Coccidioidomycosis: Recent Updates

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Abstract

Coccidioidomycosis manifests as a variety of clinical manifestations and ranges in severity from asymptomatic exposure with resultant immunity to reinfection, to fulminant, and life-threatening disseminated disease. Primary coccidioidal pneumonia represents the most common clinical form of infection, and the incidence continues to increase. Within the endemic region, primary pulmonary coccidioidomycosis represents up to 29% of all community-acquired pneumonia emphasizing the frequency with which clinicians encounter this endemic mycosis. Chronic infection develops in 3 to 5% of patients, and almost all morbidity and mortality observed in coccidioidomycosis occur in these forms (e.g., chronic pulmonary disease, extrapulmonary manifestations). This review summarizes the ecology, epidemiology, manifestations of disease, and treatment options currently available for coccidioidomycosis.

Keywords
- coccidioidomycosis
- *Coccidioides*
- Valley Fever
- treatment
- epidemiology
- review

Coccidioidomycosis is an infection caused by a dimorphic fungus endemic to the desert southwest. *Coccidioides immitis* and *C. posadasii* are transmitted by aerosolization of highly infectious and environmentally resistant spores that are inhaled when the soil is disrupted. Primary infection is often manifest as an acute respiratory illness, although the spectrum of disease ranges from asymptomatic exposure to severe and life-threatening disseminated disease.[1]

History

The first case of coccidioidomycosis was described in 1892 involving an Argentinean soldier with skin lesions.[2] In 1896, the first case within the United States was reported in a manual laborer from the San Joaquin Valley, California, with similar skin lesions.[3] This prompted further investigation into the microbiologic and infectious potential of the organism and resulted in the inadvertent infection of a Stanford University medical student in 1929. Following the development of erythema nodosum and his ultimate survival, investigators surmised his illness was similar to "San Joaquin fever," "Desert fever," or "Valley fever," a common disorder throughout central California. Further investigations led by the Kern County Health Department found most patients reported significant dust exposure, had positive coccidioidal skin test results, and for the first time identified racial differences in the risk of dissemination following primary infection.[4]

Ecology

Coccidioidomycosis is caused by two distinct species, *C. immitis* and *C. posadasii*. Initially it was thought that *C. immitis* isolates existed only in California, whereas *C. posadasii* accounted for a broader range of endemicity. However, more recent studies demonstrate considerable overlap in the geographic distribution of both species. Clinically, they are identical in their presentation and management.[5]

Coccidioides spp. are dimorphic fungi endemic to arid, desert regions. In the soil, they grow as a mold with branching septate hyphae. During periods of drought or low precipitation, in the late summer and early fall, the hyphae develop into arthrospores. During these drier periods, the arthrospores disarticulate into individual arthroconidia (spores) that become airborne and are dispersed when the soil is disturbed (►**Fig. 1**).[6]

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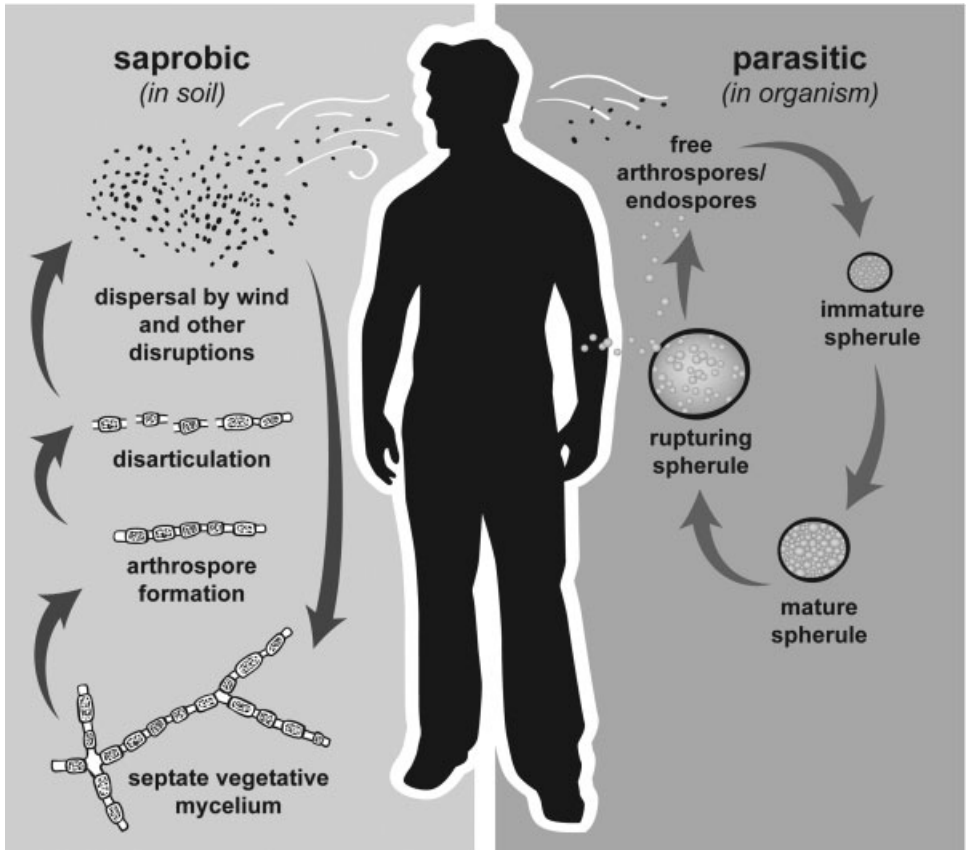

