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Authors

Stewart, Ethan R
Thompson, George R

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Update on the Epidemiology of Coccidioidomycosis

Ethan R. Stewart¹ · George R. Thompson III^{1,2,3}

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Abstract Coccidioidomycosis is an illness caused by the soil-dwelling, dimorphic fungi, *Coccidioides immitis* and *Coccidioides posadasii*, which are found primarily in niche ecological zones of the Western Hemisphere. The bulk of infections due to *Coccidioides* are found within the endemic areas of Arizona, California, Mexico, and Central America. Outcomes run the gamut from asymptomatic to a self-limited or even chronic pulmonary process, up to severe disseminated, and life-threatening disease. Patients at particular risk include the elderly, pregnant women, and members of certain ethnicities. Recent changes in the epidemiology and our overall understanding of coccidioidomycosis that pose a particular challenge to healthcare professionals include the rising incidence of disease, identification of infections thought to be acquired outside the previously described zones of endemicity, and the risks posed to the immunosuppressed population due to the increasing use of immunomodulatory pharmaceutical agents.

Keywords Coccidioidomycosis · *Coccidioides* · Epidemiology · Ecology · Geography · Risk factors

Introduction

Coccidioides spp. are dimorphic, soil-dwelling, fungi known to cause a diverse clinical spectrum of illness. Approximately 60 % of patients are asymptomatic while the vast majority of those that do appreciate symptoms experience either a mild, self-limited febrile illness or a respiratory infection that would be indistinguishable from more common bacterial or viral causes. Less than 10 % of those with symptoms develop chronic forms of infection, or sequelae from primary infection such as pulmonary nodules or thin-walled cavitory lesions. Only a minority of patients experience severe symptoms. Serious, life-threatening complications are often the result of dissemination which frequently manifests as disease of the skin, bone, or central nervous system [1, 2]. Two genetically distinct species, *Coccidioides immitis* and *Coccidioides posadasii*, lead to clinically indistinct diseases, often discerned only by the geographic location of acquisition [3–5]. This article reviews the epidemiology of *Coccidioides* spp. by summarizing the current understanding of their ecologic environment, geographic distribution, and risk factors for infection while highlighting recent epidemiologic trends such as rising incidence, discovery in non-endemic areas, and calling attention to the enlarging at-risk population(s).

Ecology

Coccidioides spp. are found uniquely within the Western Hemisphere of the globe, and the region of endemicity is further demarcated by the 40° northern and southern lines of latitude. While in its saprophytic form, *Coccidioides* lies within

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✉ George R. Thompson, III
grthompson@ucdavis.edu

¹ Department of Internal Medicine, Division of Infectious Diseases, University of California Davis Medical Center, 4150 V Street, Suite G500, Sacramento, CA, USA

² Department of Medical Microbiology and Immunology, Coccidioidomycosis Serology Laboratory, University of California, One Shields Avenue, Tupper Hall, Davis, CA, USA

³ Department of Medicine, Division of Infectious Diseases, Department of Medical Microbiology and Immunology, University of California, One Shields Ave, Tupper Hall, Rm 3138, Davis, CA 95616, USA

the soil of desert regions as it thrives within warm, arid ecological zones that provide hot summers and more temperate winters without prolonged periods of freezing [6]. These desert climates often have less than 25 cm of average annual rainfall with clay predominant, compact, low oxygen soil that leads to soluble salt deposition and an increased alkalinity [7]. Areas that satisfy these distinct criteria include desert regions of the Southwestern USA and parts of Central and South America.

Further examination of the precipitation patterns reveals that there is more to creating ideal conditions for *Coccidioides* spp. growth and dissemination than simply the minimal amounts of annual precipitation provided by desert climates. Review of seasonal weather patterns along with date of exposure models in Pima County, Arizona suggest a strong correlation between the incidence of infection and the bimodal seasonality of rainfall in that area [8]. Precipitation peaks twice yearly in the summer and the winter months in Arizona while staggered between dry, arid periods. Rainfall that is concentrated at two points separated between times of dry and dusty periods allows for what has been referred to as the “grow and blow” hypothesis. *Coccidioides* spp. tend to flourish in the soil during the wet periods when the fungal mycelia require moisture and then later disseminate in the dry stages of the year when desiccation and maturation into arthroconidia make aerosolization possible leading to inhalation and infection [9].

