Treatment for Early, Uncomplicated Coccidioidomycosis:

What is Success?

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Summary: Initial, uncomplicated coccidioidomycosis produces a variety of signs and symptoms, only some of which are evidence of continued fungal proliferation and the need for continued, re-instituted, or alternative antifungal therapy. Here we consider various convalescent patient complaints in that light.

Running Title: Treatment of early coccidioidomycosis

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Abstract

The care of primary pulmonary coccidioidomycosis remains challenging. Such infections produce a variety of signs, symptoms, and serologic responses that cause morbidity in patients and concern in treating clinicians for the possibility of extrapulmonary dissemination. Illness may be due to ongoing fungal growth that produces acute inflammatory responses, resulting in tissue damage and necrosis, and for this, administering an antifungal drug may be of benefit. In contrast, convalescence may be prolonged by other immunologic reactions to infection, even after fungal replication has been arrested, and in those situations, antifungal therapy is unlikely to yield clinical improvement. In this presentation, we discuss what findings are clinical indicators of fungal growth and what other sequalae are not. Understanding these differences provides a rational management strategy for deciding when to continue, discontinue, or reinstitute antifungal treatments.

Key Words: Coccidioidomycosis, treatment, symptoms, azole antifungals.

Coccidioidomycosis (San Joaquin Valley fever or simply Valley fever) is the result of inhaling one or more spores of either *Coccidioides immitis* or *Coccidioides posadasii* [1]. Many infections do not cause clinical illness, and patients who do seek medical attention for coccidioidomycosis often recover without ever being correctly diagnosed [2]. Even so, the reported numbers in the past decade have ranged from 10,000 to 20,000 new cases annually [3]. The vast majority of reported infections come from our states of California and Arizona, and in areas of high endemicity. In Phoenix and Tucson, approximately a quarter of community acquired pneumonia cases are due to coccidioidal infections [4, 5].

Until quite recently, medical guidance has focused primarily upon the proper approaches to patients with the most severe manifestations of coccidioidomycosis. A small percentage of all infections result in progressive fibrocavitary pulmonary complications which are plainly evident on chest imaging. In an even smaller proportion, destructive lesions develop in the skin, skeleton, meninges, or other extra-thoracic sites, representing lymphatic and hematogenous dissemination of the original pulmonary infection. These complications are well recognized sources of patient morbidity, even death, and broad consensus exists that they benefit from antifungal treatment of various sorts and for various durations [6]. Moreover, major cellular immunodeficiency states [7] clearly predispose to progressive coccidioidal infections, and there is little argument that early antifungal treatment of such patients is also warranted, even if complications are not yet evident.

In stark contrast, there are widely divergent opinions, mostly derived from personal and unpublished experience, concerning what constitutes appropriate management of newly diagnosed, symptomatic coccidioidal infections in apparently immunocompetent persons. When there were no effective antifungal agents available to treat coccidioidomycosis, we learned that a

very large proportion of such infections eventually resolve [8, 9]. Even with the advent of amphotericin B, its toxicity was such that many persons went untreated unless progression was compelling [10, 11]. With the advent of oral and relatively safe azole antifungals such as fluconazole, the prospect of early and potentially prolonged treatment became a feasible option. Unfortunately, despite the availability of fluconazole, not a single, appropriately designed clinical trial has been completed to define the benefit of early treatment for either curtailing symptoms of the immediate illness or preventing subsequent complications. Given this void, some experts recommend offering treatment to all newly diagnosed patients, reasoning that the potential for benefit is significant while the risks of azole therapy are low. Others, like us, recommend this decision be on a case-by-case basis, emphasizing the overall self-limited nature of most infections and that early treatment seems to alter immunologic responses [12] and may be associated with a risk for the late emergence of disseminated infection [13, 14]. Moreover, the use of fluconazole is neither without cost or risks. Alopecia, xerosis, and cheilitis are frequent side effects and drug interactions are common [15]. In a recent study, more than half of patients on fluconazole for coccidioidomycosis had an adverse event and nearly two-thirds of them necessitated a therapeutic change [16]. The most recent practice guidelines from the Infectious Diseases Society of America do not take a position but simply advise that typical courses of oral treatment, should they be used, range from three to six months with 400 mg per day of fluconazole or equivalent weight-based dosing, and we generally follow those recommendations for duration.

