THE TREATMENT OF COCCIDIOIDOMYCOSIS

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SUMMARY

Therapy of coccidioidomycosis continues to evolve. For primary pulmonary disease, antifungal therapy is frequently not required while prolonged courses of antifungals are generally needed for those in whom extrathoracic disseminated has occurred. Intravenous amphotericin B should be reserved for those with severe disease. Oral triazole antifungals have had a great impact on the management of coccidioidomycosis. Both fluconazole and itraconazole at 400 mg daily have been effective for various forms of coccidioidomycosis, including meningitis, although relapse after therapy is discontinued is a problem. Individuals with suppressed cellular immunity are at increased risk for symptomatic coccidioidomycosis and they include those with HIV infection, those on immunosuppressive medications, and those who have received a solid organ transplant. Pregnant women and African-American men have been identified as two other groups who are at an increased risk for symptomatic and severe infection.

KEYWORDS: Fungi; Mycotic infections; Coccidioidomycosis; Antifungal therapy.

INTRODUCTION

Coccidioidomycosis is a growing problem in the Western Hemisphere. While it has reached epidemic proportions in some of its known endemic regions[19], it is also being recognized in areas not previously thought to be associated with infection[40,60]. There have been some controversies regarding treatment of the patient with primary pulmonary disease and there are few comparative studies for more severe infection. This paper will review data on the treatment of coccidioidomycosis with an emphasis on changes in management.

Background

Epidemiology. Although first described in Argentina, coccidioidomycosis is closely linked to the San Joaquin Valley of California, where most cases were described in the 20th century. Endemic regions for infection include that valley, as well as the south-central portion of Arizona and northern Mexico[44]. However, there are other recognized regions in Central and South America. In particular, an increasing number of cases have been reported from northeast Brazil[20,60].

Pathogenesis. Most infections are acquired by inhalation of arthroconidia, which are easily dislodged from the soil-dwelling mycelium. The precise ecological niche in the soil of the causative dimorphic organisms, *Coccidioides immitis* and *C. posadasii*, is not known. Within the lungs, the fungus transforms into a unique structure, the spherule, which itself contains packets of smaller entities, endospores.

In the immunocompetent host, a robust cellular immune response, demonstrated by the presence of delayed-type hypersensitivity to antigen skin testing, controls the infection. It is presumed that immunity is life-long and protective as long as the cellular immune response does not wane due to other causes[2].

Clinical expression. Based on early studies by SMITH and colleagues[52], it is clear that 60% of all infections are asymptomatic and are detected only by the presence of a delayed-type hypersensitivity reaction on skin testing. The other 40% have a pulmonary syndrome, often indistinguishable from a community-acquired bacterial pneumonia[36,58]. Some of these patients go on to develop local sequelae. It is estimated that fewer than 1% of all infections result in the most dire complication, extrathoracic dissemination. This usually occurs within six months of initial infection and is characterized by a diminished cellular immune response to *Coccidioides* spp. Common sites of dissemination include the skin, soft tissues, bones, joints and meninges.

Diagnosis. There are several methods by which coccidioidomycosis may be diagnosed. Unlike other endemic fungi, *Coccidioides* spp. grow as moulds on routine media at 36 °C, usually within one week. Once there are aerial elements, such cultures can be significant infectious hazards if not recognized by laboratory personnel[53]. The spherule is pathognomonic if observed on histopathological staining of affected tissue. Serologic tests are available and the titer of the complement-fixation (CF) antibody is especially useful for assessing severity of disease and response to treatment. This can be performed by the traditional

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method or by immunodiffusion[45]. Tests for antigenuria and antigenemia are also available[26,27].

Treatment of the Immunocompetent Host

Primary pulmonary coccidioidomycosis. It is clear that most patients with primary coccidioidal pneumonia who are immunocompetent will resolve their clinical illness without the use of antifungal therapy. This was noted by DICKSON & GIFFORD in the 1930's[24] and is validated by studies of patients who were found to have coccidioidomycosis as a cause of community-acquired pneumonia and did well without antifungal therapy[36,58].

