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Valley Fever: Danger Lurking in a Dust Cloud

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Abstract

Coccidioides immitis and *Coccidioides posadasii* contribute to the development of Valley Fever. The ability of these fungal pathogens to evade the host immune system creates difficulty in recognition and treatment of this debilitating infection. In this review, we describe the current knowledge of Valley Fever and approaches to improve prevention, detection, and treatment.

Keywords

innate immunity; adaptive immunity; fungal pathogen; lung infection; *Coccidioides*

1. Introduction

Coccidioidomycosis is an infection caused by inhaling spores of the fungal species *Coccidioides immitis* or *Coccidioides posadasii*. The disease has commonly been termed “Valley Fever,” “San Joaquin Valley Fever,” “San Joaquin Fever,” “desert fever,” and “desert rheumatism” [1]. A high incidence of coccidioidomycosis has been reported in the southwestern United States, Central America, and South America [2, 3]. The rise in cases has contributed to hospitalization costs totaling over $2 billion for those afflicted with the illness, which include individuals with symptoms ranging from mild local infections to disseminated disease [4].

Although inhalation of *Coccidioides* is the most common mode of transmission, there are rare cases of transmission through transplanted organs or inoculation by penetration of the skin by a sharp object containing the fungus [3, 5]. While most infected individuals are asymptomatic, about 40% of individuals show flu-like symptoms, such as fever, cough,

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headache, skin rash, muscle aches, joint pain, and fatigue [1, 3, 6, 7]. In most cases the immune system resolves the infection without the need for medical intervention. However, without proper diagnosis, disseminated disease may occur, leading to increased severity of symptoms. Laboratory diagnostic testing and clinical evaluation are the most effective measures for determining coccidioidomycosis. Early detection and antifungal drug treatments aid in slowing or inhibiting the development of disease and limit tissue damage, and may prevent morbidity [2]. In this review, we aim to provide a better understanding of coccidioidomycosis and to promote awareness of these pathogenic fungi.

2. Valley Fever

2.1 Geographic Distribution of Coccidioidomycosis

Two types of coccidioidomycosis-causing fungi exist: *C. immitis* and *C. posadasii* [8]. *C. immitis* is mainly endemic to California and is often referred to as the “Californian” strain, while *C. posadasii* is distinguished as the “non-Californian” strain [8]. However, *C. immitis* has also been isolated from soil in Venezuela and Washington State, where several patients were suspected of contracting coccidioidomycosis [9, 10].

There is a relatively low incidence rate of Valley Fever on a national scale in the United States and a variable status as a reportable disease across endemic regions [11, 12]. *Coccidioides* fungi have been found in the Western Hemisphere, mostly in hot, arid areas between latitudes of 40° north and 40° south, including the southwestern United States, Mexico, and Central and South America (Fig. 1) [7, 13, 14]. Suspected sites of infection have been described as dry plains, hills, prairies, and tropical desert brush land [9]. These areas tend to have temperatures ranging from 5°C to 45°C, rainfall averaging between 125 and 500 mm, and altitudes between sea level and 800 meters above sea level [9]. With differences in reporting over time and between regions, it is difficult to determine where the fungus was contracted, and which environments propagated the development of the disease [12].

2.2 Geographic Distribution in Latin America

In 1892, one of the first described cases of coccidioidomycosis was observed in a 36-year-old Argentinian soldier by a medical intern, Alejandro Posadas, in Buenos Aires [11, 15]. However, the more recent incidence and prevalence of coccidioidomycosis in Latin America is unclear [14]. Outside of the United States, other endemic regions include Mexico, Central America, and South America. South American countries that are confirmed to harbor the illness-causing fungus include Argentina, Columbia, Paraguay, and Venezuela, though limited patient data exists to support these claims [9]. The regions of Bolivia, Ecuador, and Peru are also potential sites for harboring the fungus, but even less patient data is clearly documented for these regions.

2.3 Geographic Distribution in North America

The highest rates of coccidioidomycosis cases in North America have been reported in Arizona and California [16]. The illness has also been reported in southern Nevada, southern Texas, Utah, New Mexico, and Washington [7, 10, 13, 17]. Cases reported in Mexico

generally tend to originate in the northern region [18]. However, the true incidence of the disease is not known, since coccidioidomycosis was not a reportable disease in Mexico until recently [18].

2.3.1 California—Many of the endemic cases of coccidioidomycosis in the United States are reported in California. The incidence of hospitalizations in California at 0.89 (95% CI 0.79-0.99) /100,000 persons/year likely underrepresents the extent of the disease in the San Joaquin Valley region, which contains only 10% of California's population [19]. This underrepresentation may be due to this region's population consisting of lower-income inhabitants, who are less likely to seek medical care except in severe cases of infection [19]. Initial reports of coccidioidomycosis in the United States were published in the San Joaquin Valley of California in 1939 [1, 20, 21]. In the last quarter century, dramatic increases in the reported incidence of Valley Fever in California have brought more public attention to the disease [13, 19].

Since the fungus is spread through dust, an increase in the number of reported cases tends to occur during the harvesting season in endemic areas (Fig. 2). During World War II (WWII), several airfield training sites were built in the San Joaquin Valley. The dusty sites were suspected to have caused an 8-25% rate of new infections in those employed by the military, making it the most common cause of hospitalization at several Southwestern airbases [20]. A dust storm in 1977 in the San Joaquin Valley and an earthquake in 1994 in Northridge were also reported to have caused hundreds of cases of coccidioidomycosis in those areas of California [13]. A six-fold increase in the rates of reported cases occurred in California between 2000 and 2011 [16]. Whether this is due to increased awareness of the illness, changes in the environment, or other factors remains unknown.