What has not been addressed in any systematic way, and what we would like to focus on in this commentary, is a rational approach to the subsequent management of patients who begin fluconazole treatment shortly after a primary pulmonary infection is diagnosed. By “shortly after

diagnosis," we mean within several weeks as two recent studies illustrate that nearly half of newly diagnosed infections were delayed by at least a month [17, 18]. Clinicians who care for such patients know that they must not only decide on whether or not to initiate treatment but also additional decisions are needed both during and in the months following treatment. What constitutes a therapeutic response or a relapse is often surprisingly in question as some of the signs and symptoms could be attributed to ongoing and unchecked fungal growth, to appropriate host immunologic responses, or to idiosyncratic antifungal toxicity. It is our view that re-examining the course of coccidioidal infections with an appreciation of these difficulties might be helpful to treating clinicians in the management of future patients.

We propose that only symptoms resulting from fungal multiplication will improve as a result of antifungal therapy. The consequences of unchecked spherule propagation are clear. Spherule rupture triggers acute inflammatory responses with an influx of neutrophils and eosinophils [19-21]. Repeated cycles of spherule growth and rupture cause exponential expansion of colony forming units, and ultimately inflammation and destruction of contiguous tissue. In contrast, the presence of a dormant spherule does not cause this same inflammatory process. From this understanding, it follows that tissue destruction should be a hallmark of coccidioidal disease activity that might benefit from antifungal drug therapy whose only value is to inhibit ongoing spherule proliferation. As examples, progressive involvement or cavitation of pulmonary lesions, cutaneous ulceration, subcutaneous abscess formation, lytic bone lesions, joint synovitis, or meningitis are all indications for antifungal therapy.

Alternatively, some symptoms resulting from a coccidioidal infection, may be a result of the immunologic responses and not a reflection of ongoing fungal growth. These often last for weeks to months and may prevent patients from a return to their baseline health. The presence of these

complaints, of course, raises concerns among treating clinicians that the infection is still "active," creates the desire to "do something" to help these patients, and may result in continuing or in some instances restarting antifungal treatment. In the following discussion, we detail several such ongoing problems that are encountered frequently during the convalescence phase of coccidioidal infections.

One very common problem is ongoing arthralgias and other rheumatologic signs and symptoms. These complaints are sufficiently common to have led to the term, "desert rheumatism," as a synonym for this manifestation of coccidioidomycosis. These symptoms are likely secondary to immune complex deposition [22, 23] or other immunologic responses initially triggered by the infection, rather than infection itself within the muscles or joints, and they resolve without joint destruction or other long term sequalae. However, the development of arthralgias during the clinical course of primary pulmonary coccidioidomycosis in some cases may lead to increased patient anxiety and subsequent unnecessary diagnostic testing or inappropriate prolongation of antifungal therapy. It is important to recognize the arthralgias associated with primary pulmonary coccidioidomycosis are typically symmetrical, and affect the lower extremities more than the arms, and when in the upper extremities, affect principally the wrists. Accompanying joint effusions sufficient to be aspirated are very uncommon. It is noteworthy also that the arthralgia may present late, with a peak incidence ~20 weeks after initial infection, and interestingly, it may be more common in those treated with antifungal agents for primary pulmonary disease [14]. As such, this manifestation may be a component of the natural history of disease, or may be secondary to antifungal therapy and abate with medication discontinuation [16].

Another common management problem is persistent fatigue [24]. Among otherwise healthy college students, a quarter required follow-up care for over four months, and twice as many dropped out for a semester as did those diagnosed with mononucleosis [25]. In a recent very small study of such patients, cardiopulmonary exercise testing disclosed a striking oxygen utilization deficit, expressed as a reduced VO_2 Peak [26]. In a subsequent patient with persistent fatigue and a decreased VO_2 Peak following his coccidioidal infection, data from a right heart catheterization demonstrated reduced oxygen extraction [Franz Rischard, unpublished observation], suggesting in this patient that his fatigue might be the result of mitochondrial dysfunction. It is not clear whether these limited findings account for the frequent symptom of fatigue following coccidioidal infection, but they do suggest further studies might better define its physiologic basis. The management of fatigue is difficult, but patients often benefit from simple reassurance by the physician. Referral to physical therapists is also helpful as patients may experience significant deconditioning. No convincing data have shown a benefit to antifungal therapy in shortening the duration of this troublesome symptom.

