skin, the central nervous system and the skeletal system.

The most dangerous form of the disease is meningeal infection, which occurs in about 0.15 % to 0.75 % of extrapulmonary coccidioidomycosis [30, 31, 34]. Symptoms commonly seen with coccidioidal meningitis include persistent headache, nausea, photophobia, cervicalgia and neck rigidity, confusion and decreased cognition and memory. Focal neurologic deficits or seizures in patients may result from cerebral vasculitis or mass lesions. The concentration of organisms in the cerebrospinal fluid of patients with coccidioidal meningitis is usually low and cultures are frequently negative [39]. Complications of coccidioidal meningitis include hydrocephalus, cerebral infarction, vasculitis and relapsing meningitis [40•].

Diagnosis

Traditionally three modalities—culture, microscopy, and serology—have been the bases for the diagnosis of coccidioidomycosis [5••]. Isolation of *Coccidioides* species and/or the histologic identification of the organism in tissue are still considered as the gold standard for the diagnosis of coccidioidomycosis; however, most patients are unable to produce sputum for culture and are not ill enough to require bronchoscopy or other invasive studies; thus, serologic detection of antibodies is the most commonly used diagnostic test [38].

Coccidioides can be identified directly in respiratory secretions using potassium hydroxide wet mounts and the fluorescent stain calcofluor white; the cytologic examination (Papanicolaou stain) of a sputum specimen is also diagnostic when spherules are identified. However, the sensitivity of these methods is relatively low. The diagnosis can also be established by visualization the pathognomonic endospore-containing spherules in fixed tissue using a variety of stains, including hematoxylin-eosin, Grocott methenamine silver or periodic acid-Schiff; round spherules (10–100 μm) in various stages of development, with or without internal endospores (2–5 μm), are the most common forms. Occasionally, immature spherules in a cluster or close to each other may be confused with other pathogens, such as *Blastomyces* species [38].

The growth of *Coccidioides* species from any type of specimen is diagnostic because there is no state of colonization. *Coccidioides* species are not fastidious and can be grown on most selective and nonselective fungal and bacterial media and it is usually visually apparent in 2 to 7 days. It can be phenotypically identified (distinguishing but not diagnostic) based on the presence of septate hyphae with barrel-shaped arthroconidia and clear zones called disjunctors on microscopic examination [38]. DNA probe provides definitive diagnosis; a nucleic acid probe (AccuProbe, Gen-Probe, Inc., San Diego, CA, USA) allows rapid, specific identification once visible growth has occurred [5••]. Coccidioides cultures constitute a laboratory biohazard and are currently listed as a 'Select Agent' of bioterrorism [41]. Because of these issues, suspected and established cultures of *Coccidioides* should be handled using Biosafety Level 3 containment [5••]. In vitro susceptibility testing of Coccidioides species is not routinely performed in clinical laboratories unless a specific requirement exists. *Coccidioides* species are generally susceptible in vitro to amphotericin B, fluconazole, itraconazole, voriconazole, and posaconazole [42].

Skin testing for cell-mediated cellular response using spherulin or coccidioidin antigens is rarely practiced in the United States because the antigenic preparations are not commercially available [43]. Coccidioidal cellular immunity can be determined by other means, including measuring the in vitro release of cytokines, such as interferon-γ, in response to incubation of blood with coccidioidal antigens. The feasibility of this approach has already been proven and has shown equivalence with mycelial-based coccidioidin

[44]. This test is analogous to the currently marketed interferon-γ release (IGRA's) assays for tuberculosis and could be commercially developed [5••].

Serologic tests identifying anticoccidioidal humoral antibodies (IgM and IgG) are the most frequently employed assays for the diagnosis and prognosis of coccidioidomycosis. It traditionally has included the tube precipitin (TP) and complement fixation (CF) assays; the immunodiffusion tube precipitin (IDTP) and immunodiffusion complement fixation (IDCF) are variants of these assays that employ immunodiffusion in agar. All are very specific and relatively sensitive. The TP and IDTP assays measure an immunoglobulin (Ig) M response and are positive early in illness while the CF and IDCF assays become positive usually after 2–3 weeks of illness measuring an IgG reaction. IgG titers have prognostic implications, with high titers indicating severe or disseminated disease. Early IgM becomes measurable in the acute phase of the infection, usually between the first (50 %) and third (90 %) weeks of onset. IgG antibody becomes measurable sometimes between the second and 28th weeks after onset; declining complement fixation titers reflect the resolution of infection. In persons who resolve their clinical illness, both reactions become negative over time; persistently positive serologic findings may indicate continued infection [5••, 38]. Serologic tests for coccidioidomycosis are less likely to be positive in immunocompromised patients than among normal hosts [45]. An enzyme-linked immunosorbent assay (Premier EIA, Meridian Diagnostics, Inc., Cincinnati, OH, USA) has been widely employed for the past two decades; however, the Premier assay may be subject to false-positive results for IgM while in contrast, clinical and serological studies found a good correlation between a positive result for IgG by the Premier assay and infection with *Coccidioides* [46].

Nucleic acid amplification tests have been introduced for the detection of *Coccidioides* species in clinical specimens. Real-time polymerase chain reaction (PCR) has been used directly on clinical specimens, including respiratory secretions, fresh tissue, and formalin-fixed paraffin-embedded tissue. Rapid PCR has good sensitivity (range, 80 % to 98 %) and specificity (range, 98 % to 100 %) depending on the specimen site [38, 47].