Two recent studies have examined the role of antifungal therapy in primary pulmonary disease. In the first, patients with primary pulmonary disease were either prescribed antifungal therapy or not based on a non-random clinical decision[4]. Among 36 patients who were not given antifungal therapy, there were no adverse events after a median follow-up of 297 days. Among seven patients who continued on antifungal therapy, two developed disseminated disease after therapy was discontinued. There was no difference in the rate of improvement between those receiving antifungal therapy and those not. The second study was a 24-week, observational study among 36 patients with mild to moderate symptomatic coccidioidomycosis[12]. Twenty received antifungal treatment while 16 did not. The median time to symptom resolution was similar in the two groups and patients who did not receive antifungal therapy returned to full-time work significantly sooner.

Based on these observations and studies, it is clear that the decision to treat primary pulmonary coccidioidomycosis is not automatic and should be individualized. Patients with severe disease, including those requiring hospitalization, those with symptoms persisting for more than six weeks, and those with underlying cellular immune deficiencies, are candidates for antifungal therapy. On the other hand, healthy patients without underlying illnesses can often be observed. One clinical rule of thumb is that if a patient with primary pulmonary coccidioidomycosis is already clinically improving without therapy at the time of the initial clinic visit, then antifungals are may be withheld and clinical follow-up initiated.

When antifungal therapy is prescribed, the preferred treatment is an oral triazole with fluconazole favored over itraconazole. There are no comparative trials of these two agents for primary disease and fluconazole has come to be preferred because of its high systemic absorption and relative lack of adverse events. For either, a minimum dose of 400 mg daily is recommended. The duration of therapy is unclear but up to six months is commonly prescribed.

Sequelae of pulmonary disease. While the primary pneumonia of coccidioidomycosis is an alveolar infiltrate, over time it consolidates, resulting in a pulmonary nodule. This phenomenon is benign and does not require antifungal therapy. However, a nodule can be difficult to distinguish from a pulmonary malignancy[46] and biopsy with histopathological examination of the tissue may be required.

Occasionally, a pulmonary nodule excavates its contents into the bronchial tree, resulting in a cavity. While most of cavities are asymptomatic and do not require therapy, occasionally cough and

hemoptysis occur. In such cases, a course of an oral azole triazole antifungal, such as fluconazole or itraconazole, at 400 mg daily can ameliorate such symptoms. The length of such therapy is unclear and a course of six months is reasonable. In some instances, cavities become super-infected, either with bacteria or with other fungi, such as *Aspergillus*. In the first instance, a 5-10 day course of antibacterial antibiotics is reasonable; for the second, itraconazole at 400 mg until symptoms abate is appropriate. Cavities larger than 3 cm are unlikely to close and surgical extirpation should be considered.

A rare complication is pyopneumothorax, which occurs when a coccidioidal cavity ruptures into the pleural space. Management is primarily surgical, involving reexpansion the lung and closing the bronchopleural fistula. Pyopneumothorax is not considered extrathoracic dissemination. Oral triazole antifungals can be used in addition to surgical management.

Chronic pulmonary coccidioidomycosis consists of pulmonary infiltrates, particularly in the apical or subapical regions, with symptoms persisting for months that include cough, weight loss, hemoptysis, chest pain, and dyspnea. Sputum cultures are frequently persistently positive[48]. Both fluconazole and itraconazole at 400 mg daily appear to be effective[18,32]. Treatment is prolonged, usually for more than one year.

Diffuse, overwhelming pulmonary coccidioidomycosis occurs under two conditions. First, it may be seen in healthy hosts who are exposed to a large inoculum, such as may occur during an archeological dig[39] or laboratory accident[53]. The second scenario is among patients with underlying cellular immune deficiency, such as advanced HIV infection[51] or those on immunosuppressive medications[5]. This is a severe form of coccidioidomycosis that often results in respiratory failure.