2.3.2 Arizona—About 60% of endemic cases in the United States are reported in Arizona (amounting to about 150,000 cases annually) [12]. Only people experiencing symptoms are generally tested, so whether the expression of symptoms in some individuals and not others is due to a large concentration of the fungus or a higher rate of dissemination is unknown. During a six-month period of WWII, as many as 50% of military personnel in Arizona undergoing the coccidioidomycosis skin test showed evidence of infection. At that time, Germany protested that exposure of its prisoners of war to the fungus in work camps violated the Geneva Convention [22]. In recent years, the incidence of coccidioidomycosis has increased in the elderly, even when the increase is adjusted for age [12]. This may be because older adults are more likely to seek medical care (and receive a diagnosis of coccidioidomycosis) or have a greater susceptibility to developing symptoms, and/or may be due to the increased influx of these elderly individuals from non-endemic regions into Arizona to retire, which could affect susceptibility to the fungus (see below) [12].

2.4 Populations Affected

Although coccidioidomycosis is most common in the southwestern United States, the Southwest's growing population and tourism industry may result in people from other areas returning home with the disease before developing clinical symptoms [23]. One hypothesis is that people from endemic regions develop immunity against the infection, and visitors to

endemic regions are more susceptible to infection. This idea is certainly possible, as individuals living in endemic regions are likely to have been exposed to the fungus, successfully cleared the infection, and developed antibodies. However, evidence for this hypothesis is confounded by the fact that the symptomatology of coccidioidomycosis is non-specific, which may prevent clinicians outside endemic areas from suspecting coccidioidomycosis [24]. Coccidioidomycosis has increased from 21 to 91 cases per 100,000 between 1997 and 2006 [12]. Coccidioidomycosis may manifest as acute pneumonia, chronic progressive pneumonia, pulmonary nodules and cavities, or as disseminated extrapulmonary nonmeningeal disease and/or meningitis [23].

Ethnicity, disease status, and occupation have been associated with coccidioidomycosis incidence. Hospitalization rates have been reportedly highest among the following groups in the last few decades: African-Americans and Filipinos, males 50-years or older, pregnant individuals, acquired immunodeficiency syndrome (AIDS) patients and other immunosuppressed individuals, and those working in certain outdoor environments, such as construction workers [12, 13, 25].

2.4.1 Ethnicity—The risk of developing disseminated coccidioidomycosis is about 10-127 times greater in people of African-American and Filipino descent, due to a genetic component contributing to the development of disseminated illness [13, 25-29]. Specific genes and blood groups are suspected to influence susceptibility to severe coccidioidomycosis [30]. African-Americans are associated with increased rates of hospitalization [31]. People who identify as Native American and Asian-Pacific Islander have lower rates of dissemination than those who self-identify as white [31].

2.4.2 Age—Although coccidioidomycosis can occur at any stage of life, the risk of developing coccidioidomycosis appears to increase with age [31-33]. In the youngest age group (0-14 years old), the incidence of hospitalization is less than 1 per 100,000 [31]. Whereas the rate of hospitalization increases to 7.2 per 100,000 in the 50 years and older group [31]. As a result, coccidioidomycosis has not been well-described in children, despite it causing a substantial disease burden in the children of Central California and elsewhere [34].

2.4.3 Health Status—Individuals with primary immune deficiencies and women in their third trimester of pregnancy are at high risk of developing disseminated coccidioidomycosis [13, 16, 31]. Common concurrent conditions include: having an immunocompromised state, AIDS, Hodgkin's disease, lymphoma, organ transplantation, and pregnancy [7, 16]. Diabetes patients may also be at an increased risk of developing multiple thin-walled chronic lung cavities as a residual effect of infection [35]. Although coccidioidomycosis may cause up to 33% of the cases of community-acquired pneumonia in Arizona, less than 15% of these patients are tested for coccidioidomycosis, perhaps because many healthcare providers lack the experience and knowledge to treat the illness [36].

2.4.4 Occupation—Increased exposure to *Coccidioides* is an occupational hazard faced by individuals who work in outdoor environments close to the soil and dust including: archaeologists, military personnel, construction workers (especially those in excavation and

pipeline or highway construction), cotton mill workers, and agricultural workers [13, 25, 37-40]. In particular, personnel engaged in digging operations in dusty soil are at highest risk for infection [38]. Professions, lifestyles, and hobbies requiring travel to endemic areas also put individuals at risk of exposure to *Coccidioides* [38]. Containing and reducing human exposure to dust has been recommended as a primary measure to reduce the risk of Valley Fever [13].

2.5 Biology of Pathogen

C. immitis and *C. posadasii* are dimorphic fungi of the phylum Ascomycota, in which most known human fungal pathogens belong. Proper biosafety protocols must be observed when working with *Coccidioides* as the arthroconidia are very stable, can be viable for years under dry conditions, and are capable of becoming airborne once they are formed. Under most laboratory conditions (Sabouraud-dextrose agar, brain-heart infusion agar, potato-dextrose agar, and blood agar), *C. immitis* and *C. posadasii* require 5-10 days at room temperature to grow, forming a white highly filamentous aerial colony, which then turns tan [41]. This colony contains predominantly arthroconidia and long septated hyphae. Most soil fungi appear morphologically similar to *C. immitis* and *C. posadasii* at room temperature; however, only *Coccidioides* species are known to transition to the endosporulating spherule form (ranging in size from 10-100 microns) at mammalian physiological temperatures *in vitro* under inducing conditions and *in vivo* in animal infection models. The most successful technique to induce spherule formation *in vitro* is to culture the fungus in liquid modified Converse medium at 37-40°C [42].

