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Update on Coccidioidomycosis in the United States and Beyond

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Abstract

Coccidioidomycosis is a fungal infection that is prevalent in western United States, Central America, and South America. The infection is acquired by inhalation. It can affect persons of all ages including infants and children. The majority of cases are asymptomatic and the incidence of infection is greater during a dry summer season after heavy rainfall in prior winter. For those with symptoms, they may experience a self-limiting influenza-like illness. However, some may progress toward pneumonia or disseminated diseases involving skeletal system and central nervous system. The diagnosis is based mainly on various serology testing. Antifungal treatment is generally not required for those with mild symptoms. For those with moderate to severe infections, the mainstay of treatment is azole, with fluconazole being often considered as the first line therapy. Currently there is no effective solution to prevent coccidioidomycosis. Those who work in high-risk conditions should be given appropriate protective equipment as well as education on proper precaution.

Keywords

coccidioidomycosis, coccidioides, children

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Introduction

The discovery of Coccidioides could be seen as a case of mistaken identity. It was first described by Alejandro Posadas in 1891, who was a medical student in Argentina at the time. Posadas described a patient with a large fungal-like mass covering his cheek, along with several ulcerative vegetative lesions on his nose and numerous papules on his trunk. Upon examining the organism isolated from skin biopsy, he concluded that it resembled the spore-forming protozoan, Coccidia.[1] A year later, Emmet Rixford, a surgeon at San Francisco's Cooper Medical College, and Casper Gilchrist, a pathologist at John Hopkins Medical School, isolated tissue from a patient from the San Joaquin valley in Central California who had fungating lesions on his face and nodules diffusely in his internal organs, and also thought that the organism causing the infection was indeed a protozoan, which they named Coccidioides, meaning "resembling *Coccidia*," and *immitis*, meaning "not mild." A few years later, William Ophüls and Herbet C. Moffitt cultured material from a Californian patient that grew a mold which they initially had thought was a contaminant. However, when they transferred the mold into a rabbit, nodules developed in various tissues that contained visible organisms previously described as *C. immitis*. Thus, they were able to show that *C. immitis* was not a protozoan, but instead a fungus that existed in two forms: spherules with numerous spores inside when in tissue, and mycelia when in culture.[1]

Mycology

Coccidioides are dimorphic fungi that grow saprophytically as mycelia in arid to semiarid alkaline soil. Mycelia mature into alternating arthroconidia as the fungus grows and ages. Arthroconidia spores are the infectious form for mammals including humans. The two known species of Coccidioides are *C. immitis* and *C. posadasii*. *C. immitis* is found predominantly in California with its

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range extending longitudinally to eastern Washington state and Baja California, and extending eastward to Arizona and Utah. *C. posadasii* is found mainly in Arizona, New Mexico, Texas, Mexico, and parts of Central and South America.[2] Under dry conditions, arthroconidia are very stable and remain viable in the environment for many years. Dry dusty conditions and soil disruption promote the release of arthroconidia into the air.[3] The arthroconidia is inhaled into the host's lungs, transforms into spherules, resulting in infection. The spherule expands in size and undergoes nuclear division producing hundreds of single-celled endospores. When spherules rupture, endospores are released, and each is capable of developing into new spherules until the host's immune system or medical intervention represses the fungal growth.[4]

Epidemiology

Many key epidemiologic discoveries were due to studies conducted during periods of increased migration to the San Joaquin Valley, California, primarily through the work of Charles E. Smith. Dr. Smith began studying coccidioidomycosis as a student at Stanford University and well into his career as a professor at University of California Berkeley School of Public Health. In the 1930s, there was increased migration to California, many looking for better agricultural opportunities. These migrant workers made up half of the patients studied by Smith in the first ever epidemiology study of coccidioidomycosis of 432 cases in Tulare and Kern counties in California.[1] Smith learned that transmission of the disease was through spores. The risk of dissemination was higher in people of color compared to Caucasian, with 23 times greater among blacks and 170 times greater among Filipinos. Smith was able to perform coccidioidal skin testing on all arriving armed force recruits in Bakersfield and Taft, California. Among these recruits, the annual incidence of infection was about 20 to 25%.[1] He learned that the majority of cases were asymptomatic and that the incidence of infection was greater during the dry summer after heavy rainfall in prior winter and spring; this observation was further supported by subsequent studies.[5]