Fig. 1 Life cycle of *Coccidioides* spp.

Ecological research has focused primarily on the saprophytic soil phase and the wind, precipitation, and temperature conditions favoring *Coccidioides* growth. Most isolates have been recovered from alkaline, sandy soil, 10 to 30 cm beneath the surface.[7] However, some studies have documented that *Coccidioides* is more easily isolated from two genera of small mammals, pocket mice (*Perognathus* spp.) and kangaroo rats (*Dipodomys* spp.),[8] than it is from soil.[9,10] Questions remain as to whether *Coccidioides* requires an animal "vector" or if it is simply found in disproportionate quantities in the soil surrounding rodent burrows.[11]

Epidemiology

Coccidioidomycosis is found only in the Western hemisphere. Parts of Arizona, southern New Mexico, western Texas, and the central valley of California are known to be endemic[12–15] (►**Fig. 2**). Some regions within California and Arizona are considered "hyperendemic" including Bakersfield, CA, and both Phoenix and Tucson, AZ. Outside of the United States, there are reports of coccidioidal infections acquired in parts of Mexico as well as Central and South America,[13,16] although estimates for the burden of disease within these countries are not yet available. Beyond the Western hemisphere, sporadic cases have been reported in other countries; however, evidence suggests the majority of these were acquired via fomites originating from known endemic regions, or were misdiagnoses.

A recent report illustrates the significant burden of coccidioidomycosis outside of the traditional endemic region.[17] In fact, approximately 10% of cases were diagnosed or treated in states other than those described above, reiterating the "global playground" of our patients and the need for infectious disease practitioners in all regions of the United States to possess a working understanding of the diagnostic and treatment practices needed during the care of endemic mycoses.

Recent evidence has identified three cases of locally acquired coccidioidomycosis in southeastern Washington.[18] Soil sampling obtained from this area has also isolated viable *C. immitis*[19] confirming endemicity within this location. One of the environmental isolates is genomically identical to a clinical isolate from an affected patient, thus confirming locally acquired infection. This suggests the geographic range of *Coccidioides* spp. may be wider than previously recognized or potentially expanding due to variability and changes in weather patterns. Ongoing work will hopefully further elucidate the range of these fungi.

Consistent with the broadening range of *Coccidioides* and the population explosion within the known endemic region, the incidence of coccidioidomycosis continues to increase.[20] Construction and development of previously uninhabited areas and an influx of nonimmune individuals play a major role in this increasing trend. There is also a growing population of immunosuppressed patients who are more susceptible to disease with the availability of biologic agents.