Geographic Distribution

Efforts to isolate *Coccidioides* from the soil over a wide area in an attempt to define the geographic range have been feasibly prohibitive. Epidemiologic studies on incidence or skin testing of prevalence have been used in lieu of soil culture studies as a surrogate for the location of *Coccidioides*. The skin test has recently become commercially available again, and efforts to clarify the prevalence in new locations will hopefully begin shortly [10]. These studies helped to elucidate the deserts of Southern Arizona and the Central Valley of California as the primary areas of endemicity. Interestingly, these areas are populated distinctly by two separate species, *C. posadasii* and *C. immitis* [4]. The San Joaquin Valley region is the primary endemic region for *C. immitis*, which is found in Central and Southern California and Washington [11]. Skin testing from Kern, Tulare, and Kings counties note positive skin tests ranging from 50 to 70 % [12]. Although referred to as the “non-California *Coccidioides*,” *C. posadasii* encompasses a far broader habitat. Primarily found in Arizona, where skin testing implicates Maricopa, Pima, and Pinal counties, *C. posadasii* is also seen in southern Utah, Nevada, southern New Mexico, and western Texas [7]. The reach of *C. posadasii* is also seen down through parts of Mexico in addition to Central and South America [6]. Survey skin testing performed in Coahuila de Zaragoza, a

state in Northern Mexico, which shares a border with Texas discovered positive rates between 40 % to an excess of 90 % [6]. Further surveillance of Central and South America is hindered by limited skin testing surveys, the non-reportable disease status of coccidioidomycosis within these locations, and the fact that skin testing lacks specificity in relation to other endemic mycoses, such as *Paracoccidioides brasiliensis*, in those regions. Based upon available information, in addition to Mexico, Honduras and Guatemala are endemic areas of Central America while South American countries with *Coccidioides* includes northern Venezuela, northeastern Brazil, Argentina, Bolivia, Paraguay, and Nicaragua [6, 13].

Recent Trends in Geographic Distribution

As alluded to earlier, our established understanding of the ecology of *Coccidioides* spp. is that these organisms are located primarily in the desert climates of the Southwestern USA along with Mexico and parts of Central and South America. Three cases of coccidioidomycosis acquired in the eastern part of Washington State, an area previously thought to be non-endemic, question this assumption [14]. Many documented cases of coccidioidomycosis seen in non-endemic areas are thought to be imported during periods of travel to endemic regions. The delay in diagnosis that often accompanies these cases in non-endemic areas underscores the importance of educating travelers and healthcare providers from these regions. Of the three cases in Washington state from June 2010 to May 2011, one was diagnosed with primary cutaneous disease while the other two presented with pneumonia of which one of the two developed meningitis. Although all three cases attested to travel within endemic regions, raising the possibility of reactivation, further epidemiologic data points to acquisition from the local environment. Soil samples were collected from the environment in eastern Washington based upon histories obtained from two of the three patients in which their activities suggested possible exposure. These samples obtained on two separate occasions were found to be positive for *Coccidioides*. Whole genome sequencing further confirmed a match to the soil samples and the first patient. Data suggest that these infections were in fact acquired in the non-endemic area of eastern Washington state [14]. Although reactivation is not entirely excluded, there is concern for a shifting ecology of the fungus due to human dispersal of soil or climate change allowing for colonization of new areas [11]. Currently, investigations are ongoing in multiple other US states bordering the traditional endemic region [15].

General Risk Factors

Infection occurs through inhalation of arthroconidia that have been aerosolized from the desert soil. Although any individual exposed to *Coccidioides* spp. may develop infection, it is

apparent that specific activities and non-modifiable traits confer an increased risk.

Because coccidioidomycosis is spread through the inhalation of dust within the desert environment, those with more frequent exposure subsequently carry a greater risk of acquiring infection. This includes workers whose occupation commonly involves disruption of the soil, such as in the case of the industries of agriculture or construction [16]. Others with high levels of soil exposure to soil are also at high risk, such as those participating in military training exercises [17]. Aside from the aforementioned weather-related variations in precipitation, other meteorological phenomena such as dust storms and earthquakes in endemic areas have been linked to outbreaks of coccidioidomycosis irrespective of a person's occupation or activity [18, 19]. A high burden of disease has also been noted within state and federal correctional facilities [20]. Although the reasons for which are not entirely clear, they are suspected to be related to the transfer of immune-naïve individuals, both prisoners and staff, to highly endemic, less populated desert areas. For instance, correctional facilities within the San Joaquin Valley estimate incidences approaching 7 % of their population [21].

Age

While increased exposure to arthroconidia through residence, occupation, or activity in an endemic area has been identified as a risk factor, there are many other fixed attributes that have also been linked to an increased risk of infection. Age is one such aspect that has been identified. In Arizona, those greater than 65 years of age were found to have the highest incidence of infection [22]. Although this finding has not been fully evaluated given that much of the elderly population of Arizona is comprised of individuals who have relocated from non-endemic areas either on a seasonal or permanent basis. Another case-control study of geographically matched controls revealed that each year lived in Arizona provided a 5 % decline in the risk for acquiring coccidioidomycosis [22]. The impact of the large influx of elderly individuals to Arizona from non-endemic areas may explain their disproportionate burden of disease given that the incidence of infection within California peaks between 40 and 49 years of age [23]. Two studies to evaluate for poor outcomes or severe, disseminated disease were not able to conclusively identify age as a risk factor [24, 25]. While coccidioidomycosis affects all age groups, adults are identified as the most affected group. Further research is warranted to identify age as an independent risk factor for infection and severe disease.