The sexual cycle of *Coccidioides* species has not yet been elucidated. Although sexual structures have not been observed in the laboratory for *Coccidioides* species, there is molecular and genetic evidence to suggest the existence of a sexual cycle in *Coccidioides*. For example, molecular phylogenetic analyses indicate that different *Coccidioides* strains have undergone recombination (rather than clonal growth) [43-46]. This work was also important in clarifying that *C. immitis* and *C. posadasii*, although very closely related, are distinct species undergoing separate sexual recombination events in nature. Subsequently, work on characterizing the mating type (*MAT*) locus, which is the genomic region regulating sexual reproduction in the fungal kingdom, identified the structure of the *MAT* locus in *C. posadasii* and *C. immitis* [47, 48]. These studies found that *C. posadasii* and *C. immitis MAT* loci are arranged similarly to the *MAT* locus of *Histoplasma capsulatum*, suggesting that they have a heterothallic sexual cycle with alternating mating type genes found at a single locus. Indeed, population studies on *C. posadasii* and *C. immitis* isolates identified a 1:1 ratio of mating type alleles [48], providing further evidence for the existence of a sexual cycle in these species in nature.

2.5.1 Life cycle—*C. immitis* and *C. posadasii* are similar in their development and life cycle. The fungi have been reported to be found clustered around animal burrows and ancient Indian burial sites in high concentrations [49, 50]. A mammalian host, such as a rodent, has been suggested to act as a carrier to spread the fungi throughout an endemic area [51]. *Coccidioides* is the only alternating arthroconidia species to contribute to systemic

disease. *Coccidioides* species are dimorphic fungi with two distinct life cycle phases: saprophytic and parasitic (Fig. 3) [3, 52].

During the saprophytic phase the fungus resides in the soil, where the mycelia, or threadlike hyphae, feed off its surrounding environment of nonliving and organic matter, such as rodent corpses, in the soil [7, 51]. As the environment changes due to lack of nutrients or drying of the soil, the mycelia produce arthroconidia in alternating cells, where the arthroconidia are separated by dead cells [7, 52, 53]. Arthroconidia can remain viable for years in the soil and continue to germinate new mycelia if growth conditions are favorable [3, 7]. The fungi are also resistant to harsh conditions, such as high temperatures and high salinity, particularly in the arthroconidia form [54].

Soil disruptions, such as agricultural activities or natural disasters, can disarticulate arthroconidia and release *Coccidioides* into the air to be carried by the wind or spread during dust storms [7, 55, 56]. Not only does this increase the distribution range of the spores, but also provides the opportunity to infect additional hosts. Inhalation of the arthroconidia leads to infection in humans, but has also been described to infect horses, rodents, snakes, cats, and dogs [53, 57-59].

Once inside the host's body, the fungus transitions into its parasitic phase. The increased temperature and CO_2 concentration in the host contribute to the transformation of arthroconidia [3]. The barrel-shaped, 3 to 5 μm in size, arthroconidia begin to modify their cell wall to form a spherule with the cells inside rounding and swelling around a vacuole in the middle [3, 53]. The structural changes distinguish the fungus in its parasitic phase. Endospores begin to differentiation around the vacuole and expand the spherule for about 3 to 4 days [3, 53]. After developing hundreds of endospores, the spherule can rupture and spread its contents [3, 53]. This results in further distribution of infection throughout the body, allowing the parasite to repeat its life cycle.

2.6 Pathology and Pathogenesis

As noted above, the primary route of infection for most cases of coccidioidomycosis is through inhalation of arthroconidia into the lungs. Once the arthroconidia lodge in the terminal bronchioles, the fungus reverts to a spherical structure called a spherule; this structure enlarges and becomes filled with mature endospores. After several days of growth, the spherule ruptures releasing endospores into the surrounding tissue. Each endospore is then capable of producing another spherule [60]. Cellular immunity in the host is activated upon spherule formation as is evidenced by increased IL-17, IFNγ and TNFα production [61]. In most cases, the immune response controls the infection, and the infection is resolved without treatment. In biopsied tissue, there may be evidence for non-caseating granulomatous inflammation, and the spherules may be visible on tissue staining (Fig. 4). While the spherules may sometimes be seen on hematoxylin and eosin staining, they are best visualized using silver staining (Fig. 5).

2.7 Immune Response

2.7.1 Innate immune responses to Coccidioides—The vast majority of people develop only mild or asymptomatic disease following infection with *Coccidioides*, suggesting that the immune system normally controls infection. However, a subset of infections leads to chronic or severe disseminated disease, likely due to skewed or reduced immune responses that cannot control the fungal spread. Although innate and adaptive immune defects and immunosuppression increase the risk for severe infection, individuals with an apparently normal immune system, for unknown reasons, can also develop chronic and disseminated disease [7, 17, 62].

The innate immune system acts as the first line of defense against pathogens by recognizing and controlling the infection and activating the adaptive immune response. Little is known about how the innate immune system recognizes, attempts to control, and eliminates the fungal infection, particularly during a productive host immune response. Polymorphonuclear leukocytes (PMNs) are the first responders to *Coccidioides* infection [63]. However, the respiratory burst by these cells kills fewer than twenty percent of the arthroconidia and may drive maturation to the spherule form of *Coccidioides*. Spherules are further resistant to phagocytosis and killing by PMNs due to their large size and potential inhibition of host responses by fungal proteins [64]. Macrophages also phagocytose the arthroconidia and endospores, but may have low killing ability due to specific inhibition of phagosome-lysosome fusion by the fungus [65]. Conflicting results suggest that T cells enhance the ability of macrophages to digest arthroconidia and endospores, but only if T cells are primed before infection. Macrophage functional enhancement by T cells is mediated by IFNγ and TNFα [66].