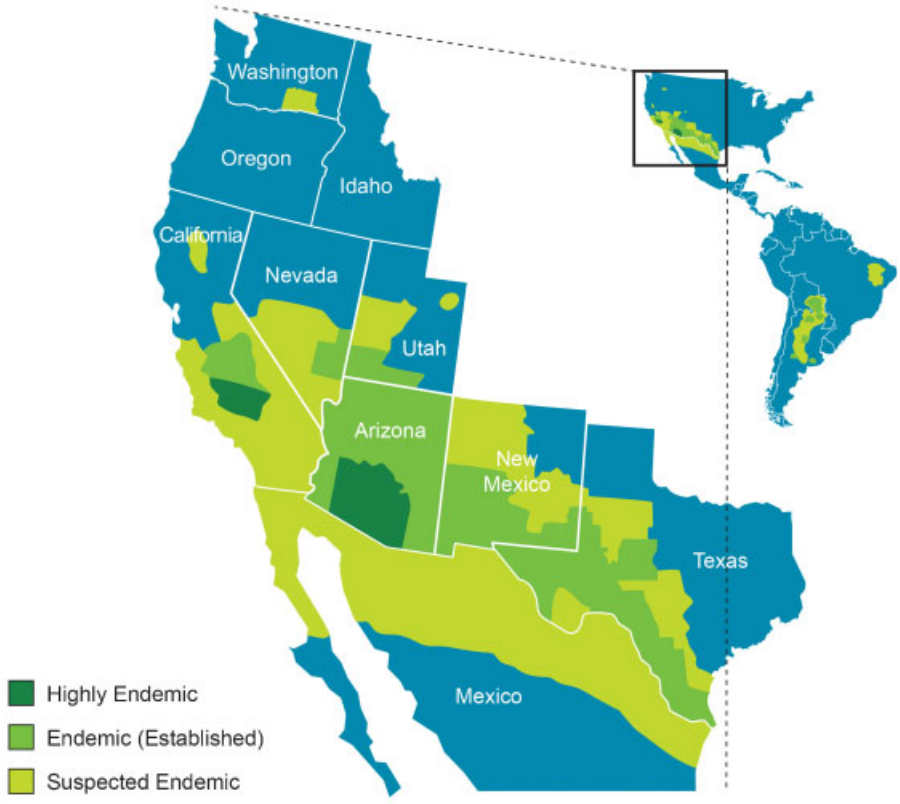

Fig. 2 Areas endemic for coccidioidomycosis.

Concurrent with the increasing number of cases is a growing financial burden in endemic areas. Hospitalizations due to coccidioidal infection were estimated to cost more than $2 billion between 2000 and 2011.[21]

Occupations with heavy exposure to the soil are known to be at an increased risk for coccidioidomycosis. Construction workers, agricultural laborers, archaeologists, and excavators are those most frequently exposed to spores while working in endemic areas.[22–24]

Patients with conditions causing suppression or altered function of T-cells are at particular risk for symptomatic and/or severe disease. This includes patients on immune-modulating medications,[25] solid organ and bone marrow transplant recipients,[26,27] and human immunodeficiency virus (HIV).[28] Other groups at risk include patients in the third trimester of pregnancy owing to the relative suppression of cell-mediated immunity during this time period, and the presence of a cytosolic estrogen receptor within *Coccidioides* spp.[29]

Ethnic predisposition for severe infection has long been recognized. Although there is no racial predilection for primary infection, higher rates of dissemination are well known in Filipinos and African Americans. The risk of dissemination is estimated to be 10 to 175 times higher in these racial groups, although the immunological mechanisms for this risk remain incompletely defined.[29] It was thought that the lower serum vitamin D levels found in darker skinned individuals may play a role in the acquisition or rate of coccidioidal dissemination given the essential role of vitamin D in both innate and acquired immunity; however, contradictory evidence has since been presented.[30]

Pathophysiology

Coccidioidomycosis is primarily transmitted via respiratory inhalation of airborne arthroconidia. Once inhaled, the arthroconidia are deposited into terminal bronchioles and enlarge to form spherules. Spherules are then filled with thousands of endospores. The spherules later rupture releasing new endospores (►**Fig. 3**) and propagating the fungal life cycle in vivo. Dissemination occurs through passage within lymphatics to extrapulmonary sites, or hematogenous spread to the bone, brain, skin, etc. Occasionally, coccidioidal infections can occur from direct inoculation following penetrating trauma causing localized, cutaneous, and soft tissue infections.

All people traveling or residing to endemic regions are at risk for infection given the highly infective nature of arthroconidia (ID_{50} as low as 1 in animal experiments). Although inhalation of a single spore may be enough to cause illness, higher spore burdens are more likely to result in significant disease and may precipitate acute respiratory distress syndrome (ARDS) with heavy exposure.

Clinical Manifestations

It is important to recognize the disparate and tremendous interpatient variability in the clinical course of

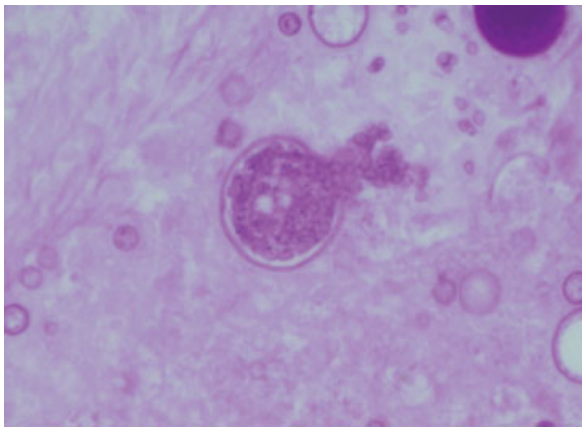

Fig. 3 A rupturing *Coccidioides* spherule producing hundreds of endospores.

coccidioidomycosis. Although up to 60% of those infected recall no symptoms and are identified by positive skin testing during epidemiologic surveys, 40% of those exposed have symptoms ranging from a mild and self-limited illness to pneumonia with severe and life-threatening complications including disseminated infection.