Gender

Based upon surveillance data from Arizona and California, infection with coccidioidomycosis has been shown to take

place with greater frequency in men when compared to women. One study reviewing cases in those states between 2001 and 2009 reported rates of infection in males ranging from 54 to 65 % as compared to women [26]. Data from Los Angeles County show a steady rise in the ratio of male to female cases from 2.1 to 5.7 between 1992 and 2003. This historic gap was closed by a sudden rise in the cases of women to more closely match the overall rise in the incidence among males. These changes occurred in 2004, marking a precipitous drop in the ratio to range between 1.4 and 2.2 between 2004 and 2011 [27]. Although the reasoning for the differences in the incidence between the two genders has not been clarified, the preponderance of males participating in high-risk activities mentioned earlier is thought to contribute partially. Elevated levels of human sex hormones which stimulate the in vitro growth of *Coccidioides* is another possible contributing factor [28]. Information regarding risk for severe disease based upon gender is limited as studies commenting on this either provide conflicting results, are of small number, or rely on biased study populations such as military personnel.

Pregnancy

One particular risk factor patently associated with the female gender is pregnancy. Although infection with *Coccidioides* spp. during pregnancy is an overall rare outcome at only 0.02 % [29], there is an apparent correlation between the risk of developing severe or disseminated coccidioidomycosis and progression to the later stages of pregnancy extending to the immediate postpartum period [30]. As postulated earlier with respect to gender differences, alternations in human sex hormones, such as 17 β -estradiol and progesterone, when linked with the reduced cell-mediated immunity of pregnancy, are likely to account for the greater susceptibility to infection during this time [28]. In one review of 81 cases in the literature by Crum et al., a striking correlation was noted between the timing of infection with regard to the trimester of pregnancy and dissemination. Fifty percent of those pregnant woman with disseminated coccidioidomycosis were diagnosed in the first trimester, 62 % in the second, 96 % in the third, and 71 % in the postpartum period [31]. Even when accounting for the possibility of inflated rates due to reporting bias, the trend between increasing stages of pregnancy and severe disease seems to be established.

Ethnicity

Reports in the medical literature regarding an association between infection from *Coccidioides* spp. and ethnicity have been seen dating back several decades. While often critiqued for their lack of generalizability, such early reports from military bases allow for examination of race while standardizing variables such as activity and housing. One such study by

Smith et al. reported rates of dissemination among African Americans ten times that of Caucasian military personnel [32]. Another report supporting ethnic predilection for coccidioidomycosis under circumstances which accounted for differential exposure was an outbreak associated with a dust storm in Kern County, California [18]. Acute pulmonary disease in African Americans compared to Caucasians was documented at a rate of 67 vs. 19 per 100,000 while disseminated disease was noted in 23.8 vs. 2.5 per 100,000. In addition to Blacks, people of Asian and Filipino descent are also thought to be at disproportionate risk for disseminated disease [25]. The reasons for ethnic variations for *Coccidioides* infection are not entirely clear but are likely to be explained by immunogenetic differences in T cell function. Additional research to realize the basis for these perceived differences in the risk of coccidioidomycosis between races is ongoing.

Immunosuppression

As alluded to earlier in discussion regarding the link between disseminated disease and pregnancy in addition to ethnicity, cell-mediated immunity is thought to play a key role in the immune regulation of coccidioidomycosis. Many conditions, as the result of either disease or iatrogenesis, in which T cell function is impaired, place patients at risk for severe or disseminated infection due to coccidioidomycosis.

Diabetes is another condition associated with infection affecting tens of millions of Americans. One retrospective review of 44 diabetic patients who were otherwise immunocompetent were compared with 285 case-matched controls. This study revealed that cavitory disease and relapse of infection were more common in diabetic patients, and when compared to mild hyperglycemia, those with serum glucose concentrations greater than 220 mg/dL were seen to carry greater risk for dissemination [33]. Although diabetes has a role in multiple aspects of immune regulation, including T cell function, it is evident that increasing glycemia augments the activity of coccidioidomycosis.

Patients with malignancy, particularly those with hematologic disorders, are also vulnerable to developing severe infection due to *Coccidioides* spp. Nearly half of all coccidioidomycosis infections and hematologic malignancy occur in those with non-Hodgkin's lymphoma or chronic lymphocytic leukemia (CLL) [34]. Therapies to combat these malignancies also confer risk for disseminated disease, such as anti-neoplastic agents and high-dose corticosteroid therapy [35].