Different proteins, lipids and genomic material found on and within pathogen subsets termed pathogen-associated molecular patterns (PAMPs) can be recognized by pathogen-recognition receptors (PRRs) on antigen presenting cells. Recognition of *Coccidioides* by a subset of these PRRs, Toll-like receptor 2 (TLR2) and TLR4, promotes TNFα production and mediates a cell-mediated response to *Coccidioides* in vitro [67, 68]. Another PRR important in recognition of fungal invasion, dectin-1, appears to promote innate immune cells to direct T_h1 and T_h17 effector responses in part by reducing inflammatory cytokine production [69]. Additionally, several *Coccidioides* antigens have been identified with variable ability to induce adaptive immune responses [68].

Dendritic cells (DC), as professional APCs, are a critical link between innate and adaptive immune responses. *Coccidioides* antigens induce maturation, and activation of DCs and *Coccidioides* antigen-pulsed DCs can reverse the lymphocyte anergy found in disseminated disease [70]. IL-12-induced T_h1 responses are critical for effective/productive immunity against *Coccidioides* infection. DCs are a major source of IL-12, and activated DCs present antigen and costimulatory signals to naïve T cells; thus, DCs might be expected to play an important role in host immune responses to *Coccidioides*. Together, the few studies evaluating DC responses during coccidioidomycosis suggest that DC activation and antigen presentation is functional in patients with disseminated disease [3]. However, it is unclear whether the DCs in these patients promote an effective or detrimental response to

Coccidioides. Perhaps the DCs in patients with disseminated disease induce ineffective T helper effector responses or promote immune tolerance. One study characterizing DC functions in mouse models of infection found higher TLR2, TLR4 and costimulatory molecule expression and IL-12 production in DCs of resistant mouse strains, compared to susceptible mouse strains [71].

2.7.2 Adaptive immune responses to Coccidioides—Coccidioidomycosis induces both cell-mediated and humoral immune responses. Protective immunity requires a strong T_h1 skewed response resulting in production of IFNγ and IgG2a antibodies. Asymptomatic immune patients demonstrate a strong delayed-type hypersensitivity (DTH) reaction and low levels of complement forming antibodies in their serum, while severe disease is usually found in patients with low DTH reactions and high titers of complement forming antibodies [70, 72]. Recovery from severe disease is associated with decreased complement forming antibodies and increased DTH reaction [70]. Symptomatic patients develop T cell anergy against *Coccidioides* that is generally specific for this fungus and is reversible with disease remission [70, 73, 74].

It would therefore appear that humoral immunity plays a weak role in protection against this infection. As outlined above, the titer of complement forming antibodies correlates well with disease severity. In further support, serum from vaccinated mice does not protect from arthrospore infection, or depending upon the analysis, is less critical than T cells for protection [75]. However, using a vaccine model, it was found that vaccine protection is less effective in the absence of B cells, and that a B cell gene expression profile is associated with protection to arthroconidia [76]. Thus, the role of B cells and antibodies in controlling infection or protection against repeat exposure remains unclear.

Further evidence supporting the critical role of T cells in immunity to *Coccidioides* has been demonstrated using mouse models of infection and evaluation of risk severity in patients. Mice lacking $CD4^+$ or $CD8^+$ T cells are more susceptible to disease, and T cells transfer protection to naive animals [77, 78]. There is a high risk for dissemination and death in immunosuppressed individuals during organ transplant, HIV infection and neoplasia [79]. In HIV patients, the risk of severe disease increases with lower $CD4^+$ T cell numbers [80].

The type of effector T cell response mounted against *Coccidioides* appears to determine disease severity. T_h1 effector responses, particularly IFNγ and TNFα production, are widely accepted as providing protective immunity against *Coccidioides* that results primarily in mild or asymptomatic disease. Assessment of T cell activation by CD69 expression in coccidioidomycosis correlates with T_h1 effector cytokines and has been suggested to be a potential marker for measuring a productive cellular response to *Coccidioides* [81]. In contrast, T_h2 effector cytokine responses have largely been associated with more severe disease, perhaps in part due to the ability of these cells to suppress macrophage activation and T_h1 differentiation. While T_h2-associated cytokines decrease productive immune responses against *Coccidioides* in mice, in patients it is unclear if T_h2 effectors have any direct effects on immunity to *Coccidioides*, and overall T_h2 cytokines are not produced in response to *Coccidioides* antigens [3, 82]. T_h17 effector responses have not yet been measured in patients with coccidioidomycosis; however, evaluation of infection in

immunized mice indicates that disease susceptibility increases with the loss of T_h17 functionality [83].

Regulatory T (Treg) cells are known to modulate immunity during infection, and their suppressive function can be beneficial or detrimental depending upon the site or stage of an infection. Very little data exists evaluating the impact of Tregg cells on coccidioidomycosis. Reduced survival following infection in phagocytic NADPH oxidase-deficient mice correlated with an expanded Treg cell population in the lung [84]. IL-10 producing cells, that may be secreted by Treg cells or T_h2 cells, have been found in clusters adjacent to granulomata during coccidioidomycosis [85]. However, the role and relative importance of IL-10 production in the granuloma and Treg presence in the lung is unknown.

2.7.3 Immune evasion by Coccidioides—Most pathogens utilize multiple mechanisms to escape host immune detection, and *Coccidioides* express several documented virulence factors that contribute to infection [86, 87]. As noted above, arthroconidia and spherules are highly resistant to destruction by PMNs. The outer wall of arthroconidia appears to protect from phagocytosis, as removing the outer wall increases uptake of the arthroconidia. In contrast, the immune system builds a response against the spherule outer wall glycoprotein (SOWgp). *Coccidioides* endospores do not express SOWgp, thus avoiding immune detection by cells responsive to this antigen during a time when *Coccidioides* can be more efficiently phagocytosed. The spherules are further protected from the immune system by the production of proteases that digest antibodies. Finally, *Coccidioides* produces urease and induces host production of arginase I, both of which contribute to local tissue damage and enhance infection. Thus, while the host immune system fights to actively block infection or eliminate *Coccidioides*, the fungus has its own mechanisms to circumvent, avoid or prevent immune surveillance.