The predominant symptoms of primary coccidioidal pneumonia include cough, fever, and pleuritic chest pain. Differentiation from community-acquired pneumonia in primary infection can be difficult without additional testing and the diagnosis is often not initially considered even in endemic areas.[31]

However, within the endemic region primary coccidioidal pneumonia accounts for 17 to 29% of all cases of community-acquired pneumonia[32,33] and some have suggested routine coccidioidal testing for all patients with pulmonary symptoms within these regions. Unfortunately, patients may experience profound fatigue for weeks to months after resolution of acute pneumonia[34] with a delay in diagnosis not uncommon. If early diagnosis and the initiation of treatment in a timely fashion alter the natural history of the disease has yet to be determined.

Radiographic features are nonspecific and exhibit significant variation in appearance during the course of primary infection. Patients may have a normal and unrevealing chest X-ray, although classic findings include segmental or lobar pneumonia. Pleural effusions can occur in a small proportion of patients and vary from small and clinically insignificant effusions to empyema requiring thoracopic surgery. The pleural fluid is often exudative with a high percentage of eosinophils.[35] The size of the effusion does not correlate with risk of dissemination.[36,37]

Pulmonary coccidioidomycosis often has associated intrathoracic lymphadenopathy with hilar and/or mediastinal nodes enlarged in up to 20% of patients undergoing computed tomographic (CT) imaging.[38] Traditionally, lymphadenopathy was thought to demonstrate regional spread from the pulmonary parenchyma to the lymphatic system and represent early disseminated disease. However, further studies have disproven this presumed association.[39]

Severe presentations of primary coccidioidomycosis are uncommon and are typically observed in patients with underlying immunological deficits or following a high burden of exposure resulting in diffuse multilobar pneumonia. Respiratory failure and ARDS may be seen in these groups.[40] Miliary disease also has been reported in acute pneumonia and indicates hematogenous or lymphatic spread. Imaging findings show multiple, small, millet-seed nodules throughout the lung parenchyma that is radiographically indistinguishable from tuberculosis.[41]

It is essential to follow pulmonary infiltrates from *Coccidioides* to resolution with repeat imaging 2 to 3 months after the initial infection. The initial infiltrate may "heal" with a resultant pulmonary nodule and persist for decades (►**Fig. 4a, b**). If an antecedent history of coccidioidomycosis is not known, or patients are not adequately educated about the sequelae from their initial infection, these nodules can be indistinguishable from malignancy and in many cases, unfortunately, undergo surgical resection. Efforts are ongoing in an attempt to differentiate coccidioidal nodules from nodules caused by other etiologies.[11,41,42] Despite the inclusion of skin testing and serologic testing in these protocols, positive noninvasive testing with an unclear temporal relation to radiologic findings is not typically helpful and certainly does not rule out the possibility of malignancy.

Complications of Primary Infection

As the acute infection resolves, initial infiltrates or nodules can also undergo excavation resulting in thick- or thin-walled cavities (►**Fig. 5**). The cavity may vary over time and can result in significant complications even in immunocompetent hosts.[43] Ruptured cavities near the pleural surface can result in bronchopleural fistulas or a hydropneumothorax.[41] Small cavitary lesions may resolve spontaneously, but in some cases surgical resection or debridement may be required although this option is reserved for those with continued symptoms or complications attributed to coccidioidal cavities.

A small proportion of patients with acute pneumonia will develop chronic fibrocavitary disease.[38] Patients experience persistent cough and sputum production as well as fevers, night sweats, and weight loss.[41] In most cases, serological testing will remain positive. Various radiological abnormalities can be present including infiltrates involving multiple lobes and areas of cavitation.[43] Additional complications of cavitary disease include the development of a fungus ball by either *Aspergillus* spp. or a bacterial superinfection.[41] Occasionally, hyphal forms of *Coccidioides* spp. have been isolated from cavitary lesions, suggesting the presence of a coccidioidal fungus ball.[44]

Extrapulmonary coccidioidomycosis can involve any organ system. Disseminated disease more frequently occurs in patients with known immunosuppression, severe comorbidities, or those of African American or Filipino ethnicity. However, approximately 1 to 3% of "immunocompetent" patients develop extrapulmonary manifestations.[43] The most common organ systems involved include skin, bones, joints, and lymph nodes. Infection in the bone can occur by direct inoculation but often is caused by hematogenous spread. Vertebral osteomyelitis is one of the most

