Coccidioidomycosis in African Americans

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Coccidioidomycosis is caused by *Coccidioides* species, a fungus endemic to the desert regions of the southwestern United States, and is of particular concern for African Americans. We performed a PubMed search of the English-language medical literature on coccidioidomycosis in African Americans and summarized the pertinent literature. Search terms were coccidioidomycosis, *Coccidioides*, race, ethnicity, African, black, and Negro. The proceedings of the national and international coccidioidomycosis symposia were searched. All relevant articles and their cited references were reviewed; those with epidemiological, immunologic, clinical, and therapeutic data pertaining to coccidioidomycosis in African Americans were included in the review. Numerous studies documented an increased predilection for severe coccidioidal infections, coccidioidomycosis-related hospitalizations, and extrapulmonary dissemination in persons of African descent; however, most of the published studies are variably problematic. The immunologic mechanism for this predilection is unclear. The clinical features and treatment recommendations are summarized. Medical practitioners need to be alert to the possibility of coccidioidomycosis in persons with recent travel to or residence in an area where the disease is endemic.

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Coccidioidomycosis, also called *valley fever*, is caused by inhaling airborne arthroconidia (spores) of the fungus *Coccidioides*.[1,2] Although 60% of people are asymptomatic, most clinical infections are self-limited pulmonary infections acquired in the southwestern United States, where the fungus is endemic.[3] Risk factors for severe or disseminated infection include racial heritage (such as African or Filipino) and medical conditions such as pregnancy or cell-mediated immunodeficiency (eg, use of immunosuppressant medications, infection with human immunodeficiency virus [HIV], or receipt of a transplanted organ).[1] Because of increasing populations and thriving tourism in the endemic area, coccidioidomycosis is a disease of interest not only to physicians in the Southwest but also to practitioners anywhere whose patients have resided in or traveled to areas where the disease is endemic.[4]

To examine closely the risk of African American race on the clinical characteristics pertaining to coccidioidomycosis, we performed a PubMed search of the English-language medical literature on coccidioidomycosis (through March 2010) specifically as it relates to African Americans, with the following search terms: *coccidioidomycosis*, Coccidioides, *race*, *ethnicity*, *African*, *black*, and *Negro*. In addition, the proceedings of the national and international coccidioidomycosis symposia were searched for references. All relevant articles and their cited references were reviewed; those with epidemiological, immunologic, clinical, and therapeutic data pertaining to coccidioidomycosis in African Americans were included in the review; articles without race-related information pertaining to coccidioidomycosis or the absence of a comparative group were excluded. Single case reports were not included. In this review, we used the exact terms (ie, *Negro*, *black*, *colored,* and *African*) as they were reported in the original text. The current article summarizes the diagnosis, treatment, and management of coccidioidomycosis and highlights specific issues for the African American population.

MYCOLOGY AND IMMUNOLOGY

Coccidioides is a dimorphic fungus that thrives in the soil of portions of the southwestern United States (Figure 1) and northern Mexico.[3,6] Two recognized species cause indistinguishable infection in humans: *Coccidioides immitis* and *Coccidioides posadasii*.[1,3] *Coccidioides* species grow as branching septate hyphae when the soil is moist. As the soil dries, thick-walled arthroconidia form[6]; when the soil and hyphae are disrupted, the disarticulated arthroconidia (spores) may become aerosolized.

Human infection is caused by inhaled arthroconidia, which reach the lower respiratory tract and change to a tissue phase called spherules. The spherules increase in size and produce hundreds of endospores, which are subsequently released into the tissue and form new spherules, thereby continuing the life cycle (Figure 2).[3]

When the host inhales *Coccidioides* arthroconidia, the normal immune response occurs in 2 phases.[3] The early immune response consists of an influx of neutrophils, eosinophils, monocytes, and natural killer cells. After the arthroconidia become spherules, the early innate response is ineffective, and the cell-mediated immune response begins. Persons who have innate or acquired deficiencies in any aspect of cell-mediated immunity may be at risk of severe or disseminated infection.[3]