2.8 Diagnosis and Treatment

2.8.1 Diagnosis—Early diagnosis of coccidioidomycosis is significant to prevent disseminated disease, to reduce costs of hospitalizations and treatment, and to avoid persistent infection leading to tissue damage or death [2]. However, it is difficult to diagnose early infection for a couple of reasons. As described above, most individuals are asymptomatic. Some people exhibit flu-like symptoms, but do not seek medical evaluation because their immune system resolves the infection over time without medication. This also contributes to an underestime of reported annual coccidioidomycosis cases. These limitations in self-diagnosis can lead to severe symptoms of chronic pneumonia, meningitis, or bone and joint infection if the infection becomes a disseminated disease [3].

Individuals with coccidioidomycosis also have difficulties obtaining proper diagnosis from clinicians and laboratory testing. One assessment for patients who have persistent lung infection is to obtain a radiographic examination. The results are frequently misinterpreted and patients are diagnosed with lung cancer, even though they may be infected with *Coccidioide*s, which gives similar results on the X-ray [88]. There are other laboratory tests used to identify coccidioidomycosis, but they have limitations. Two commonly used diagnostic tests, enzyme immunoassay testing and sputum testing, help determine if a

patient has been infected with *Coccidioide*s. Enzyme immunoassay testing uses a patient's blood sample to measure *Coccidioides* antibodies. However, as many as 82% false-positive results for coccidioidomycosis have been reported with the antibody test [89]. These findings question the utility of the test for clinicians to diagnose the infection. Sputum culture requires a more invasive procedure to collect the sample, but provides a more accurate result for diagnosis. Doctors can also evaluate patients by performing biopsies, joint effusions, or lumbar punctures [2].

2.8.2 Treatment—Most patients resolve coccidioidomycosis without need of treatment. However, patients with chronic pulmonary or disseminated disease may require antifungal therapy [2]. Common antifungal drugs prescribed include: amphotericin B deoxycholate, lipid formulations of amphotericin, ketoconazole, fluconazole, and itraconazole [2]. Even though treatment is beneficial in clearance of infection, it may come at a cost to the patient, both financially and physically. Patients who require long term medication of antifungal drugs can spend up to $20,000 annually on top of hospital bills [2]. Harmful side effects are associated with using antifungal drugs, such as amphotericin B, which span from mild symptoms of nausea, vomiting, fever, and hypoxia, to severe side effects of anemia, hypertension, hyperthermia, and dyspnea [90]. Routine follow-ups to the physician are recommended after clearance of infection every 3-6 months for about 2 years to prevent developing further complications or disseminated disease [2]. However, chronically-infected patients may need long term follow-up through examinations and laboratory testing.

While there is limited data available for successful outcomes of treatment of immunocompromised individuals, one study demonstrated a significant reduction in relative risk for developing symptomatic coccidioidomycosis among patients treated with infliximab, a TNFα antagonist used for patients with autoimmune disease [91].

2.8.3 Vaccines—The development of a successful coccidioidomycosis vaccine has long been a research goal despite numerous challenges. A successful vaccine should show protective efficacy for both immunocompetent and immunocompromised individuals [92]. Many vaccines developed to protect against coccidioidomycosis have failed to show conclusive results for various reasons, some of which we summarize below. Vaccines containing killed organisms have shown optimum protection in animal models but failed in human Phase III trials due to inadequate dosing. These vaccines also resulted in major side effects and pain, which presented an additional issue. One potential solution for improving these killed vaccines is to eliminate side effects while preserving the key immunogens by fractioning the vaccine components [93]. Other vaccine trials in humans, which utilized auxotrophic mutants or attenuated live organisms, showed some survival advantages but failed to completely clear the fungus. Due to the inherent potential risk of reversion to virulence of an attenuated mutant that exists for a live vaccine, recombinant proteins such as rAg_2/Pra, rGel1, and CSA, have been pursued for vaccine trials. The majority of the recombinant antigens of *Coccidioide*s have failed to meet the benchmark of protection required in murine vaccine trials [3]. Since these candidate vaccines failed to show necessary protection and ability to stimulate an effective immune response during animal testing, they will not be tested in humans.

Recent research has shown that vaccines with purified plasmid DNA provide superior protection against coccidioidomycosis [92]. Currently, research is focused on pursuing a potential adjuvant vaccine designed to stimulate the appropriate level of immune response [92]. Another line of research for a new potential vaccine involves complementary DNA expression library immunization (ELI), which is under development along with use of parasitic cell wall proteins. Parasitic cell wall proteins can stimulate protective immunity against *C. posadasii* infection in mice and are considered the most protective antigens against coccidioidomycosis thus far [94].

3. Concluding Remarks

Research and recognition of coccidioidomycosis has progressed slowly since the first patient was diagnosed in 1892. However, increasing awareness of coccidioidomycosis can contribute to improving methods to prevent and combat this disease. Prevention is the first step to managing this fungal infection. One way to do so is by locating areas with high prevalence of *Coccidioide*s. Because the fungus is endemic to certain regions of the United States, researchers can study soil sampling in those areas. In turn, the public can be informed to be cautious when a particular site contains high levels of *Coccidioides*. Further improvement in technology of an on-site test for *Coccidioides* in the soil could add the benefit for turn-around time of evaluating a potential habitat for the fungus. Another preventive measure would be to understand the weather patterns during increased coccidioidomycosis cases. Dry periods after wet winters or summer have been associated with an increase in the rate of coccidioidomycosis cases for California and Arizona [53]. Collecting data on temperature changes and wind patterns, along with reports of coccidioidomycosis, will be informative in assessing correlations between environmental changes and infection rates. With these findings, individuals can consider seeking medical attention if they have symptoms related to Valley Fever during periods of increased likelihood of infection. Remaining indoors during dust storms, for example, provides a preventive approach against exposure to arthroconidia.