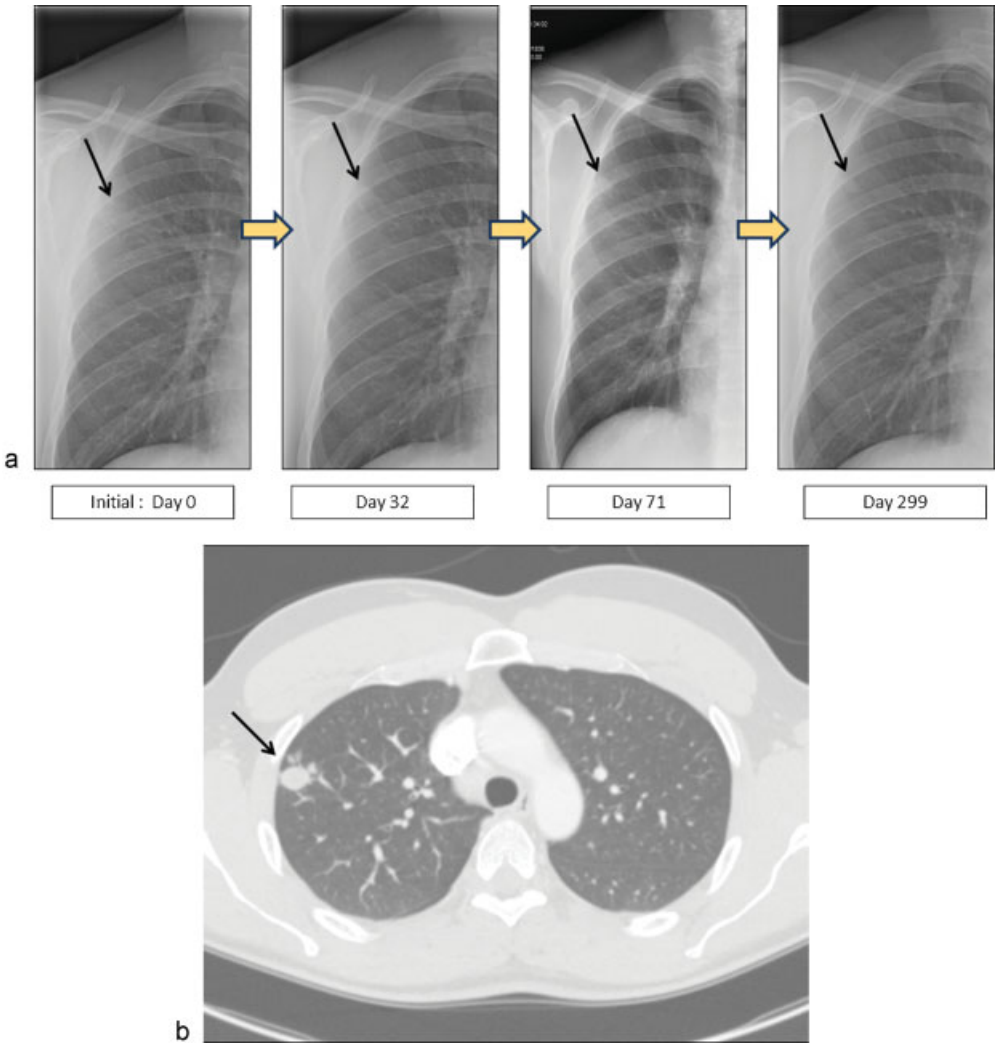

Fig. 4 (a) A patient referred for evaluation of a pulmonary nodule. On review, previous chest X-rays documented the resolution of primary coccidioidal pneumonia with a resultant pulmonary nodule (arrow). (b) The patient also underwent CT scan of the chest for further characterization of the nodule prior to referral.

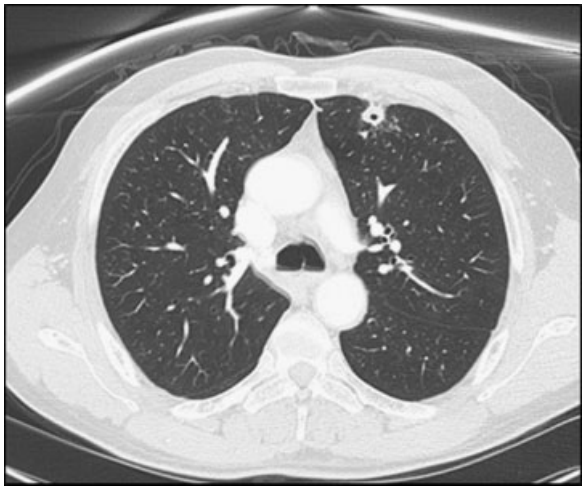

Fig. 5 A thick-walled cavity caused by coccidioidomycosis abutting the pleura.