Headache during the care of primary pulmonary coccidioidomycosis patients may be particularly worrisome to treating clinicians due to the possibility of underlying coccidioidal meningitis and the concern of missing this severe potential manifestation of disease. It should be remembered that headache is extremely common in uncomplicated disease, up to 81% in one report [14], and relents in severity and frequency over the first few weeks of infection. In contrast, the headache observed in coccidioidal meningitis may wax and wane but generally increases in severity with the development of additional symptoms over the same time frame. In patients with headache as part of their otherwise uncomplicated primary infection and in whom

fluconazole is started, examination of the CSF is strongly urged to ensure that the headache is not a symptom of meningitis.

The fourth troubling finding either during or after fluconazole therapy is persistent, or increasing complement fixing antibody titers [27]. Quantitative complement fixation (CF) testing for coccidioidal antibodies was originally described over 60 years ago from a single research laboratory dedicated to the study of coccidioidomycosis [28]. One of the important findings in that description was that higher titers were associated with more extensive coccidioidal infection, and titers $\geq$1:32 were more frequently associated with dissemination. However, that relationship was observed in untreated patients, before even the availability of amphotericin B, much less the now widely used azole antifungals. The first reassessment of that relationship in treated patients has only recently been published [29]. In this observational study of over 400 patients with coccidioidomycosis the pitfalls of attempts at patient risk-stratification by serologic titers alone were clearly shown. In fact, 17% of patients with uncomplicated primary pulmonary coccidioidomycosis exhibited CF titers $\geq$1:32. It is unclear if these patients exhibited a higher inoculum exposure to arthroconidia compared to patients who exhibited comparatively lower peak CF titers (<1:16). Additionally, prior work has also shown the absolute CF titer at the completion of antifungal therapy, unless it was increasing or >1:256, is not predictive of later relapse [30]. These observations serve as a useful reminder to the treating clinician that serologic results are only one component of the decision-making process.

Within the weeks and months following the discontinuation of antifungal treatment, a common patient concern is the "relapse" of symptoms, such as fatigue and malaise. These symptoms, while common during coccidioidal infections, also overlap substantially with common and inconsequential infections. On such occasions, evaluation may identify a viral

upper respiratory illness. However, in the absence of identifiable evidence new or progressive lesions, symptoms are generally transient and will resolve within a few weeks, and reinstitution of antifungal therapy is not required.

One important approach to the management of coccidioidal infection that is not frequently emphasized is longitudinal care. This should consist of planned follow-up visits at six- to twelve-week intervals whether or not antifungal therapy is prescribed. This approach has several salutary effects. First, it relieves the clinician of the imperative of providing antifungal therapy because the patient may not be seen again. It allows the clinician and the patient to ascertain whether certain symptoms, particularly those felt to be due to immunological response rather than fungal growth, will improve over time without specific therapy. It may also preclude the need for lumbar puncture and CSF analysis in those presenting with pulmonary coccidioidomycosis and headache.

During the follow-up of patients with pulmonary coccidioidomycosis, it is common practice to review patient symptoms, examination findings, and repeat CF testing, since these titers typically fall over time with patient improvement and can be used prognostically. Although an increase in patient CF titers may occur with treatment failure or a relapse of disease, this phenomenon may be observed in patients during therapy who otherwise appear to have resolved their illness or even years later. Although the exact cause of this phenomenon is unknown, possible explanations include endemic re-exposure to *Coccidioides* with an amnesic immunologic response, subclinical granuloma rupture and/or degradation with *in vivo* "re-exposure", diffusion of fungal antigens from otherwise well controlled fungal residual nodules, or transient local immunosuppression with a temporary lack of host control. Additionally, some patients may persistently maintain a positive complement fixation titer, despite a lack of

symptoms, for years off antifungal therapy [29]. Moreover, use of the coccidioidal skin test as a marker for protective immunity not reduce this uncertainty because a negative test does not always indicate failure of the immune system to control the infection [30-33]. For this reason, treating physicians should not insist on an undetectable CF titer prior to stopping antifungal therapy in patients with otherwise uncomplicated disease.