Improving diagnostic testing and early detection can also increase prevention of disseminated disease. Not only could patients benefit from early recognition, but also a more accurate number of reported cases could be tracked. Monitoring patients during acute infection could in understanding the mechanisms and progression of disease. This is critical in filling gaps in knowledge of Valley Fever for physicians. One uncertainty is whether a patient needs to be treated with antifungal drugs. If treatment is found to be needed, it is not known which drug is most effective, which dosage should be administrated, and what should be the duration of usage. Another question to be addressed is when a patient has cleared infection, how long should the patient continue to be followed-up?

Further research in the development and proliferation of the fungus in the host can aid in our understanding of an effective approach to clear the pathogen. It is unclear what regulatory events contribute to the transformation of arthroconidia into spherules after entry into the body. Characterizing the signaling for the transformation could contribute to preventing early infection. Studying the fungus could also contribute to the development of a vaccine. A number of vaccines have been developed and tested. Indeed, several coccidioidal antigens

have shown protective properties against the fungus in animal models. Thus far, however, a successful vaccine showing long term immunity in humans has not yet been achieved [95-97]. Overall, the approach to resolve this hidden danger in a dust cloud is to improve detection methods for *Coccidioide*s, improve reporting of infection cases, and better understand the immune response as a way of predicting which patients are at risk for disseminated disease.

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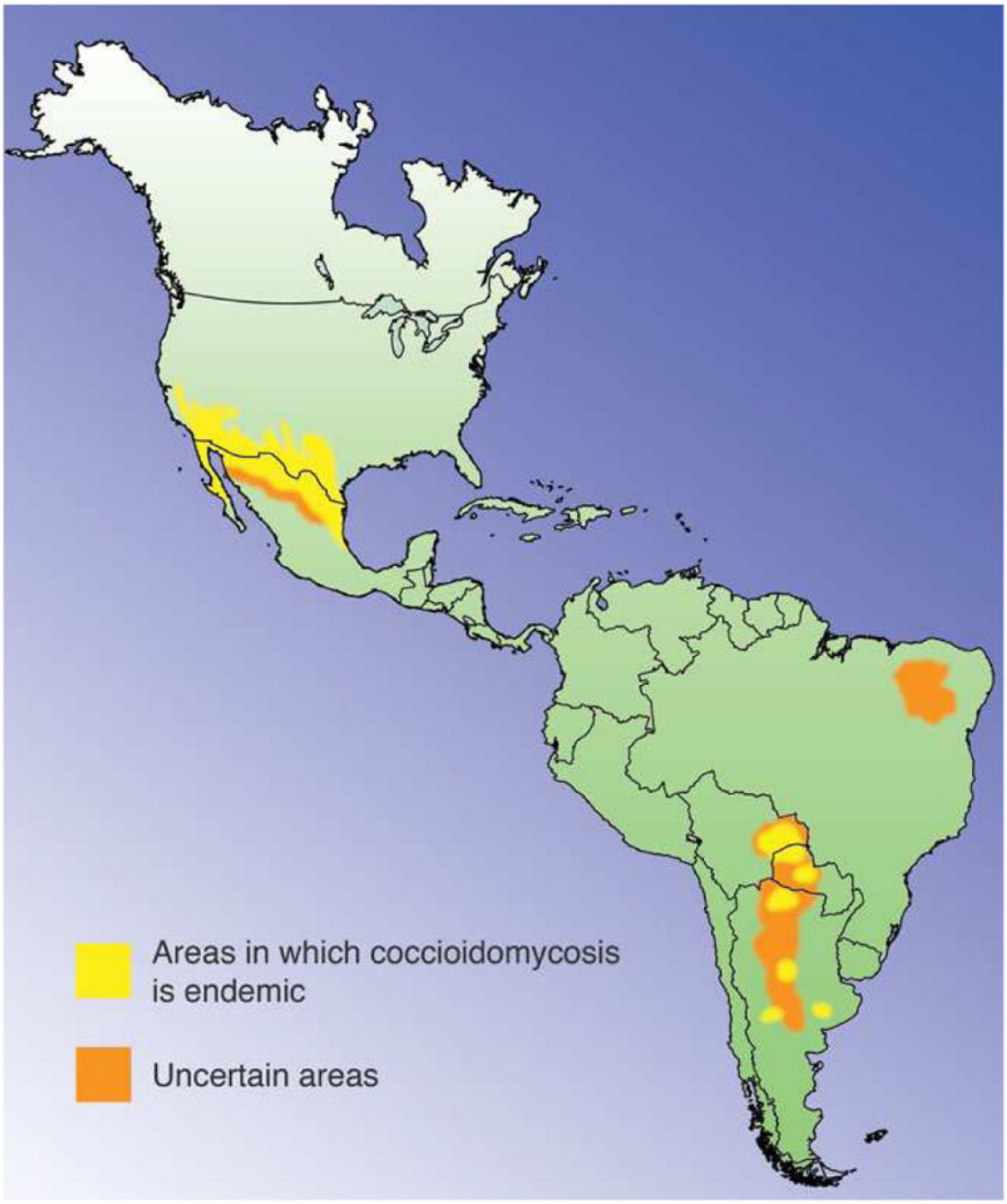

Figure 1.
Geographic distribution of valley fever across the Americas.