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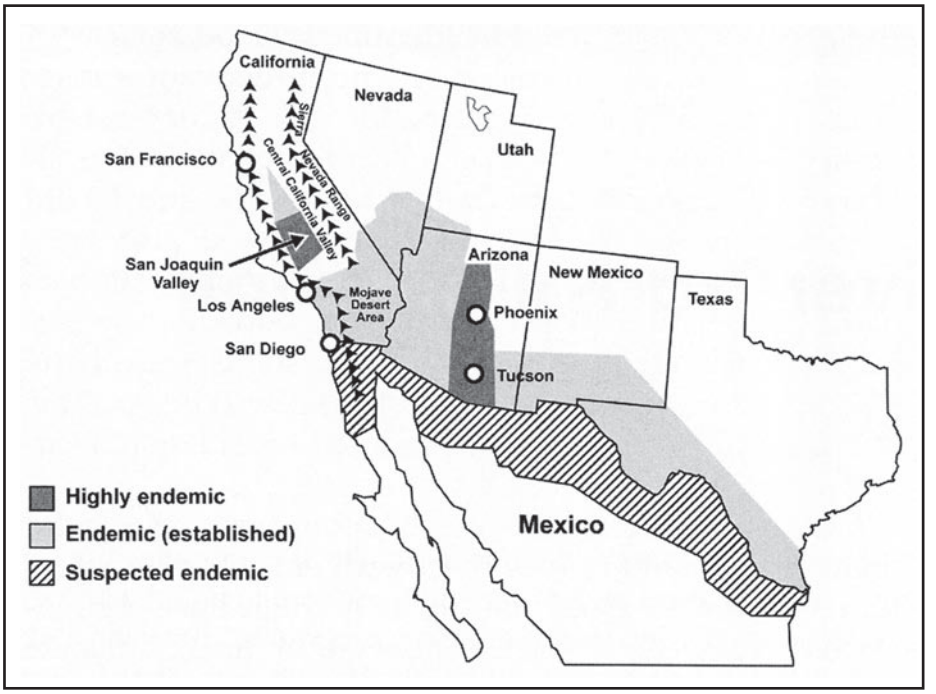

FIGURE 1. Geographic distribution of coccidioidomycosis. Areas of heavy concentration (dark gray) are in the San Joaquin Valley of California and in the Sonoran desert of Arizona. Adapted from *Liver Transpl*,[5] with permission.

The underlying mechanism accounting for the vulnerability of African Americans to severe or disseminated coccidioidomycosis is unknown. This vulnerability is not associated with outdoor occupations or activities,[3] which may increase the exposure frequency or inhaled dose. Although the genetic basis for this increased susceptibility is unknown, susceptibility to severe infections has been associated with HLA class II antigens (HLA-A9 and HLA-B9 antigens)[3] and ABO blood group B[7]; however, these associations may merely reflect an increased proportion of phenotypes with these HLA types and blood group B among persons of Filipino or African descent.[3] In a case-control study, the HLA class II-DRB1*1301 allele was a marker for severe disseminated coccidioidomycosis, regardless of race.[8] If an immunologic basis accounts for the vulnerability, it does not seem to be the result of an inherent inability to mount a cellular immune response to *Coccidioides,* as evidenced by the ability of African Americans (even those with disseminated infection) to react to skin testing[9] or mount a response to experimental vaccination[10] comparable to that of other racial and ethnic groups.

INCIDENCE AND PREVALENCE

Recent population growth in the southwestern United States, where *Coccidioides* is endemic, has been rapid and racially diverse. For example, from 2000 to 2008, the population in Arizona increased 26% to more than 6.5 million persons.[11,12] During that same period, the number of African American residents in Arizona increased by 73%.[12] The Southwest also serves as a winter vacation destination for an increasing number of travelers and part-time residents, who may return home after having acquired the infection.[11,13]