In 1977, a massive dust storm struck through San Joaquin Valley. In the 3 months following the dust storm, 397 new cases of coccidioidomycosis were confirmed by serology; however the number of cases that were unreported were speculated to be much greater.[6] Coccidioidomycosis outbreaks were also seen after natural disasters. In January 1994, the Northridge Earthquake shook the San Fernando Valley of Los Angeles. Within 7 weeks after the earthquake, over 200 cases of coccidioidomycosis were reported.[7]

In endemic areas, coccidioidomycosis is an occupational hazard for any worker exposed to dusty conditions related to soil disturbances. Agriculture workers are often seen most at-risk, but there are many other occupations that have reported outbreaks as well. These include archeologists and civilian construction crew members.[8,9]

In the United States during 2011 to 2017, a total of 95 371 coccidioidomycosis cases from 26 states and DC were reported to CDC. The number of cases was 22 634 in 2011, 8232 in 2014 and significantly increased to 14 364 cases in 2017. More than 95% of cases were reported from Arizona and California. Reported incidence in Arizona decreased from 261 per 100 000 persons in 2011 to 101 in 2017, whereas California incidence increased from 15.7 to 18.2, while other state incidence rates stayed relatively constant during this period. Patient demographic characteristics were largely males and among adults aged >60 years in Arizona and adults aged 40 to 59 years in California.[10] Children younger than 5 years and between 5 and 19 years accounted for 0.5% and 8.2% of the reported cases, respectively.[10] In an epidemiologic study in children in California in 2000 to 2016, the annual pediatric incidence increased from 0.8 per 100 000 in 2000 to 5.2 in 2006. The highest incidence rate during the study period was in the 12 to 17-year age group.[11]

The rise of cases of coccidioidomycosis is multifactorial. One possible contributing factor is the increase of susceptible people traveling and relocating to areas where the fungus is present. Climatic and environmental changes have also been faulted, as the fungus proliferation is greatly dependent on the weather and soil. For instance, with warmer climates come drier soil and more dust storms. In addition, improvement in awareness, surveillance, testing and diagnosis of the disease by healthcare providers could be contributing to increased recognition and reporting of the disease. Of note, coccidioidomycosis has been nationally notifiable in the United States since 1995.[10]

Beyond the southwestern region of the United States, Coccidioides infection is prevalent in part of Mexico, Central America and South America. For example, in the 19-case series from Northeast Brazil, all patients were young males and came from semiarid areas of the country, and that the majority of cases were associated with armadillo hunting.[12] It is likely that coccidioidomycosis is underreported as this infection is not a required reportable disease in most of these countries.

Clinical Manifestations

Typically, a healthy child's immune system can overcome coccidioidal infection without overt clinical symptoms.

A symptomatic child may have a self-limited influenza-like illness with generalized fatigue, fever, cough and chest or back pain. Although in a smaller proportion of patients, the infection may progress to extensive pulmonary involvements or disseminate to other organ systems including lymph nodes, cutaneous lesions, and may even extend to the central nervous system and skeletal system.[13]

A 2013 retrospective study of pediatric coccidiomycosis in California reported pulmonary infections to be the most common clinical presentation. Other reported clinical manifestations included osteomyelitis, meningitis and disseminated disease.[14] Primary pulmonary coccidioidomycosis tends to be more severe in immunocompromised individuals. However, healthy individuals who inhale a large amount of Coccidioides spores can develop severe symptoms as well. The symptoms of pulmonary coccidioidomycosis include cough, fever, dyspnea, anorexia, night sweat, loss of appetite, muscle and joint pain.[14] Having pulmonary coccidioidomycosis is a risk factor for subsequent pulmonary sequelae which include pulmonary nodules and pulmonary cavities. Cavitary or nodular lesions are generally asymptomatic however some patients may experience dry cough, chest pain or hemoptysis.

Cutaneous lesions can be seen in several stages. Exanthem may be seen during primary pulmonary coccidioidomycosis; this includes transient maculopapular rashes and erythema nodosum.[15] Erythema nodosum has been shown to be a good prognostic sign. Disseminated coccidioidal disease may present with skin ulcers or granulomatous ulcers. Primary cutaneous lesions without systemic infection are rare. Direct skin inoculation of arthroconidia can lead to a chancroid-like lesion that is distinct from skin lesions seen in pulmonary or disseminated disease.[16] Coccidioidal meningitis commonly presents with a chronic headache; other associated symptoms include altered mental status and focal neurological deficits, nausea and vomiting and meningismus on examination. The most common complication of coccidioidal meningitis is hydrocephalus.[17]