Figure 2.
A tractor disrupting soil and creating a dust cloud, which potentially could be spreading the fungal arthroconidia.

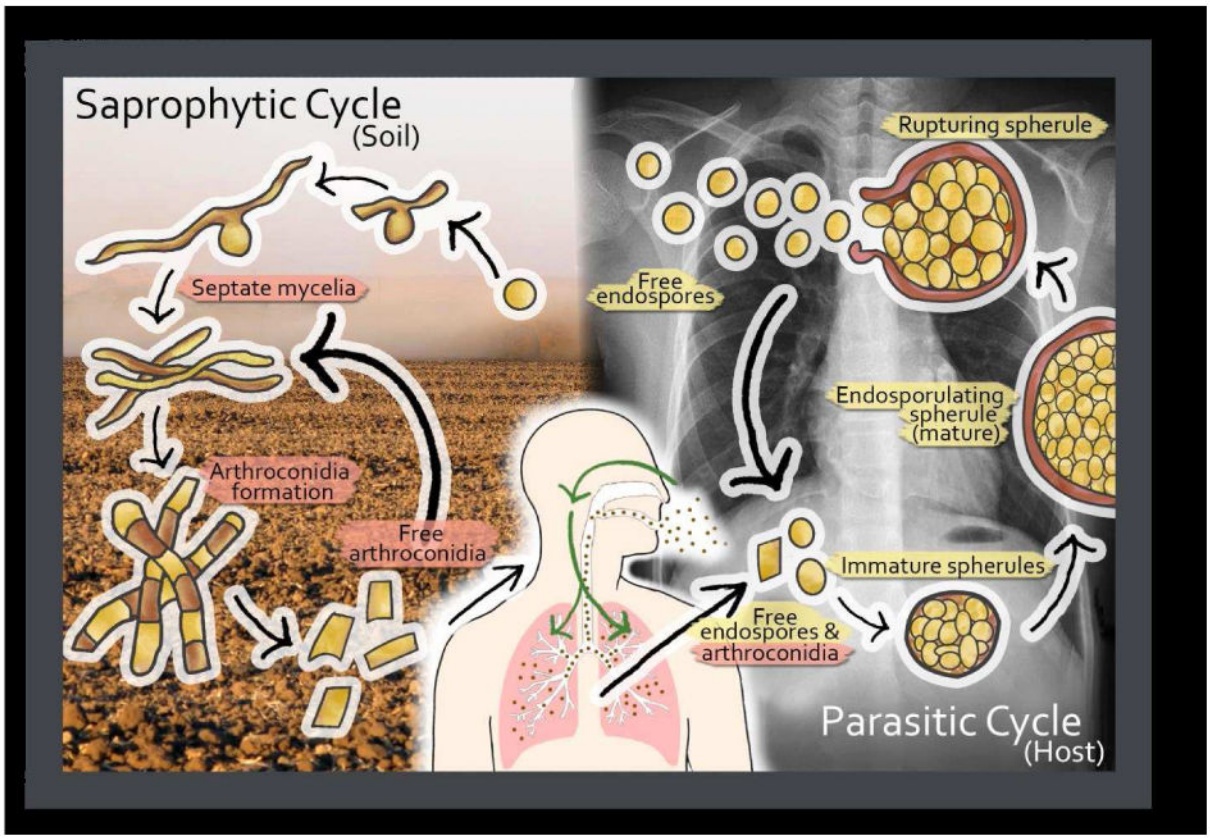

Figure 3.
Coccidioides immitis and *Coccidioides posadasii* life cycle in its two phases within the soil and host.