An estimated 150,000 new cases of coccidioidomycosis infection occur each year.[11,13-15] Most (>95%) occur in California and Arizona[6]; 60% occur in Arizona.[15] Coccidioidomycosis is recognized as a reemerging infectious disease,[3,16] with an overall incidence that almost tripled between 1999 and 2007 in Arizona and California.[17,18] In Arizona during 2007, the most recent year with available data, the highest incidence of newly reported cases (pulmonary or extrapulmonary) was in the African American community (53 per 100,000 population); in the white population, the incidence was 37 per 100,000.[14,15]

Many factors may account for the increased incidence of reported coccidioidomycosis. The increase in the influx of new residents to Arizona and other endemic areas increases the number of previously unexposed persons at risk of newly acquired infections.[2] In addition, to support this rapid population expansion, large numbers of construction and development projects occurred during the past decade. These types of projects often disrupt the soil and lead to

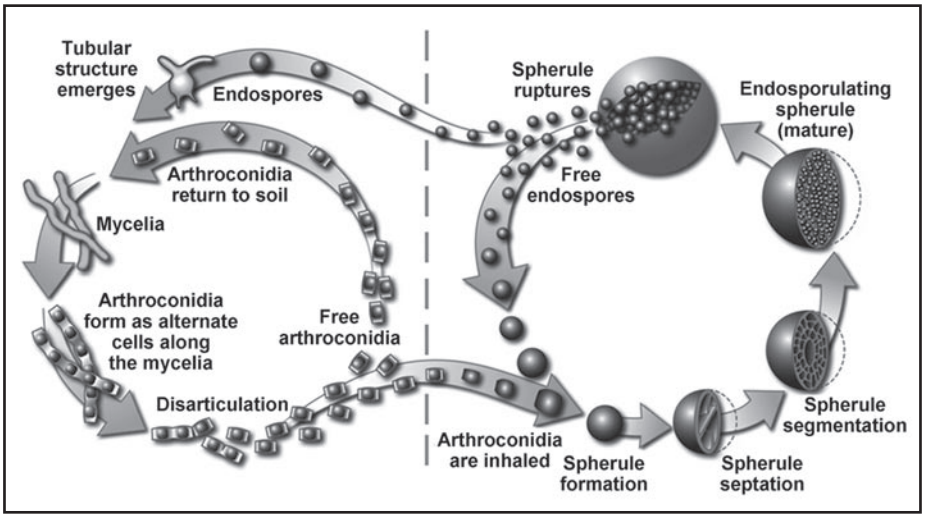

FIGURE 2. Life cycle of *Coccidioides* (Saprophytic cycle left, Parasitic cycle right).

aerosolization of *Coccidioides* spores.[2] Nonhuman activities such as earthquakes, dust storms, and landslides also disrupt soils and have been associated with an increased incidence of infection.[11,13,19]

COCCIDIOIDOMYCOSIS IN PERSONS OF AFRICAN DESCENT

With the same level of exposure, persons of any particular race are not more likely or less likely to inhale airborne spores than persons of another race. Therefore, there is no known difference in the racial susceptibility to primary coccidioidomycosis.[20] Of note, reported incidence data cite only identified cases, usually on the basis of symptoms, and do not reflect all primary coccidioidal infections, 60% of which are asymptomatic. Skin test reactivity to spherulin or coccidioidin more accurately reflects a history of coccidioidal illness, whether or not symptoms are present. Studies of skin testing for coccidioidomycosis have corroborated the assertion that there is no racial predisposition to primary pulmonary coccidioidomycosis. A study that described reactivity to coccidioidin antigens in 2770 white and Negro schoolchildren who were identified as new residents of Maricopa County, AZ, showed no significant differences between Negro (38.6%) or white (35.1%) persons.[21] Similarly, the skin test conversion rate of approximately 13% among boys aged 14 to 18 years working in detention camps in Los Angeles County in 1965 was similar among whites, Negroes, and Mexican Americans.[22]