difficult-to-manage non-central nervous system (CNS) complications. It requires systemic antifungal therapy and may require surgical debridement to control the infection and provide stabilization of the spine.[45]

Patients with disseminated disease often have significantly elevated complement fixation (CF) titers and management of these patients has significant variability among providers. Many physicians recommend routine cerebrospinal fluid (CSF) analysis and/or bone scans in all patients if serum CF titers are more than 1:16. However, recent work has found this approach unhelpful and patient symptoms and exam findings should instead guide diagnostic testing rather than an algorithmic approach to patient management.[46]

Meningitis is the most feared complication of extrapulmonary coccidioidomycosis. Coccidioidal meningitis most frequently develops within the first few months after initial infection, although cases have been observed years after the

primary infection.[47] Additionally, treatment of acute coccidioidal infections does not appear to alter the rate of dissemination,[48] and after cessation of antifungal therapy following resolution of acute disease, patients must be followed up for recurrence or the development of symptoms compatible with extrapulmonary dissemination.

Although meningitis may present with a rapid course, it more frequently represents chronic meningitis with vague symptoms and an insidious onset. Patients with a history of coccidioidal infection and persistent headaches should be evaluated for possible CNS disease by radiographic imaging and lumbar puncture. Other less common symptoms include nausea, vomiting, and vision changes related to increased intracranial pressure.[49] Diagnosis is confirmed by serological testing for *Coccidioides* spp. from spinal fluid, as fungal cultures are frequently negative. Associated findings within the CSF include a leukocytosis with lymphocytic predominance, occasionally eosinophils, and a low level of glucose.

Vasculitis with resulting cerebral infarction occurs in up to 50% of patients with CNS disease in some series. Pathological examination of tissue from these patients has revealed endarteritis obliterans[50] and may require adjunctive treatment with high-dose corticosteroids, although there is no consensus of opinion on this approach to therapy. Hydrocephalus occurs in 30 to 50% of patients[47] and requires urgent neurosurgical evaluation and prompt relief of the elevated intracranial pressure when feasible. These sequelae of CNS disease account for the highest mortality in coccidioidomycosis.[50]

Diagnosis

A flu-like illness following travel or residence within an endemic area suggests the diagnosis. Concurrent features such as the development of a skin rash and/or a peripheral eosinophilia are additional diagnostic clues suggesting the illness is coccidioidomycosis rather than bacterial or viral in origin.

Acute infection can be difficult to diagnose owing to the nonspecific and myriad presentations of the disease. It is common for the diagnosis to be delayed, even within the endemic region among practitioners familiar with the disease. As the vast majority of patients fully recover following acute infection, a significant number of patients are never diagnosed making the exact burden of infection difficult to estimate.

Isolation of *Coccidioides* spp. in culture is the most definitive method of diagnosis. The organism can be recovered from biopsied specimens, sputum, and skin lesions, while isolation from other sites (e.g., CSF, pleural, or joint fluid) is much less common. Isolation from any location or body fluid is diagnostic of proven infection.[43] *Coccidioides* spp. do not require special media for growth and the organism can be recognized 3 to 5 days after inoculation onto routine media. The mold form of *Coccidioides* produces highly infectious arthroconidia as soon as 72 hours after initial growth. This form represents a significant risk of inhalational exposure to laboratory personnel and all specimens should be handled under biosafety level 3 conditions.

Identification of the characteristic spherules or endospores on pathologic specimens also confirms the diagnosis. Spherules are typically 20 to 80 μm in diameter and are best observed with periodic acid–Schiff or Gomori methenamine silver stains. The tissue often demonstrates a granulomatous reaction with fibrosis and caseation in chronic lesions.

Owing to the challenges of demonstrating proven infection, and the risks inherent with laboratory isolation of the mold form, noninvasive methods are more frequently employed. Latex agglutination assays and enzyme-linked immunoassays demonstrating serologic positivity are commercially available but are not specific.[51,52] Testing of CSF or sera by these methods commonly results in false-positive findings, limiting their clinical utility or usefulness in epidemiologic evaluation.[53]

Immunodiffusion and CF testing remain the most specific method for diagnosis,[37] although it is important to recognize interlaboratory variation. Testing is based on identification of IgM or IgG antibodies to coccidioidal antigens by immunodiffusion. In acute infection, nearly half of patients will have detectable IgM within the first week and approximately 90% by the third week.[43,54] Although IgM decreases over time, IgG becomes detectable within 1 to 3 months of acute infection and often persists for 6 to 8 months or longer. Quantitative results from CF testing are helpful in assessing disease severity, correlating with patient symptoms, and assessing a therapeutic response.[35] Although the CF titer is used as a surrogate marker for the burden of disease, immunocompetent patients with a low CF titer may have significant, albeit sequestered, infection, such as within the CNS or a joint space.[43]

