

## Common Mistakes in Managing Pulmonary Coccidioidomycosis

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### ***Abstract***

Coccidioidomycosis (Valley Fever) is a common disease in Arizona and certain other parts of the Southwestern United States. Despite this, there is a surprising lack of awareness, neglect in diagnosis, and inadequacy of management by many clinicians in these endemic regions. This review discusses why early diagnosis of coccidioidal infection is valuable to patient care and offers a variety of management options that are particularly useful and others which often are of little value.

### ***Introduction***

Coccidioidomycosis (Valley Fever) should be a familiar and well-managed disease for Arizona primary care clinicians, and specialists in pulmonary medicine or infectious diseases. In many years it is the second most commonly reported infectious disease to the Arizona Department of Health Services. It also constitutes nearly a third of all community acquired pneumonias (CAP) in Phoenix and Tucson (1-3). Coccidioidal infections in Arizona are responsible for two-thirds of all infections reported in the United States (4). Despite its expected frequency, in primary care practices it is common not to consider the diagnosis or to order necessary testing. In one study from Maricopa County, serologic tests for Valley Fever were ordered in less than 20% of persons with CAP (5). Furthermore, when specialists are referred patients with newly diagnosed Valley Fever, their management strategies vary widely, frequently falling outside of treatment guidelines developed both by the American Thoracic Society and the Infectious Diseases Society of America (6, 7).

There are reasons why a gap exists between medical practices and optimal management of patients with Valley Fever. Although the Arizona Board of Medical Examiners issues approximately a thousand new licenses each year, most recipients have neither received their doctorate nor postgraduate education in Arizona. As documented by the Arizona Department of Health Services, only 12% of surveyed Arizona clinicians graduated from an Arizona medical school, only 47% received house staff training in Arizona medical centers, and only 16% had received CME training in Valley Fever within the past year (8). Moreover, a large majority of Arizonans moved to this state relatively recently, previously lived outside of the coccidioidal endemic region, and are themselves unfamiliar with the disease. Finally, since so many persons

eventually resolve their illness whether or not treated with antifungal drugs, some clinicians perceive coccidioidomycosis not to be a serious public health problem and not an important diagnosis to make.

In this article, we will first address the last of these causes for the inattention to coccidioidomycosis and provide the evidence that southwestern clinicians, especially within the Arizona counties of Maricopa, Pima, and Pinal, should include Valley Fever frequently in their differential of CAP and other pulmonary syndromes. We will then highlight a number of what we believe are commonly made mistakes in diagnosis and management of coccidioidal pneumonia and its pulmonary sequelae. Admittedly, this will occasionally involve areas of personal opinion, albeit formed over many years of practice within the Phoenix and Tucson, Arizona areas. We also acknowledge the possibility that we “have it wrong” and that some management strategies that we believe are mistakes are in fact better approaches than we give them credit. The real purpose of this review is to provoke increased discussion by our colleagues within the endemic region about what constitutes best practices and what are not necessary or even counter-productive for our patients.

***What is “simple,” uncomplicated early coccidioidal infection and why should clinicians be concerned about it?***

Coccidioidomycosis is an infection that results after inhaling one or more spores (arthroconidia) of either *Coccidioides immitis* (the species usually found in California) or *Coccidioides posadasii* (the species usually found in Arizona and every other endemic region other than California) (9). As few as one spore is lethal to mice in experimental coccidioidomycosis (10) and likely similarly low exposures are sufficient to cause infection in humans. Based on conversion rates and prevalence rates of coccidioidal delayed-type dermal hypersensitivity in Pima County and in Bakersfield school children, respectively (11, 12), the risk of infection is estimated to be approximately 3% per year although there is year-to-year variation as a result of weather patterns (13, 14). Also, it was found in 2007 that the median time of residence within Arizona for newly diagnosed coccidioidal infections was 12 years (15) which suggests approximately a 4% annual risk. Based on older epidemiology (16, 17), it is thought that a third of infections result in clinical illness sufficient to seek medical attention. If you apply these overall estimates to the resident populations of the highly endemic counties of Arizona and California and assume that a portion is already immune because of past infection, estimated new infections would be 150,000 and medically important illness would occur in 50,000 patients each year.