Treatment

The American Thoracic Society recently published updated guidelines for the treatment of fungal infections, including coccidioidomycosis [48••].

Primary pulmonary coccidioidomycosis is usually self-limited and does not require specific treatment in individuals without risk factors for chronicity or disseminated disease. Therapy of primary pulmonary disease is recommended when symptoms persist for more than 6 weeks or for severe acute cases. The drugs of choice are either fluconazole (400 mg/day) or itraconazole (400 mg/day) for 3 to 6 months.

In contrast, therapy for primary pulmonary coccidioidomycosis should be considered for patients with impaired cellular immunity (HIV infection with peripheral blood CD4 cell counts less than200/mL), immunosuppressive therapy (cancer, solid-organ transplants, anti-TNF therapy, etc. [49]) and in those with co-morbidities such as diabetes, chronic lung disease, chronic renal failure, congestive heart failure or known risk factors for dissemination (pregnancy, African-American or Filipino-American heritage). These patients should be treated with fluconazole (400 mg/day) or itraconazole (400 mg/day) for 3 to 6 months or longer depending on clinical response. As mentioned, declining titers of serum IgG anticoccidioidal antibody indicate treatment effectiveness.

Chronic pulmonary coccidioidomycosis (chronic pneumonia, nodules or cavities with symptoms >3 months) should always be treated. Azole therapy (fluconazole or itraconazole 400 mg/day) is generally prolonged, with a minimum course of 12 to 18 months or longer depending on clinical response. Treatment beyond 18 months should be considered in patients with underlying immunocompromising conditions. Two new triazoles, posaconazole and voriconazole, have recently become available. Unfortunately, neither has been studied in a randomized, controlled trial for coccidioidomycosis, but there are small series and case reports suggesting efficacy of both in refractory cases [50].

Amphotericin B is currently reserved for the most severe cases of coccidioidomycosis or those that do not respond to azoles. In spite of its proven track record, the requirement for parenteral administration for long periods is inconvenient, frequently necessitating hospitalization and prolonged intravenous access. Furthermore, its well-known side effects and toxicity will sometimes require discontinuation of therapy despite a life threatening systemic infection [51].

Although there is no evidence that the newer lipid formulations of amphotericin B possess any greater efficacy than the conventional amphotericin B deoxycholate preparation, the lipid formulations are better tolerated and allows treatment with a reduction in renal and other toxicities [51].

For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (5 mg/kg/d) or amphotericin B (0.7–1.0 mg/kg/d) is recommended as the treatment of choice until clinical improvement, followed by an azole regimen for at least another year [48••].

All forms of disseminated coccidioidomycosis require antifungal therapy. Meningitis represents a special situation because antifungal therapy should be continued throughout a patient's lifetime due to the virtual certainty of relapse

when treatment is stopped; without treatment, the outcome of patients with coccidioidal meningitis is poor. In one study, 90 % of patients died within 1 year, and 100 % died within 2 years [52].

The treatment of choice for coccidioidal meningitis is fluconazole. The recommended dosage is 400 mg orally, daily; there are anecdotal reports of doses as high as 800 to 1000 mg, decreasing the daily dose if clinical improvement is achieved [53]. Itraconazole, 400–600 mg, daily, is an alternative. Intravenous amphotericin B deoxycholate is considered ineffective for coccidioidal meningitis, but intrathecal amphotericin B (IT-AMB) is considered as another alternative, with or without concurrent azole therapy. The dose of IT-AMB ranges from 0.1 to 1.5 mg per dose, administered at intervals ranging from daily to weekly. Regardless of the choice of antifungal agent, hydrocephalus, a major contributor to coccidioidal meningitis related morbidity and mortality, may develop and require a shunt [40•, 48••].

Prevention of Coccidioidomycosis

The combination of increasing incidence of disease, a growing population in the endemic area, and the lack of a highly effective drug treatment justifies efforts to prevent (rather than treat) this disease [6]. Vaccination against coccidioidomycosis has been argued to be a cost-effective intervention and a feasible endeavor, since natural infection almost always confers lifelong immunity to reinfection [54]. The Valley Fever Vaccine Project, a university-based consortium, has identified and cloned immunogenic proteins that have proven effective in the prevention of deaths and fungal burdens in mouse models of coccidioidomycosis. This suggests that a vaccine for use in humans could be created. A candidate vaccine comprised of a fusion protein based on two antigens has been selected and is currently in pharmaceutical development under the sponsorship of this project, with the goal of evaluating the safety and immunogenicity in humans [6]. Despite such progress, further work is needed [38].

Conclusions

Coccidioidomycosis is the oldest and most virulent of the major mycoses and it's incidence in recent years has noticeably increased in California and Arizona. The clinical manifestations of coccidioidomycosis have a broad spectrum, ranging from an absence of symptoms to severe life-threatening infection, thus clinicians in endemic areas need to consider the disease in the differential diagnosis to order the appropriate tests. Isolation of *Coccidioides* species is still considered as the gold standard for the diagnosis; however, since most patients are unable to produce sputum for culture, serologic detection of antibodies is the most commonly used diagnostic test. Even though current azole therapy has several advantages over older drugs, more potent agents are still required to attain complete biological cure.

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