Coccidioidomycosis has a broad spectrum of disease, which is thought to result from disparities in inoculum size, host defenses, and other resistance factors that are not understood. Up to 60% of infected patients with primary coccidioidomycosis have no symptoms.[23] Symptoms usually begin 1 to 3 weeks after inhaling arthroconidia.[19] Patients with primary pulmonary coccidioidomycosis can have acute or subacute features of a flulike illness or progressive pneumonia. The symptoms may be indistinguishable from those of community-acquired pneumonia, and the disease may occur with any combination of the following: fever, cough, dyspnea, chest pain, weight loss, fatigue, or headache. Various rashes are seen in 14% to 33% of patients with primary pulmonary coccidioidomycosis[13,24] and may help distinguish it from community-acquired pneumonia.[25] The presence of erythema multiforme or erythema nodosum portends a favorable prognosis for resolution of infection.[6,24,26] Erythema nodosum has been observed less frequently in African Americans than in whites.[23,27-29]

In prospective series of military personnel receiving medical attention for coccidioidomycosis, dissemination occurred in 3% to 5.7% of symptomatic patients.[30,31] Similarly, the percentage of symptomatic patients in a large retrospective study with dissemination was 4.7%.[32] Risk factors for dissemination include age, immunocompromised state, advanced pregnancy, and race. Dissemination due to hematogenous spread of the organism typically occurs early in the course of disease, although the clinical presentation may occur months to years after the initial respiratory illness.[24]

Risk of Dissemination

Although there is no apparent racial predisposition to primary pulmonary infection, a number of studies indicate a

racial predisposition toward the development of severe or disseminated disease (eTable; a link to which is provided at the end of this article).[3] The earliest epidemiological studies in California raised concern of the effect of race in coccidioidomycosis[27,33] because extrapulmonary infection was 14 times more likely to develop in African Americans than in whites.[23,27] Other groups at risk included Filipinos (the disease was 175 times more likely to disseminate) and Mexican Americans (3 times more likely).[27] The authors could not exclude the possibility that occupational exposure placed these patients at higher risk of acquiring the infection, rather than an increased inherent likelihood for the disease to disseminate.[27,33] Shortly thereafter, a prospective evaluation of serial skin test conversion in military personnel in southern California during a 3-month period showed similar rates of coccidioidin skin test conversion and hospitalization for acute coccidioidomycosis, although 4 (8%) of 49 "colored troops" had disseminated infection, whereas none of 34 whites had disseminated infection.[31] After a California dust storm in 1977, in which uniform exposure was assumed, approximately 25% to 50% of black patients had disseminated disease[34-36] (as well as 38% of Asians[35]), compared with 0% of whites.[35] Moreover, 2 studies of cases at Naval Air Station Lemoore, where all patients had similar occupations and equal exposure, showed that approximately 7% of the exposed population was black, with dissemination rates ranging from 23.5% to 50%, whereas approximately 77% to 84% of the total population was white, with dissemination rates ranging from 0% to 2.3%.[30,35] (Filipinos accounted for 8.4% of symptomatic patients, and 21% of them had disseminated infection.[30]) African Americans have been disproportionately represented in a case series of coccidioidal spondylitis (in which 75% of cases were in African Americans in a community characterized as 25% black)[37] and in 2 case series of meningitis. One of those 2 series showed that 16% of coccidioidal meningitis cases were identified in African Americans in a community of 3.4% African Americans,[38] and the other series noted that 33% of coccidioidal meningitis cases were in blacks within a community that was 8% black.[39] Location of residence within the greater metropolitan area of Tucson, AZ, did not affect the risk of coccidioidomycosis in African Americans.[40]