HIV is an acquired immunodeficiency in which predilection for disseminated disease due to *Coccidioides* spp. is well documented. The contribution of cell-mediated immunity is again illustrated as the risk of coccidioidomycosis infection has been shown to be inversely correlated with CD4 cell counts [36]. Although the incidence of disseminated coccidioidomycosis in HIV positive patients has declined with the

advent of combination antiretroviral therapy, conferring protection from disease, a history of candidiasis along with the use of an azole drug was also seen to result in a reduced risk for coccidioidomycosis [37].

Recent Trends in At-Risk Populations

As touched upon earlier, the immunosuppressed population carry a distinct risk for the development of severe or disseminated *Coccidioides* infection. This ranges from, but is not exclusive to, patients with diabetes, rheumatic disease, hematologic malignancy, and HIV. Additionally, in certain cases, the treatment alone places a patient at greater risk for infection. The advent of and increasing use of immunomodulatory agents that target cell-mediated immunity is a trend that warrants increased awareness of healthcare providers on the risks of coccidioidomycosis in these populations. Chemotherapeutic agents and high-dose corticosteroids (equivalent to >20 mg/day prednisone) have traditionally been identified as conferring risk of infection; however, the increasing prevalence of tumor necrosis factor- α (TNF- α) antagonists along with immunosuppression accompanying solid organ or hematopoietic stem cell transplantation recipients is also of rising concern [38–40].

In one retrospective study taking place within several institutions within the Southwest found that of 247 patients with inflammatory arthritis receiving TNF- α treatment in comparison to 738 patients with inflammatory arthritis on other non-biologic therapy, the relative risk of developing symptomatic coccidioidomycosis to be 5.23 [38]. Patients receiving allogeneic stem cell transplantations in Arizona were also reviewed in another study that noted active coccidioidomycosis after transplantation in 11 of 426 patients (2.6 %) [40]. Also taking place within Arizona, a retrospective study among liver transplant recipients noted a rate of 2.4 % [41].

Given this quantifiable risk, the question of appropriate care, specifically with regard to screening and prophylaxis, is raised. In the case of the use of TNF- α , there are no recommendations to support the use of prophylaxis. Screening for coccidioidomycosis should be considered for patients with a history of residence within endemic areas; however, given that most cases are thought to be the result of acute infection rather than reactivation, screening serology is likely to serve as a baseline testing for use along with consideration of longitudinal serologic, radiographic, and clinical monitoring while on therapy [42]. Guidelines are also absent for transplantation recipients, although it should be noted that the risk will vary based upon a number of factors including the particular tissue donated and level of immunosuppression; however, institutions within endemic areas do support screening and prophylaxis. Unlike in those receiving TNF- α , the risk for reactivation of coccidioidomycosis appears to be

greater among transplant recipients. For example, with regard to allogeneic stem cell transplantation, institutions within endemic areas recommend screening prior to transplantation in addition to azole prophylaxis for 1 year until engraftment occurs and all immunosuppressive medications have been discontinued [40]. This level of prophylaxis is provided to patients with no history of coccidioidomycosis and negative serology, although increasing durations of prophylaxis are recommended to be tailored for those with a history of, positive serology for, or active disease with coccidioidomycosis in consultation with an Infectious Diseases Specialist. Overall, clinicians should have a high-index of suspicion when treating immunosuppressed patients within endemic areas as clinical presentations may be atypical and the sensitivity of serologic testing may be impeded by immunosuppressive agents [43]. Further research is needed to analyze the potential benefits of screening and prophylaxis in this population in order to produce guidelines with evidence-based support.

Conclusion

Infection due to *Coccidioides* spp. represents an increasing concern to public health. Not only have the number of cases been seen to increase over the past several years in areas and populations known to be endemic but also the overall epidemiology has been noted to change. The desert climate zones within the 40° northern and southern lines of latitude that have traditionally confined this organism to specific endemic regions appear to no longer be boundaries for the mycelium of *Coccidioides* spp. as evidence of the acquisition of infection has been found outside of these areas. Additionally, an increasing number of people are at risk for infection with the expansion of housing developments and placement of correctional facilities within endemic areas along with the significant rise in the use of immunomodulatory medications. In light of a broadening scope of locations and populations in which coccidioidomycosis may be seen, heightened awareness on the part of the public and of healthcare professionals is warranted for the early recognition of disease and consideration of treatment. Additional research into the outcomes of screening, prophylaxis, and treatment of high-risk populations would allow physicians to make informed decisions with their patients regarding their care.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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