On a case-by-case basis, infrequently a clinician may encounter a situation that might prompt antifungal treatment longer than 6 months in otherwise uncomplicated pulmonary coccidioidomycosis. Examples could include an extensive infiltrate, a frail patient just beginning to recover from illness, a pulmonary lesion abutting a major vessel (eg aorta, pulmonary artery), development or progressive enlargement of a symptomatic cavity, or the new onset of hemoptysis near the end of treatment period. Such situations are unusual, and most will not require treatment durations longer than those recommended by the current IDSA guidelines.

The lack of a proven benefit of antifungal therapy in uncomplicated primary pulmonary coccidioidomycosis remains an area of clear controversy. Our training manual describing this general approach is available online [34] or in hard copy upon request (vfever@email.arizona.edu). Some experts in the field recommend no treatment for most patients with primary infection and instead to manage patients by periodic reassessment of symptoms and radiographic findings to assure resolution of symptoms without antifungal treatment. However, others propose treatment of all symptomatic patients in the hopes or facilitating more rapid resolution of symptoms and possibly preventing future complications. Despite significant investment in a now terminated NIH-sponsored randomized placebo-controlled trial (ClinicalTrials.gov, study NCT02663674) designed to examine symptomatic improvements in primary coccidioidal pneumonia, this debate persists - do patients benefit from

antimicrobial therapy, or in fact does the disease simply need to "run its course" with patient symptoms driven by a continued immune response unrelated to ongoing pathogen replication. Retrospective studies have not provided compelling evidence fluconazole is effective in the amelioration of patient symptoms, and in some patients dissemination has followed years after discontinuing such early treatment [13, 14]. One potential problem with these past studies is that most have primarily included fluconazole patients while other triazoles may in fact be more efficacious as has been demonstrated *in vitro* [35], in animal models, and in the only comparative study of treatment in coccidioidomycosis [36]. It is possible fungicidal agents currently in development [37, 38] may improve patient symptoms compared to the fungistatic triazoles currently in use although this will need to be carefully examined in clinical trials.

To summarize, there are several unresolved outcomes in patients with newly acquired coccidioidomycosis that include rheumatologic complaints, persistent fatigue, and unexplained behavior of complement fixing antibody titers. In patients seen by us on referral from other treating physicians, we see on a regular basis these complaints or serologic results being used as the basis for continued, dose escalated, or reinstituted antifungal therapy. Since we know that rupturing spherules produce acute inflammatory host responses and this, if unchecked, results in tissue necrosis, the absence of worsening focal lesions, either in the lung or elsewhere, strongly suggests that spherule rupture and propagation has ceased. If there is no fungal growth, we would argue that the static effect of azole antifungal drugs should be of no additional value. Following this logic, for patients with newly diagnosed coccidioidal infections in whom their pulmonary process has abated and no focal lesions of extra-thoracic dissemination are evident, we follow the IDSA guidelines and continue antifungal therapy, typically fluconazole 400 mg daily, for no more than three to six months. We address rheumatologic complaints with non-

steroidal anti-inflammatory drugs, and for those with persistent fatigue, physical therapy is often very useful to assist in hastening its resolution. As for persistent or increasing complement fixing antibody titers in otherwise uncomplicated infections, we do not use these alone as an indication for antifungal therapy unless there are physical findings of destructive lesions or radiographic evidence of disease progression or recurrence.

We hope that this discussion, based upon our collective personal experience, brings into focus the lack of non-randomized controlled studies to guide treatment duration in newly recognized coccidioidal infections. While we are comfortable with our approach to managing such patients, it is based upon our expectations of what spherule replication produces and anecdotal accumulated experience rather than upon published evidence of patient outcomes. This, in fact, would be a very useful area for future investigation.

Conflict of Interest disclosure.

Dr. Galgiani is Chairman of the Board and a significant stock holder of Valley Fever Solutions, a company that is developing nikkomycin Z as a treatment for coccidioidomycosis. All other authors have nothing to disclose.

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