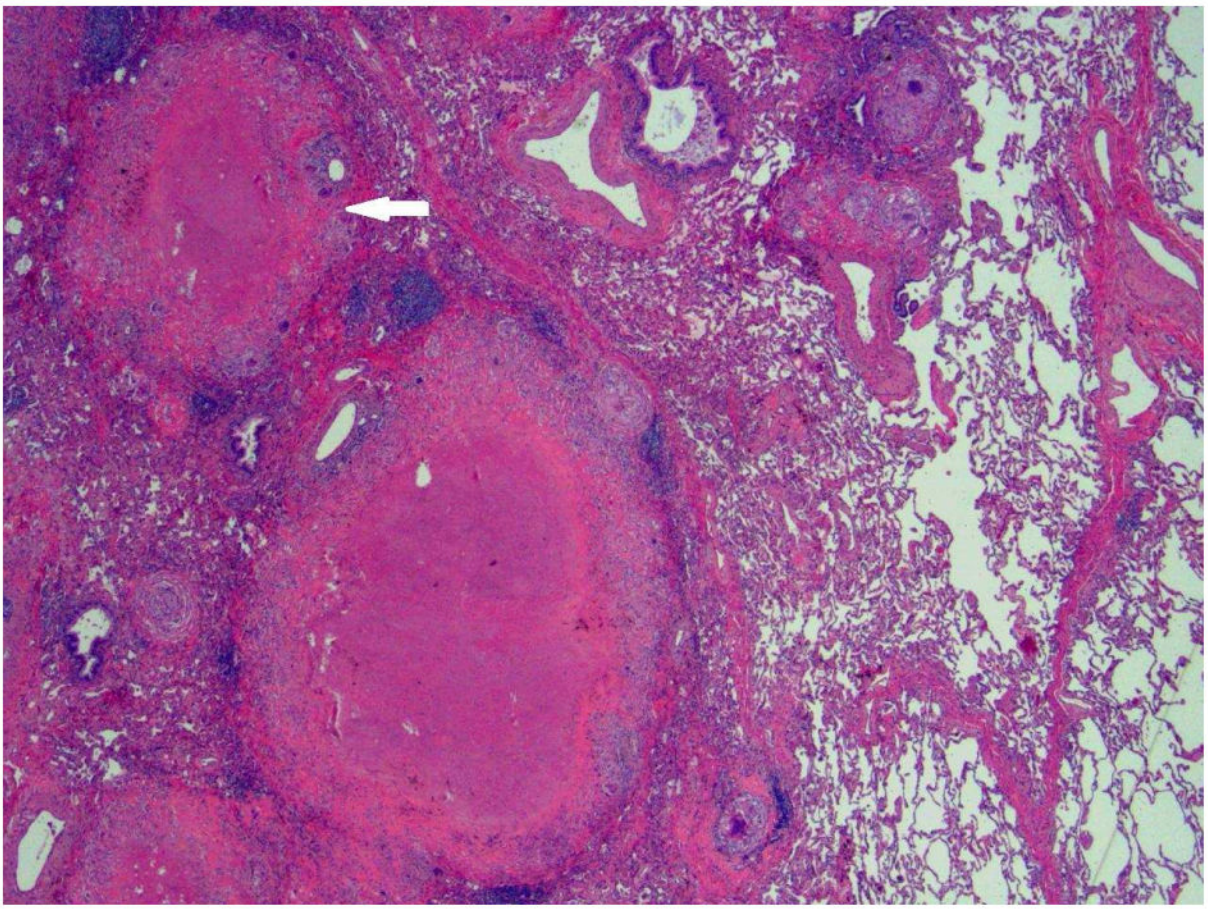

Figure 4.
Hematoxylin and eosin stain of a Valley Fever infected lung, demonstrating granulomatous inflammation. White arrow points to granuloma. Image courtesy of Dr. Williams Pitts (UCSF Fresno).

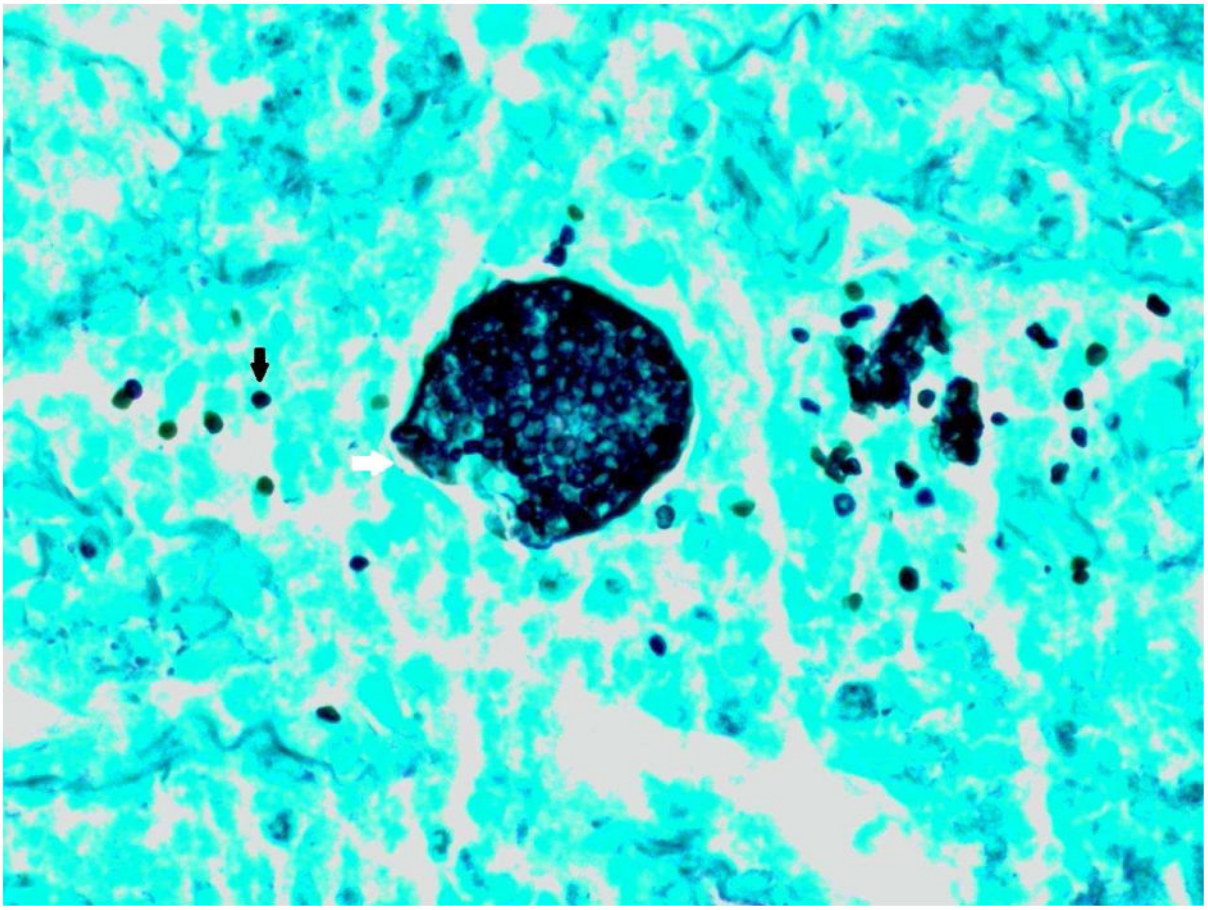

Figure 5.
Silver staining showing a spherule full of endospores with free endospores around it. Black arrow indicates an endospore, white arrow points to a spherule containing many endospores. Image courtesy of Dr. Williams Pitts (UCSF Fresno).