A small percentage of patients do not have a detectable antibody response. This usually occurs in patients with significant immunosuppression or early in the course of infection prior to the development of coccidioidal antibodies. Diagnosis in selected solid-organ transplant recipients can be particularly difficult due to the decreased sensitivity of serological testing in this population. This potentially can be explained by the hindered immune response due to antirejection medications. Multiple test modalities may be needed as well as repeated testing over time to detect an immune response in these patients.[55]

Antigen detection can be used to assist with diagnosis, particularly in patients unable to exhibit a robust immunological response. Prior diagnostic testing of patients with coccidioidomycosis noted that these patients had false-positive testing for *Histoplasma* urinary antigen. Owing to this, a coccidioidal urinary antigen test was developed exhibiting a sensitivity of 71% in highly immunocompromised patients.[40] It should be noted that the sensitivity varies greatly in different patient populations and antigen testing generally has little clinical utility in immunocompetent patients. Similarly, serum (1→3)-β-D-glucan (BG), an antigenic component of the fungal cell wall, has been evaluated in the diagnosis of coccidioidomycosis, with disappointing results.[56]

Owing to the need for rapid and sensitive diagnostic testing, interest has increased for polymerase chain reaction

(PCR)-based testing for coccidioidomycosis. Previous studies have demonstrated excellent sensitivity and specificity on isolate material and from sputum in active cases. However, results from the study of other clinical sites have not been as promising.[57,58] PCR-based testing appears to have a high negative predictive value, although the sensitivity is overall similar to fungal cultures. Additional testing on clinical samples is needed for further evaluation of the utility of PCR in coccidioidal diagnostics.[59]

Treatment

There are stark differences in treatment practices between physicians in the treatment of acute coccidioidal pneumonia. Many physicians advocate for observation rather than antifungal treatment, as most patients will eventually clear the infection without long-term sequelae. However, the relative infrequency of significant toxicity with short-term triazole use has prompted others to insist on the treatment of virtually all symptomatic patients with coccidioidomycosis. Treatment of acute pneumonia theoretically may reduce the duration of symptoms, although speculation that treatment may reduce the risk of dissemination appears without merit—a single observational study has suggested there is unlikely to be a significant impact on dissemination rates in those receiving and those not receiving antifungal therapy for acute coccidioidal pneumonia.[48]

Current guidelines recommend treatment of patients with underlying immunosuppression, significant comorbidities, those with prolonged infection, and those with CF titers exceeding 1:32.[5,60] Additionally, most clinicians experienced in the care of coccidioidomycosis have a low threshold to treat African American or Filipino patients given the severity of disease that is commonplace in these ethnicities. Other factors favoring treatment include weight loss of more than 10%, night sweats for longer than 3 weeks, infiltrates of more than one-half of one lung or portions of both lungs, and prominent or persistent hilar adenopathy.[60]

Prior to the availability of azoles, amphotericin B was the only available agent with reliable antifungal activity, subjecting patients to prolonged intravenous therapy and significant risks for the toxicity inherent with polyenes. The development of triazoles thus revolutionized the care of coccidioidomycosis. Fluconazole has excellent bioavailability, is available as an oral formulation, has few drug–drug interactions, and is well tolerated even at high doses.[41] It has been demonstrated effective for the treatment of coccidioidomycosis and is the preferred agent for pulmonary and CNS disease.[61]

The duration of therapy varies on the site and severity of disease. Typically, 3 to 6 months is preferred for primary pulmonary disease and many recommend clinical follow-up for a year or longer after initial infection.[60] In contrast, chronic pulmonary disease often requires life-long therapy to preserve lung function and avoid continued lung destruction. Although there are no studies evaluating the recommended interval of serological testing, typically testing is performed every 2 to 4 months depending on disease severity and the clinical response to treatment.[43]

The efficacy of itraconazole for extrapulmonary disease and chronic infection has been well established[62] and it is accepted as the preferred therapy for skeletal disease based on a blinded comparative study with fluconazole.[61] Itraconazole is available in both solution and capsular form. The capsule and oral solution are not bioequivalent and are thus not interchangeable. The solution is preferred due to improved bioavailability. Patients should be counseled to take itraconazole solution on an empty stomach, as it is best absorbed in the fasting state. In contrast, the capsules require a high-fat meal with an acidic beverage to maximize absorption.[41] Itraconazole serum levels should be evaluated to ensure clinically relevant concentrations are observed, and in patients with levels less than 0.5 μg/mL, adjunctive measures to enhance absorption should be reviewed at each visit.