More recently, population-based studies of coccidioidomycosis in Kern County, California, in 1991[32] and in 1995 to 1996[41] showed that blacks had a disproportionate percentage of disseminated infection (31% of all disseminated cases were in blacks, but blacks accounted for only 6.7% of all coccidioidal infections[32]) and an increased rate of dissemination (22%), whereas a similar increase in dissemination was not noted for Hispanic or Asian patients.[32,41] Among 223 patients at Naval Medical Center San Diego (1994-2002), 44% of African American patients with coccidioidomycosis had extrapulmonary infection, and the risk of disseminated disease was 42 times higher in African Americans than in whites (the risk of disseminated disease in Filipinos and Hispanics was also significantly higher).[24] A small study of 59 active duty military personnel at Naval Air Station Lemoore did not find a statistically increased risk of dissemination among African Americans compared with whites, but 6 African Americans had coccidioidomycosis, 2 of whom had disseminated infection.[42] In addition, 71 patients with disseminated coccidioidomycosis at the University of Arizona from 1996 to 2007 were retrospectively reviewed: blacks had a 2.5-fold increased risk of meningitis, an 11-fold risk of nonmeningeal dissemination, and a 40-fold risk of vertebral disease. These differences could not be attributed to immunosuppression.[43]

Independently of race, several conditions, such as pregnancy, HIV infection, or exogenous immunosuppression, increase the risk of complicated coccidioidomycosis. The effect of race in addition to these factors is variable. Pregnancy is a known risk factor for dissemination, especially in the third trimester. Among 33 pregnant women with coccidioidomycosis in 1951, 24 were white (2 of whom contracted coccidioidomycosis in the third trimester and had nonfatal dissemination) and 6 were Negro (all of whom had fatal dissemination regardless of the trimester when the infection was acquired).[44] The article did not mention differences in the access to or timeliness of medical attention for patients of different racial groups.[44] A review of 81 cases of coccidioidomycosis during pregnancy showed that pregnant African American women had a 13-fold increased risk of coccidioidal dissemination compared with their white counterparts (P=.007).[45] A multivariate analysis of patients infected with HIV (most of whom had CD4 cell counts <200/μL) showed that blacks had an increased risk of symptomatic coccidioidomycosis (odds ratio, 4.9; 95% confidence interval, 1.9-12.4) compared with whites.[46] However, among transplant recipients, race did not confer an increased risk.[47]

Risk of Hospitalization and Death

Not only are African Americans at increased risk of extrapulmonary infection, but also they are at increased risk of severe infection requiring hospitalization. In Tulare County, California, in 1991, 27% of patients with pulmonary coccidioidomycosis were hospitalized; independent risk factors for hospitalization in a multivariate analysis included male sex, black and Asian races, and age older than 20 years.[48] Among 113 Navy personnel hospitalized for pulmonary or extrapulmonary coccidioidomycosis, black or Filipino race (compared with white) was the strongest risk factor for hospitalization (odds ratio, 7; 95% confidence

interval, 3.6-13.9).[49] Analysis of California hospital discharge data from 1997 to 2002 indicated that black race (in addition to county of residence, older age, male sex, HIV infection, and pregnancy) was strongly associated with an increased risk of hospitalization.[50] Similarly, in a survey of data from Arizona from 1990 to 1995, rates of hospitalization were greater among African Americans (and among persons >55 years and male patients; all $P<.01$).[51]

Other studies have identified an increased risk of death due to coccidioidomycosis in African Americans. A 1959 autopsy series[52] indicated that Negroes were disproportionately represented not only in coccidioidal dissemination but also in death compared with whites; a concurrent autopsy series showed that rates of death due to tuberculosis were similar between the races.[52] Among 212 deaths directly attributed to coccidioidomycosis in hospitalized patients in Arizona from 1959 to 1975, the relative risk of death for blacks compared with that for whites was 5.7.[53] Whether these deaths resulted from an inherently more aggressive infection, poor access to quality medical care, or another cause is unknown.

LIMITATIONS OF LITERATURE

Most of the aforementioned studies are problematic to various degrees; their strengths and weaknesses have been summarized (eTable). Additionally, most of the studies are retrospective, which is a particular problem for studying coccidioidomycosis because asymptomatic or mild to moderate forms of the infection may be unrecognized, leaving only a minority of the more severe cases identified and treated by medical practitioners (and subsequently reported to public health officials). Many studies encompass very small numbers of African Americans within primarily white populations. Few of the cited studies discussed methodology for the determination of race; one author noted that the determination of race by visible examination was sometimes problematic.[31] Racial heterogeneity was never addressed in these studies. Moreover, studies do not mention the possibility of bias that may have occurred because of possible differential access to and quality of medical care between the races. Finally, whether the introduction of safe and effective antifungal treatment has altered the apparent risk of severe or disseminated coccidioidomycosis among any racial groups has not been clearly delineated.