A common misconception among primary care clinicians is that coccidioidomycosis, as it presents to clinicians for care, is usually a mild and inconsequential illness. That many textbooks refer to the initial illness as a “flu-like” syndrome only helps to perpetuate this idea. In fact, all the evidence indicates that those seeking medical care for a documented coccidioidal infection have a very debilitating disease. Evidence from otherwise healthy college students indicates that they are twice as likely to drop a semester of study because of Valley Fever than for mononucleosis (18). More recently,

the Arizona Department of Health Services found that i) Illness lasted an average of 6 months, ii) 75% of employed persons stopped working, half missed two or more weeks, and iii) 40% were hospitalized (15). It is simply not tenable to expect that patients seeking care because of early coccidioidomycosis will not be significantly impacted and that accurate diagnosis is unnecessary.

Most clinical coccidioidomycosis presents as community acquired pneumonia (CAP), not as a mild “flu-like” illness. Signs and symptoms include cough, chest pain, fever and profuse night sweating, weight loss, and commonly profound fatigue. Occasional patients have peripheral blood eosinophilia, *Erythema nodosum*, or *Erythema multiforme*, any of which should heighten suspicion for Valley Fever within its endemic areas. However, most patients do not have these findings, and the most common complaints are not at all specific to coccidioidal pneumonia. In two prospective Arizona studies, CAP in ambulatory patients was due to coccidioidal infection as frequently as 29% of the time (2, 3). In these studies and also in an earlier study (19), it was not possible to differentiate with any degree of precision which patients had coccidioidomycosis from those with other types of pneumonia without specific laboratory testing.

Despite the high probability that Arizona patients with CAP are infected with *Coccidioides* spp., evidence indicates that most clinicians do not try to establish this diagnosis. In one study of two separate medical groups in Maricopa County, coccidioidal testing was done for patients with CAP in only 2% and 13%, respectively (5). As a result, many patients are treated needlessly with antibacterial drugs (2, 3, 5, 20). If illness is protracted, further evaluation may be undertaken to exclude the possibility of malignancy and may include bronchoscopy, percutaneous needle aspiration, or even thoracotomy. If coccidioidal infection had been considered early in the evaluation, many such invasive procedures might be avoided as unnecessary. **The frequent lack of testing of CAP patients living in or visiting endemic regions for Valley Fever is a major deficiency in routine primary care of these patients and one that can easily be rectified by simple changes in practice patterns.** The Arizona Department of Health Services, the Maricopa and Pima County Medical Societies, and the Arizona Chapter of the Infectious Diseases Society of America have all endorsed testing such patients with CAP for coccidioidomycosis.

### ***Applying a pathogenic model of coccidioidomycosis to managing Valley Fever CAP.***

How does infection cause illness? In general, the pulmonary illness evolves through three or four phases. Initially, fungal proliferation starts from the inhaled arthroconidium transforming into a mature spherule followed by multiple cycles of spherule rupture, each taking several days to complete. With each spherule rupture, hundreds of endospore progeny are released into the pulmonary tissue (21). A key concept is that it is spherule rupture and not the presence of the spherule itself which triggers an acute inflammatory response (21-24). It is the acute inflammation which produces the pulmonary symptoms, fever, night sweating, and weight loss. If fungal proliferation

continues unchecked, it is the ongoing inflammation that produces tissue destruction, fibrosis, and pulmonary cavitation. That inflammation and tissue destruction are the result of ongoing rupture of spherules and not caused by the mere presence of spherules is a pivotal concept. In a second phase, effective cellular adaptive immunity is stimulated by the coccidioidal infection and this inhibits spherule rupture which in turn reduces and eventually eliminates the stimulus for acute inflammation. Although a growing literature implicates Th-1 mediated mechanisms (9, 25-29), the fine details have not been fully defined. In the third, convalescent phase, whatever damage was caused by the acute inflammatory process of the first and second phases resolves either by healing or fibrosis and the symptoms caused by the inflammation abate. For many patients, there follows a fourth phase which involves protracted fatigue and inanition which can dramatically interfere with return to a normal sense of well-being. It is distinguished by an absence of symptoms of ongoing inflammation or evidence of progressive tissue damage.