Initial therapy should begin with amphotericin B. While there are data in other fungal infections that lipid preparations of amphotericin B are superior in efficacy compared to the deoxycholate formulation, no such study has been performed in patients with coccidioidomycosis. Because of this, either deoxycholate amphotericin B at 0.7 mg/kg daily or a lipid preparation at 3 mg/kg daily infused intravenously is recommended. Some experts would simultaneously add a triazole antifungal, such as fluconazole or itraconazole at 400 mg daily, to the regimen. The frequency of amphotericin B infusions may be decreased over time as the patient clinically improves.

Extrathoracic dissemination. This is defined as clinical disease outside the thoracic cavity. For treatment purposes, it can be divided into disease that excludes the central nervous system (CNS) and that which involves the CNS. Patients may have single or multisite dissemination. The skin, soft tissues, bones and joints are the most common sites non-CNS dissemination.

For severely ill patients with multisite dissemination, the management is the same as for those with diffuse pulmonary coccidioidomycosis and includes initial amphotericin B with a triazole antifungal. However, for less severely ill patients, particularly those not requiring hospitalization, an oral triazole antifungal alone is reasonable initial therapy. In a comparative trial of fluconazole 400 mg daily and itraconazole 200 mg twice daily, patients with skeletal infections responded significantly better to itraconazole. Overall, response rates were lower and relapse rates were

higher among those on fluconazole, but were not significantly different in either case. Serum drug concentrations did not appear to predict response to therapy[32]. Based on this, either fluconazole or itraconazole at 400 mg daily is recommended for mild to moderate disseminated coccidioidomycosis, but itraconazole is preferred for those with bone and joint disease.

The length of therapy for disseminated disease is undefined. At least one year of therapy should be considered. A useful tool for monitoring the response to therapy is the CF titer. This should be obtained every six to 12 weeks and decline with effective treatment. A low (≤ 1:4) or undetectable CF titer suggests control of fungal growth. If the patient is otherwise stable, it is reasonable at this point to consider reduction or discontinuation of antifungal therapy. However, a low CF titer does not predict whether relapse will subsequently occur, which may be seen in up to 30% of patients[32]. Hence, close clinical follow-up is required. Another monitoring tool is the coccidioidal skin test. A positive reaction indicates that the patient has developed an appropriate cellular immune response and limited data indicate that this finding plus a low CF titer predict a lower risk of relapse[43].

CNS disease represents a unique form of coccidioidal dissemination. The most common presentation is a basilar meningitis, manifested by headaches and decreased cognition[15]. Without appropriate therapy, coccidioidal meningitis is uniformly fatal[59] and intravenous amphotericin B is not effective. Initial therapeutic attempts involved the direct installation of amphotericin B into the subarachnoid space[28]. The most direct route is into the basal cistern[38]. This requires considerable skill and attention and should only be done by an experienced practitioner. Other routes include through reservoirs placed in the lateral ventricles or by installation through a lumbar route using a hypertonic solution. In this case, the patient is placed in Trendelenburg position to allow drug to enter the basilar cisterns[54]. One successful method employed a programmable pump and a catheter placed in the basilar cistern subarachnoid space[9].

In 1990's, studies indicating that both oral fluconazole[31] and itraconazole[57] were effective for meningeal disease and ushered in a new era in the management of coccidioidal meningitis. While it is generally agreed that the minimum dose of either triazole should be 400 mg daily, higher doses, especially of fluconazole, have been used and many experts prefer to use oral fluconazole 800 mg daily as the initial dosage. A case report study indicated a relapse rate of 78% when therapy was discontinued[23], leading to the recommendation that triazole therapy for coccidioidal meningitis should be life-long.

Coccidioidal meningitis may be complicated by hydrocephalus. This is manifested by worsening headache and cognition with markedly elevated CSF protein concentrations. In general, it is not reversible with drug therapy and requires surgical intervention with a CSF shunt. Vasculitis, cerebral infarction and brain abscesses may also occur[11]. There are no clear management strategies for these complications other than to continue antifungal therapy. There are limited data on the use of the two newer triazole antifungals, posaconazole and voriconazole, in various forms of coccidioidomycosis. Both appear to be effective in some instances where either fluconazole or itraconazole have failed[17,37].