In a 2019 retrospective review of extrapulmonary manifestations of coccidioidomycosis in children, the organ involvements were bones, particularly spines, and joints (33%), mediastinum (19%), central nervous system (19%), cervical lymph nodes (15%), larynx (6%), and skin (5%).[18] Children older than 10 years tended to have more than 1 organ involvement and tended to develop bone disease, joint disease, as well as meningitis. Those 6 years of age and younger tended to have laryngeal disease and mediastinal involvement. Approximately 20% were noted to have comorbid conditions varying from immunocompromised conditions, chromosomal disorders, diabetes mellitus, hereditary spherocytosis, seizure disorders to eczema. The study found Non-Hispanics over the age of 10 years were more likely to experience severe progressive disease.[18]

The information on coccidioidomycosis in infants remains limited. In a retrospective study of 13 infants, the majority presented with upper and/or lower respiratory tract infection. The most common presenting symptoms included fever (77%), cough (61%), and respiratory distress (38%). Disseminated disease was noted in this cohort including pericardial effusion, neck abscess, and lesions in the cerebellum, basal ganglia and temporoparietal skull. All patients survived to hospital discharge. The majority of the patients had resolution of chest radiograph and coccidioidal antibody titers.[19]

Due to the varied clinical presentations that can mimic other diseases. it is common for patients to be misdiagnosed with and treated for a non-coccidioidal disease when they initially present to healthcare providers. Delay in correct diagnosis and proper treatment could lead to disease progression and dissemination. A review of children in California with the diagnosis of coccidioidomycosis noted that 65% were initially misdiagnosed, with 56% being diagnosed with pneumonia.[13] In the endemic regions, children with pneumonia who do not respond to antibiotics should be investigated for coccidioidomycosis.

Diagnosis

Once coccidioidomycosis is suspected, there are several diagnostic tests available. Generally serological testing is used. Initial laboratory work-up may show elevated erythrocyte sedimentation rate and elevated eosinophils.[20] Coccidioides enzyme immunoassay (EIA) of serum is an easy to obtain test with a relatively rapid turnaround time. A 2008 retrospective review of 706 EIA tests performed on 405 patients found up to 90% sensitivity. However the age of patients in the study was not reported.[21]

Serum complement fixation (CF) antibody titers tend to be higher in patients with disseminated disease. In a retrospective study in children with coccidioidomycosis, those with CF titers greater than 1:128 tended to have longer hospitalizations.[22] CF test can be negative early in the disease course. Nevertheless, CF titers are useful in monitoring disease activity and treatment response.[21] Another useful diagnostic test is coccidioidal antigen in urine, serum and cerebrospinal fluid (CSF). The test is generally positive in patients with an extensive disease and the CSF antigen may be a sensitive biomarker in patients with coccidioidal meningitis.[23]

The presence of spherules in tissue samples is diagnostic of coccidioidomycosis.[24] Several special stains are available for microscopic detection of Coccidioides spherules. These are the calcofluor white fluorescent stain and KOH wet mount. The calcofluor white fluorescent stain is sensitive for coccidioidomycosis, however it may also stain plant material. KOH wet mount is easily prepared but difficult to interpret, thus is seldom used. Histopathological stains include Grocott methenamine silver (GMS), Periodic acid Schiff, and Hematoxylin-eosin; GMS is the most sensitive.[25]

Fungal cultures can detect Coccidioides. Samples may be obtained from blood, CSF, and respiratory samples. Typically it takes between 4 and 5 days for growth to be observed on culture media. A review of culture data from Laboratory Sciences of Arizona in Phoenix metropolitan area between 1998 and 2003 found the highest recovery rate for respiratory tract samples (8.3% n = 10 372). Blood cultures have a recovery rate of 0.4% (n = 5026) and CSF samples had a rate of 0.9% (n = 2280).[25,26] Culture of the organism is potentially hazardous to laboratory personnel because spherules can convert to arthroconidia-bearing mycelia in culture plates. Physicians should inform the laboratory immediately if there is a suspicion of coccidioidomycosis. A DNA probe is used to identify Coccidioides species in cultures, thus reducing risk of laboratory exposure.[26]

Skin testing with intradermal antigen inoculation leading to a delayed type hypersensitivity was not available from the early 1990s until recently, therefore this test was not clinically used as a means for diagnosing coccidioidomycosis. Currently there is an FDA-approved skin test, however it is for a subset of the population between the ages of 18 and 64 years to identify if the person was infected with Coccidioides previously. It is not currently approved for use in pediatric populations.[27]

Treatment

Coccidiomycosis is often self-limited in immunocompetent individuals including children. The treatment plan in uncomplicated pulmonary coccidioidomycosis involves regular follow-up to ensure that infection remains uncomplicated. For those with moderate infections the mainstay of drug therapy is azole. Fluconazole is often the first-line treatment as it has high bioavailability and good safety profile. It can be administered through an intravenous route and an oral route.