How long it takes for each of these phases to evolve varies widely among different patients and produces the clinical range of illness from subclinical infections that do not lead to an office visit to infections that produce serious illness, even life-threatening pulmonary failure. However, at the time of diagnosis, assessing patients with respect to where they fall along this evolution from active fungal proliferation to convalescence can be a useful means of arriving at an individualized management program.

Role of antifungal treatment in early coccidioidal infection. Early coccidioidal pneumonia will usually resolve eventually whether treated or not, and evidence is lacking as to whether antifungal treatment is useful for patients to hasten resolution of illness or to prevent subsequent complications. Because of these uncertainties, opinions vary widely regarding whether to treat all patients on the hope that treatment is beneficial or to only treat a subset of newly diagnosed patients with risk factors for complications, with more extensive pneumonia, or with a protracted course of illness. If treatment is begun, the usual dosage would be 200 – 400 mg per day of fluconazole and continued usually for three to six months and sometimes longer than a year, even in the absence of co-existing immunosuppression, diabetes (30), or evidence of complications (3, 31).

Considering the pathogenesis of coccidioidomycosis, the potential value of early antifungal drug treatment would be to reduce or eliminate fungal growth and consequent spherule rupture. The result of treatment would therefore be to assist in the evolution of the first and second phases of illness. How it might help in speeding up convalescence, is less clear. Importantly, for phase-four patients, those with protracted fatigue with no objective evidence of ongoing inflammation or tissue destruction, there is very little reason to expect that an antifungal drug would offer any benefit since in such patients fungal proliferation has already stopped. While a variety of supportive measures including physical therapy for reconditioning may be very helpful for these patients (see below), continued antifungal drug treatment seems inappropriate and even counterproductive.

Although the exact value of antifungal treatment is an unsettled issue, there is consensus that after coccidioidomycosis is diagnosed, additional diagnostic studies in search of an etiology can be curtailed and whatever antibacterial agents have been initiated prior to the accurate diagnosis can be stopped. These are immediate and very tangible benefits of early diagnosis whether or not an antifungal is used. Additionally, as evidence of ongoing inflammation decreases, antifungal treatment that might have been started can be reassessed and in many patients discontinued.

Role of coccidioidal serology tests in management. Detecting anti-coccidioidal antibodies is a valuable means of diagnosing coccidioidal infections (32, 33). Also, when coccidioidal serologic tests were originally described and all tests were done by a single research laboratory, there was a useful relationship established between severity of extrapulmonary infections and the magnitude of complement-fixing titers (34). Unfortunately, there is currently considerable variation in the quantitative results that are obtained from different laboratories as they conduct their testing. Even serial results obtained from the same laboratory may vary because of factors unrelated to actual changes in the clinical status of the patient. In general, once the diagnosis of coccidioidomycosis is established, further coccidioidal serology tests should be restricted to titration of complement fixing antibodies either by the originally described procedure or by its surrogate, quantitative immunodiffusion (32). Even then, results and their changes over time should be only one part of the overall evaluation of the patient's clinical status and may well be discounted if they are inconsistent with the rest of the evaluation.

Strategies for avoiding common mistakes in managing early coccidioidal infections. One very common mistake in the management of early uncomplicated coccidioidal pneumonia is to concentrate on treatment with antifungal drugs to the neglect of patient education which often is more important to the overall success of management. Patients who receive a new diagnosis of Valley Fever often have many questions and concerns about what this will mean for them. Providing a clear description of what Valley Fever is and how it needs to be managed often is very helpful in reducing anxiety. The Arizona Department of Health Services has printed material about Valley Fever that they distribute free of charge to help with patient education (available at <http://www.azdhs.gov/phs/oids/epi/valley-fever/index.htm>), but it is likely that additional explanations tailored to the patient's specific situation will also be valuable.

A second common mistake is to excessively follow a patient's pulmonary process with repeated CT scans. Whether or not a CT scan of the chest was involved with the initial evaluation of the presenting illness, it is frequently possible to continue management without this imaging once the etiology is established. Often the higher resolution of CT scans in comparison to plain views of the chest is simply unnecessary to guide subsequent management since relatively small changes in the shape of pulmonary infiltrates and hilar nodes provide little useful insight into what next steps ought to be taken. For example, if a pulmonary nodule is so small that it cannot reliably be seen on plain films, there may be no benefit to tracking its size one way or another. Avoiding unnecessary CT scans reduces both radiation exposure and cost.