Furthermore, these studies have many sources of potential bias. Sampling bias was probably an issue in one of the earliest studies, in which the original California series began with the tabulation of disseminated coccidioidomycosis ("coccidioidal granuloma"); later, as these cases of dissemination were recognized as an uncommon manifestation of the common "San Joaquin fever," the more common cases of pulmonary coccidioidomycosis were added to the series, causing a large overrepresentation of an uncommon problem. In addition, case series collected from tertiary care referral centers may not have adequately controlled for potential referral bias.[24,43] The effect of publication bias (ie, the lack of publishing negative results) is unknown. The sheer number of studies indicating a risk of severe coccidioidal disease in African Americans effectively argues that such a risk does exist. However, most of the studies are problematic, and the hererogeneity of methodology and results makes it difficult to estimate the true risk of severe infection, dissemination, and death due to coccidioidomycosis in African Americans.

MANAGEMENT

Treatment of coccidioidomycosis varies according to the clinical manifestations and anatomical sites of the infection. Specific antifungal drugs and treatment plans have recently been outlined in guidelines of the Infectious Diseases Society of America.[54] The first step in management is to define the extent of a patient's disease.[55]

Optimal treatment of patients with self-limited pulmonary infection is an unsettled issue. Many experts do not recommend specific antifungal therapy in this situation; instead, they recommend careful follow-up every 3 to 6 months for 1 to 2 years to document resolution or to identify early signs of either progressive or disseminated disease.[54] An argument has been made for treating all symptomatic patients to lessen both the severity of symptoms and the duration of disease, but no data for primary coccidioidomycosis exist to support this argument. Current guidelines do recommend that treatment be offered to patients who are less likely to do well with primary pulmonary coccidioidomycosis, including those who have diabetes mellitus, who are pregnant, or whose heritage possibly includes a high-risk race.[54]

Some experts advocate that all African Americans with coccidioidomycosis be treated (even those with very mild infections) because of the preponderance of studies that indicate a higher risk of severe or disseminated infection; however, no data are available to show that this strategy will prevent or decrease the risk of disseminated disease in African Americans.[54] Because caution is appropriate in interpreting the available data on racial predisposition to complications of coccidioidomycosis, caution is also warranted in making any race-specific treatment recommendations. However, carefully monitoring the course of coccidioidomycosis in African Americans is always reasonable.

Some patients with coccidioidomycosis (including African Americans) who always warrant use of antifungal therapy include those with severe pneumonia, chronic

progressive pulmonary disease, or disseminated disease. Use of azoles is preferable for initial treatment of coccidioidomycosis. Fluconazole (400-800 mg/d) and itraconazole (200 mg twice daily) are commonly used azoles, and fluconazole is the currently preferred therapy for meningeal infection. For patients with fulminant, nonmeningeal infection, some experienced clinicians prefer amphotericin B (0.5-0.7 mg/kg daily intravenously) with a transition to oral azoles when the status of the infection has stabilized.[54]

CONCLUSION

Coccidioidomycosis is a fungal infection endemic to the southwestern United States. Numerous retrospective studies have suggested that African Americans have an increased risk of severe or disseminated coccidioidal infections, but many of these studies are small and subject to potential bias. Prospective, controlled epidemiological studies are required to give a clearer picture of the true risk of complicated coccidioidomycosis among racial groups. Further study into the nature of inherent vulnerability to coccidioidomycosis should be conducted. Ultimately, such information may be useful to clarify whether the approach to treatment of these patients should be modified. However, in the absence of such information, clinicians need to have a high index of suspicion of coccidioidomycosis in persons with recent travel to or residence within the Southwest; when infection is diagnosed, medical practitioners should be alert to the possibility of early disseminated infection and provide long-term follow-up after the initial presentation and treatment.

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