Asymptomatic cavitary or nodular lesions in general require no treatment. If patients with cavitary lesions or nodules are symptomatic despite azole therapy, surgical removal should be considered.[28] Infants and children with pulmonary coccidioidomycosis with prolonged or progressive clinical signs and symptoms should be treated with fluconazole 6 to 12 mg/kg once daily for about 3 to 6 months.[28] For skeletal coccidioidomycosis, the treatment is generally much longer at least 1 to 2 years, depending on the clinical response. For coccidioidal meningitis, the treatment should be lifelong.[28]

Amphotericin B, including its lipid formulations, is another viable choice of treatment. While the side effect profile is extensive, it is an effective antifungal agent.[29] There is a lengthy list of potential adverse effects of amphotericin B such as infusion reactions (nausea, vomiting, rigors, and chills), electrolyte derangements and nephrotoxicity. Therefore, an abundance of caution and forethought is required before treatment with this drug. The use of amphotericin B should be reserved for patients with disseminated disease or disease unresponsive to azoles. The drug has been used in conjunction with azoles for patients who have severe diseases. As with fluconazole treatment, duration of treatment should be determined on a case by case basis.[30]

Women who are being treated with azoles should be counseled on contraceptive use and avoiding pregnancy as azoles are teratogenic.[28] Treatment of coccidioidomycosis in pregnant women requires thoughtful consideration of treatment plan in relation to gestational age. Due to teratogenicity with azoles, it should be avoided during the first trimester. Azole therapy can be reconsidered during the second and third trimester of pregnancy.

In regards to breastfeeding, fluconazole is reported as having no known adverse effects in infants according to the American Academy of Pediatrics.[31] Fluconazole does become bioavailable in breast milk and to neonate at a level that could potentially be harmful.[32] However it is important to note that systemic fluconazole has been used in neonates in treatment of candidiasis with limited side effects.

There is a recent case report of severe disseminated coccidioidomycosis in a 4 year-old child with clinical response to immunomodulatory approach. The infection was not responsive to antifungals alone. With the addition of interferon-γ and dupilumab, the child demonstrated rapid resolution of clinical symptoms.[33] Thus, immunomodulatory biologic agents may have a role in the treatment of severe coccidioidomycosis.

Prevention

There is no simple solution to prevent coccidioidomycosis. As described above, the incidence of disease is found in endemic areas especially during times of natural phenomenon, and prevention of aerosolization is not easily achievable. Individuals who work with soil that may

contain Coccidioides should be educated on basic knowledge of the fungus and its clinical symptoms. Those who work in these conditions should be given appropriate personal protective equipment as well as education on proper hygiene and precaution to prevent the infection.[34]

We believe that the best preventive tool for both adults and children is the education of the general public. Health departments in all endemic areas should be proactive in the distribution of information on coccidioidomycosis. In Los Angeles, California, the public health department has made an effort to appeal to a broad demographic by delivering information in the form of stickers, posters, webpages, and flyers. Since the risk of acquiring coccidioidomycosis increases during windy seasons, there should be public warnings to citizens to avoid outdoor activities during windy weather. For children, considerations should be made to decrease outdoor recess and playtime while in school during windy or dusty conditions. Face masks should be worn by adults and children when an exposure to dusty environments is unavoidable. Efforts to reduce dust during construction should be implemented.[35]

Education for clinicians is also essential. Pediatricians in endemic areas should consider coccidioidomycosis in their differential diagnoses in children presenting with chronic cough, prolonged fever, pneumonia that is not responsive to appropriate antibiotics, culture-negative meningitis or osteomyelitis. If serological tests are negative but clinical suspicion remains high, providers should consider retesting. Retesting when there is high clinical suspicion is the key to the diagnosis.

Efforts to create a vaccine for coccidioidomycosis have been underway for some time. The last human trial was in the 1980s, using killed whole spherule immunization. The study did not show significant protection against the infection.[36] Currently there are no available vaccines for coccidioidomycosis. However, formulating a vaccine for children living in an endemic area could be the key in primary prevention of coccidioidomycosis.

Author Contributions

Alisha K. Bajwa: drafted the manuscript.
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