A third management issue frequently mishandled by both primary care clinicians and specialists alike is the very common complaint of fatigue in patients with coccidioidal pneumonia. In the first phases of illness where there is focal evidence of ongoing inflammation, fatigue is expected and handled as part of the overall illness. However, in what we termed the “fourth phase” above, where inflammatory markers have resolved and focal ongoing damage no longer exists, patients are frequently not adequately managed. In our experience, which is very consistent with published descriptions, Valley Fever can be responsible for protracted fatigue, even after all other signs of infection have resolved. For example, in his excellent 1956 monograph, Fiese (35) writes:

“Profound fatigability and lassitude may persist for months after an otherwise uneventful recovery. Such residual symptoms are often alarming to the patient who is aware of the serious complications. It is important that the physician remember the frequency of post-infection lassitude, so that he may reassure the patient who fears that his disease is becoming disseminated.”

This has been especially striking in patients who have never before had fatigue as a significant ongoing complaint. In addition, because of the lack of normal activity, patients invariably become deconditioned and may not know how to methodically recondition, which can compound the disability, leading to frustration and sometimes reactive depression. We would encourage clinicians to provide such patients medical recommendations to employers to allow time away or reduced workloads to facilitate recuperation. In addition, a logical adjunct to help with the reconditioning would be a referral to a physical therapist to establish baseline levels of strength and endurance, set goals, and to provide a structured plan to accelerate the process. Although there does not yet exist a literature addressing the specific methods most effective in a physical therapy rehabilitation program, general reconditioning strategies would be most appropriate.

A fourth management mistake involves an overly aggressive handling of effusions that sometimes occur with early coccidioidal infection. Parapneumonic effusions associated with coccidioidal pneumonia are frequent if looked for carefully (36). However, on occasion they are not small and may be noted in patients prior to diagnosing the pulmonary process as coccidioidomycosis. As it turns out, coccidioidal parapneumonic effusions are generally self-limited and do not normally need aggressive drainage or decortication (37) as would often be employed for bacterial pleural infections. As a result, without early diagnosis of the coccidioidal etiology, it is very likely that unnecessary procedures would be instituted. This is especially true in pediatric patients where early video assisted thoracic surgery (VATS) is increasingly used for bacterial empyemas (38).

***The consequences of coccidioidal pneumonia: Their management and mismanagement.***

Nodules. Approximately 5% of coccidioidal pulmonary infections leave a nodule, visible by plain radiographs, in the region of the infiltrate. Undoubtedly, this number is even higher with CT scans. Often coccidioidal nodules are asymptomatic and their appearance is indistinguishable from cancer, including increased metabolic activity on PET/CT scan (39, 40). One benefit of early diagnosis of coccidioidal pneumonia is that when the acute pneumonia evolves into a residual nodule, the etiology of the lesion is known and no further evaluation is necessary. In that regard, asking the patient about a past diagnosis of coccidioidal pneumonia and associated X-rays may establish that the nodule is benign. However, the antecedent acute pneumonia is often not identified and the nodule is detected as an incidental finding. In such cases, the most important issue is to determine if the lesion is malignant and the approach to this should be the same whether coccidioidomycosis is or is not in the differential. Once it is determined that the asymptomatic nodule is due to coccidioidal infection, a common mistake is to initiate antifungal therapy. Treatment at this stage has no effect since its stability indicates that there is no fungal proliferation for an antifungal to inhibit. Periodic evaluation with plain radiographic views of the chest is reasonable but, as with the surveillance of acute coccidioidal pneumonia, in most cases follow-up with CT scans is unnecessary.

Fibrocavitary chronic coccidioidal pneumonia. Another occasional consequence of coccidioidal pneumonia is the development of a cavity, sometimes with surrounding fibrosis. Much of the time cavities are single, often very peripheral near the pleural surface, with little or no surrounding infiltrate (so called “thin-walled” cavity), and asymptomatic. Others have more surrounding infiltrate or an air-fluid level within the cavity, can over time involve additional segments of the lung, and can produce symptoms such as pleuritic pain, cough, and hemoptysis.