The role of the newer azoles, voriconazole, posaconazole, and isavuconazole, in the care of coccidioidomycosis has yet to be defined primarily due to cost concerns when these agents are used as primary therapy. The extended-spectrum triazoles have excellent in vitro activity against *Coccidioides* spp. and both voriconazole and posaconazole have proven useful in patients intolerant of, or refractory to, other antifungal agents.[63,64] Voriconazole is an attractive choice for meningeal disease due to its penetration and detectable levels within the CSF.[41] However, treatment is limited by toxicity with long-term use,[65] frequent drug–drug interactions, and the need for therapeutic drug monitoring.[66] Posaconazole has also proven efficacious in pulmonary and disseminated disease.[64] Although therapy is well tolerated with few adverse events, there are no studies to date to suggest it is more effective than fluconazole or itraconazole in humans.[67] Isavuconazole is the newest member of the triazole class and experience in the treatment of coccidioidomycosis with this agent is limited currently.

Pregnancy represents a unique challenge in the treatment of coccidioidomycosis given the teratogenicity of azoles in the first trimester.[68] The relative immunosuppression of pregnancy and elevation in host estrogen levels promoting in vivo fungal growth have prompted the use of amphotericin B formulations in this population with lipid formulations generally preferred. Some experts recommend azoles during the second and third trimester when the risk of teratogenicity is lower to avoid prolonged intravenous amphotericin B administration.

Meningeal disease can be particularly challenging to manage. Most physicians recommend treatment of mild to moderate meningitis with fluconazole due to its excellent bioavailability and penetration into the CSF. The typical fluconazole dose is 400 mg/day but doses of 800 to 2,000 mg/day are commonly used for meningeal disease.[47] Antifungal therapy should be continued indefinitely given the high relapse rates when therapy is discontinued.[69,70] Occasionally, physicians still are forced to use intrathecal amphotericin; however, this approach is reserved for patients with severe disease or cases in which azoles fail given the toxicity of intrathecal therapy.[69,71]

There is no consensus of opinion regarding optimal therapy for patients with refractory infection requiring salvage therapy. Antifungal resistance has not been proven to play a significant role in patients failing traditional therapy and reports of *Coccidioides* isolates with elevated fluconazole minimum inhibitory concentrations (MICs) are rare.[72] Although susceptibility testing is available in reference laboratories, its usefulness in guiding treatment decisions has not been studied. In addition, MIC determination is performed in the mold phase, while the spherule/endospore (S/E) phase MICs are theoretically more applicable to patient care.[5] Lipid amphotericin B formulations are preferred for moderate to severe disease and refractory cases to regain control of the infection. Alternatively, extended spectrum triazoles have been used in cases of more limited disease, although therapeutic drug monitoring is recommended when using these agents.[5]

Echinocandins have minimal inherent activity against *Coccidioides* spp. and should not be used as monotherapy in the treatment of coccidioidomycosis. They have demonstrated potential efficacy when used in combination with other antifungal agents in murine models of infection.[73] Recently, salvage studies have also demonstrated their potential utility.[74]

New Directions

Studies of patients with chronic and disseminated disease have noted decreased production of interferon-gamma (IFN-γ)[75,76] and defects within the interleukin-12/IFN-γ pathway.[77,78] Owing to these findings, there has been interest in the administration of IFN-γ to enhance the host response to coccidioidomycosis. Prospective trials have not been performed, but successful adjunctive use in salvage therapy has been reported,[79] although long-term use is limited by both patient tolerability and expense.

The antifungal drug nikkomycin Z has been long awaited and may represent a breakthrough in the treatment of coccidioidomycosis. It has demonstrated excellent in vitro activity against *Coccidioides* spp., has a unique mechanism of action, and studies have shown efficacy in naturally infected dogs and experimentally infected mice.[80,81] Recent work has focused on developing a dosing framework in preparation for phase 2 and 3 clinical trials.[82]

It has been recognized since the 1940s that individuals who recovered from coccidioidomycosis have durable immunity to reinfection, with the exception of severely immunosuppressed patients.[83] These observations suggest a role for a vaccine to be developed protecting recipients from symptomatic disease. Despite extensive work on development, no commercially available vaccine exists to date.

Conclusion

Coccidioidomycosis continues to represent a significant medical problem within endemic regions. Substantial questions remain regarding the ecology, epidemiology, immune response, and optimal treatment of this infection.[11] The National Institutes of Health and Centers for Disease Control and Prevention have recently redoubled efforts to answer many of these questions and significant advances have been made in a short time. A large-scale double-blind placebo controlled trial has also been proposed in an attempt to clarify the role of antifungals in the treatment of primary pulmonary coccidioidomycosis. The next decade will undoubtedly see the answers to many of the oldest questions in this field, and our patients care improved as a result.

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