There is a role for surgical therapy in coccidioidomycosis. For pulmonary disease, it is useful in the diagnosis of nodules, extirpation of pulmonary cavities, and in the management of pyopneumothorax[6,34]. Its utility for disseminated disease entails biopsy of suspect lesions and reducing the size of inflammatory masses, although the latter has not been rigorously compared to antifungal therapy alone. Stabilization of vertebral lesions is a critical element[55] and surgical evaluation should be considered in all patients with coccidioidomycosis involving the spine. Placement of CSF shunts is required for the management of coccidioidal meningitis complicated by hydrocephalus[33].

Treatment of the host with immunodeficiency

Because the cellular immune response is critical to control of coccidioidomycosis[2], patients with such an immune deficiency require special consideration. Most experts would recommend antifungal therapy for all types of coccidioidomycosis, including primary pulmonary disease, in such patients. The form of therapy depends on the severity of illness and the anatomic site of disease.

HIV Infection. Prior to the advent of potent antiretroviral therapy, coccidioidomycosis was a significant opportunistic infection in patients with HIV infection living in the coccidioidal endemic region[3,29]. However, with control of viral replication and immune reconstitution, the incidence and severity of coccidioidomycosis in this group has decreased[41]. Data suggest that at a peripheral CD4 cell count ≥ 250/μL, a specific cellular immune response to coccidioidal antigens is maintained[1]. Based on this, among patients on potent antiretroviral therapy with undetectable plasma HIV RNA who have CD4 cell counts ≥ 250/μL, coccidioidomycosis can be managed in the same manner as that for immunocompetent hosts.

In patients with lower CD4 cell counts, all patients should receive antifungal therapy. For those with severe disease requiring hospitalization, initial therapy with amphotericin B combined with a triazole antifungal is recommended, as discussed above for diffuse pulmonary disease. For less severe disease, an oral triazole antifungal, either fluconazole or itraconazole at a daily dose of 400 mg, is reasonable.

Only a few cases of immune response inflammatory syndrome (IRIS) occurring during HIV and coccidioidal infection have been reported and some of these are not convincing[21,42]. Clinical experience suggests coccidioidal IRIS is very rare. Because of this, potent antiretroviral therapy need not be delayed at the time of antifungal therapy.

While one study suggested a small benefit of antifungal prophylaxis among highly immunosuppressed HIV-infected persons living in the coccidioidal endemic region[62], this approach is not recommended given its cost and potential adverse events. Starting and maintaining potent antiretroviral therapy is the most effective method for reducing the incidence and severity of coccidioidomycosis HIV-infected patients[41].

Drugs associated with immune suppression. Medications that treat autoimmune and other inflammatory conditions have been associated with increased risks of active coccidioidomycosis[47]. These include corticosteroids, cancer chemotherapy[22], and antibodies directed against cytokines. The latter has been an area of recent study. BERGSTROM and colleagues first noted an increased risk with inhibitors of tumor necrosis-(TNF-α), with monoclonal antibody inhibitors having a greater impact than the TNF-α antagonist etanercept[8]. TAROUMIAN and colleagues have published their experience among patients with rheumatological

diseases living in the coccidioidal endemic region[56] and found that in many instances, immune modulating treatment could be restarted during antifungal therapy and, in some cases, antifungal therapy could eventually be discontinued.