A common mistake is the overtreatment of asymptomatic thin-walled cavities. While such lesions may spontaneously close or expand, there is no evidence that treatment alters such cavities. Similarly, despite their peripheral nature, very few such cavities rupture into the pleural space (see below). While surgical removal is occasionally an appropriate management strategy, most asymptomatic cavities can safely be observed with periodic plain films of the chest without surgical intervention.

Management of symptomatic, complex, or expanding cavities may involve oral azoles such as fluconazole (41) or surgical resection (42). Formulating the selection and timing of these two options is highly individualized. However, we would underscore that surgical management is often technically more challenging than might appear from an examination of the radiographic images. In experienced hands, video assisted thoracoscopic surgery (VATS) is increasingly utilized (43). However, some situations still require more extensive thoracotomy. It is highly recommended that patients be referred to thoracic surgeons who are specifically experienced in resecting coccidioidal lesions.

Ruptured coccidioidal cavity. As indicated above, it is surprising how few coccidioidal cavities rupture, resulting in a bronchopleural fistula and collapse of the lung. Their occurrence is most frequently in otherwise healthy athletic males and about half the

time it is the first clinical manifestation of the coccidioidal infection (44). Because rupturing spherules are inflammatory, cavity rupture results in a pyopneumothorax with an air-fluid level rather than a simple pneumothorax as would be typical of a spontaneous pneumothorax or a ruptured pulmonary bleb. Failure to make this distinction often results in a delay in diagnosis.

Once diagnosed, it is possible that oral azole antifungal therapy with re-expansion of the lung using chest tubes may resolve the problem. However, very frequently this is not effective in closing the air-leak and surgical resection of the ruptured cavity is needed. As with surgical intervention of other coccidioidal pulmonary lesions, a surgeon familiar with managing such problems is preferred.

Diffuse coccidioidal pneumonia. Occasionally, the initial coccidioidal pneumonia is widespread, involving several areas of both lungs and requiring intensive care and ventilatory support (45). Most cases of diffuse reticulonodular coccidioidal pneumonia are the result of fungemia in a severely immunocompromised patient (46-48). In Arizona patients with untreated AIDS, with this pattern, the coccidioidal infection frequently co-existed with *Pneumocystis* spp. infection (49). Not appreciating this can lead to initiating steroids and pneumocystis treatment which if antifungals are not also begun will exacerbate the coccidioidal infection. Less frequently, a very similar radiographic appearance can occur in immunologically normal persons following high-inoculum infection such as can occur at archeology excavation sites (50, 51). In contrast to where fungemia is responsible, patients with high-inoculum infections do not usually have extrapulmonary infections and often respond very quickly to treatment.

### ***New advocacy for improving the care of patients with coccidioidomycosis.***

The Valley Fever Center for Excellence, established in 1996 at the University of Arizona, promotes education, research, and improved care for coccidioidomycosis. As part of its program it established in 2009 a clinical network which later was named the Valley Fever Alliance of Arizona Clinicians (VFAAC). This year, the VFAAC Board of Directors published a Valley Fever tutorial for primary care clinicians that is available on the Center's website ([https://www.vfce.arizona.edu/resources/pdf/Tutorial\\_for\\_Primary\\_care\\_Physicians.pdf](https://www.vfce.arizona.edu/resources/pdf/Tutorial_for_Primary_care_Physicians.pdf)) or by requesting a copy directly from the Center. The purpose of VFAAC is to link clinicians in Arizona who are interested in and experienced with coccidioidomycosis and to provide among them avenues of communication. Clinicians interested in becoming members of VFAAC can submit an application form which is reviewed and approved by the Board of Directors at one of its meetings held several times each year. Thus far VFAAC has expanded to over 125 clinicians. VFAAC membership is encouraged for any clinician licensed by the Boards of Medical Examiners, Osteopathic Examiners, Nursing, Physician Assistants, Behavior Health, Physical Therapy, or Occupational Therapy. Clinicians interested in learning more about VFAAC can contact the Valley Fever Center at [vfever@email.arizona.edu](mailto:vfever@email.arizona.edu).



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