Transplant recipients. Allogeneic solid organ transplant recipients living in the coccidioidal endemic region have an increased for developing coccidioidomycosis, particularly during the first year after transplantation[13]. All patients living in an endemic region should be screened for coccidioidomycosis before transplantation. BLAIR has offered an approach to their management[10]. Those with a documented medical history of prior active coccidioidomycosis are recommended to receive fluconazole 200 mg daily for at least six months. For those with a positive serologic test, fluconazole 400 mg daily for one year is recommended followed by life-long suppressive therapy with 200 to 400 mg daily. If the patient is found on screening to have evidence of clinically active coccidioidomycosis or has had active disease within one to years, transplantation is ideally deferred and the patient treated with fluconazole 400 mg daily. Once the active infection is clinically resolved, transplantation may proceed and antifungal therapy is then continued indefinitely.

Within the endemic area, it has been proposed that antifungal preventive therapy be universal. In a recent report, no instances of post-transplant coccidioidomycosis occurred among 143 evaluable liver transplant recipients when receiving fluconazole 200 mg daily for one year, compared to 2.9% of recipients where fluconazole was given on a targeted basis[35]. Although adverse events weren't reported in the universal group, the authors note the potential of fluconazole and other triazole antifungals to inhibit CYP 3A4 and result in elevated tacrolimus levels. Moreover, the use of voriconazole has resulted in an increased risk for squamous cell carcinoma of the skin in organ transplant recipients[61].

Donor-derived coccidioidomycosis has become an important issue given recent reports[14,16,25]. If an organ from a donor with active coccidioidomycosis is transplanted, the donor should receive antifungal therapy. The possible scenarios and their management have recently been detailed by SINGH and colleagues[50].

Any form of active coccidioidomycosis that occurs after transplantation merits therapy in an allogeneic solid organ transplant recipients. In the absence of controlled trials, amphotericin B, either as the deoxycholate or a lipid formulation, is recommended for severe disease while an triazole antifungal is appropriate for patients who have mild or moderate illness. Once the patient is clinically stable, therapy with fluconazole at 200 to 400 mg daily should be continued indefinitely.

The pregnant patient. Pregnancy represents a unique condition for coccidioidomycosis. The incidence of symptomatic and severe disease is high when coccidioidal infection is acquired during or after the second trimester. On the other hand, for women who already have a coccidioidal infection, the disease usually does not worsen during the course of pregnancy[7].

The use of azole antifungals during pregnancy has been controversial. Initially, these agents were considered teratogenic and it was recommended that they not be used at any time during pregnancy. However, review of the literature demonstrates that the risk of fetal abnormalities is restricted to the first trimester. Therefore, while azole antifungals should be avoided during the first trimester, they may be considered as a treatment option after this time[7].

Race and gender. African-American men have been found to have a markedly increased risk of developing symptomatic coccidioidomycosis[30,52]. Moreover, they are known to be admitted to the hospital for coccidioidomycosis at higher rates than other groups[49]. It has been suggested that Filipino men have a similar risk. However, many patients of these backgrounds resolve their coccidioidal infection without sequelae. Based on this, while such patients should be followed particularly closely for persistent infection or extrathoracic dissemination, preemptive therapy for otherwise resolving disease is not required.

RESUMO

Tratamento da coccidioidomicose

A terapia da coccidioidomicose continua a evoluir. Para a doença pulmonar primária, o tratamento antifúngico frequentemente não é necessário, enquanto períodos prolongados de tratamento antifúngico são geralmente necessários para aqueles nos quais houve disseminação extratorácica. A anfotericina B intravenosa deve ser reservada para pacientes com doença grave. Antifúngicos triazólicos orais têm tido um grande impacto no manejo da coccidioidomicose. Tanto fluconazol quanto itraconazol em doses diárias de 400 mg foram eficazes contra várias formas de coccidioidomicose, incluindo a meníngea, embora recaídas após a interrupção da terapia ainda constituam um problema. Indivíduos com supressão da imunidade celular apresentam risco aumentado para a coccidioidomicose sintomática, incluindo pacientes infectados pelo HIV, em uso de medicações imunossupressoras, e os que receberam transplantes de órgãos sólidos. Mulheres grávidas e homens afro-americanos foram identificados como dois outros grupos que apresentam risco aumentado de infecção sintomática e grave.

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