# Valley Fever

## (Coccidioidomycosis)

A Training Manual for
Primary Care Professionals

Prepared by

THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Valley Fever Center
for Excellence

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## Preface

The phrase, Valley fever, should be familiar to all who live in or travel to the western United States, especially the low deserts of Arizona and the Central Valley of California where this disease, coccidioidomycosis, is intensely endemic. That 50,000 persons each year, or approximately 1% of the population within the most endemic regions, is a common estimate of the number who are seen in primary, urgent, or emergency care facilities for newly acquired Valley fever infections. Recent estimates from the Centers for Disease Control and Prevention (CDC) put this number even higher. In contrast, numbers of newly diagnosed Valley fever reported to the CDC have been between 10 and 20 thousand annually, underscoring that many patients are managed for their pulmonary or other clinical syndrome as if they have something else. In recent years, there has emerged a greater appreciation for this discrepancy and the negative impact that undiagnosed Valley fever has on patient care and medical costs. Early diagnosis of Valley fever by primary care professionals reduces patient anxiety, unneeded diagnostic tests, and excessive use of antibacterial agents. Identifying patients at risk for or already with evidence for uncommon but serious complications reduces morbidity and structural damage and residual disability. With this revised edition of *Valley Fever (Coccidioidomycosis), A Training Manual for Primary Care Professionals*, we hope to raise the standard care throughout all of the Valley fever endemic regions and beyond.

The purposes of this booklet are two-fold. First, it is intended to be one of the tools to enable a new clinical practice, begun in September, 2018, by the Arizona practice of Banner Health. However, all of the tools developed by the Valley Fever Center for Excellence and Banner Health are publicly available at https://vfce.arizona.edu/education/banner-valley-fever-clinical-practice-toolbox, and they should be applicable to primary, urgent, and emergency care practices throughout the Valley fever-endemic regions. Medical centers, health maintenance organizations, or other medical groups interested in bringing this program to their site for their clinicians can arrange to do so by contacting the Center through its website, vfce.arizona.edu.

Second, this publication is designed to be a convenient reference for the office shelf or the clinician's coat pocket. The information contained is not intended to be an exhaustive review of the disease. Rather, the content was selected for its relevance and usefulness to busy first-line practitioners, especially within Valley

fever-endemic regions. In this revised edition, we have added flow diagram following the C-O-C-C-I process (described in detail in this manual). In addition to being published here, it is also available as a handy, free-standing four-fold reference guide.

We hope you find this information helpful. Formatting and printing of this version of *Valley Fever (Coccidioidomycosis) Tutorial for Primary Care Professionals* was made possible by unrestricted educational grants to the Valley Fever Center for Excellence from Nielsen BioSciences, whose support we greatly appreciate. We also thank, Duc J. Vugia, MD, MPH, Chief of Infectious Diseases Branch, California Department of Public Health and Clinical Professor, Department of Epidemiology and Biostatistics, University of California, San Francisco for his helpful comments.

Respectfully,

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# SECTION 1:
## OVERVIEW OF COCCIDIOIDOMYCOSIS

## Mycology

The fungal species that cause Valley fever are in the genus *Coccidioides: C. immitis* and *C. posadasii*. Originally, all strains were designated as *C. immitis,* but in 2002 genetic analysis segregated strains into two distinct groups. Strains now designated *C. immitis* in most cases originate from infections contracted in California, Baja Mexico, and recently recognized regions of southeastern Washington state.[1] Those designated *C. posadasii* are from infections contracted in Arizona and elsewhere. At the present time, most clinical laboratories do not determine species for new isolates. Unless that unusual step is taken, the simple designation of new isolates as *Coccidioides* spp. will avoid confusion.

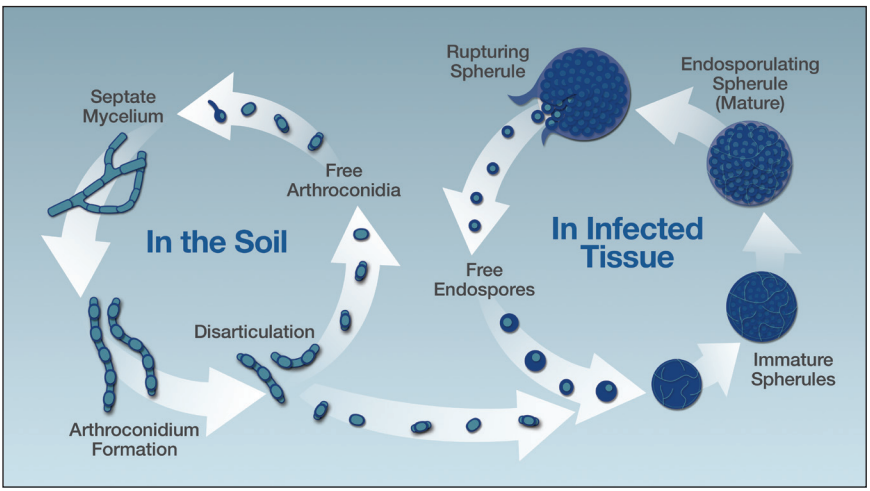



Figure 1. The life cycle of *Coccidioides* spp.

In the soil (Figure 1), *Coccidioides* spp. survive as mycelia, growing beneath the surface at a depth ranging from inches to a few feet. Since the fungus is an obligate aerobe, oxygen content is a major factor limiting the depth that it can survive in the dirt. During rainy periods, mycelia proliferate and grow closer to the surface. When the rains cease and the ground dries, the mycelia stop elongating. Along their length, every other cell undergoes autolysis, losing its internal contents, and the polysaccharide cell walls become extremely brittle. The remaining barrel-shaped viable single cells (known as arthroconidia) are then easily disrupted by even slight air turbulence.

The size of each arthroconidium is approximately 3-5 µm. This is small enough to readily become airborne, remain suspended in the air for protracted periods of time, and, if inhaled, penetrate deep into the lungs, thereby establishing an infection. At that point, an arthroconidium initiates growth in a spherical shape and enlarges, frequently to as much as 75 µm in diameter. Inside this growing spherule, nuclear division occurs repeatedly, the cell membrane and wall invaginates to repeatedly transect the internal space, dividing into many scores of subcompartments, each containing viable cells, termed endospores. In active infections, a mature spherule ruptures its outer wall and releases the endospore progeny, each of which can develop into another spherule. If specimens containing spherules are cultured in a laboratory, growth reverts to the mycelial form.

**Table 1. Valley Fever at a Glance.**

- Caused by a fungus (*Coccidioides* spp.).
- Other names:
  - Coccidioidomycosis, Cocci, San Joaquin Valley fever, Desert Rheumatism.
- Results from inhaling a spore.
- Varying severity:
  - Mild (60%), medical care not sought.
  - Moderate (30%), illness requiring medical attention.
  - Complicated or Severe (10%).
- Person-to-person spread does not occur; isolation unnecessary.
- Most people develop lifelong immunity to second infections.

## Spectrum of disease

Approximately two-thirds of infected persons have symptoms so mild that they see no need for medical attention. Of the approximately one-third of infected persons who do suffer a clinical illness, the symptoms are primarily those suggesting community-acquired pneumonia (CAP). For most such patients, it is not possible without specific laboratory testing to distinguish Valley fever from pneumonia caused by bacteria or other etiological agents.[2,3] Other symptoms include body aches and rashes which has prompted the synonym of "desert rheumatism."

Whether diagnosed or not, most infections are eventually controlled by induction of cellular immunity, but the associated illness often lasts for many weeks or many months. Approximately 5% to 10% of all infections, with or without symptoms, result in pulmonary sequelae, and 1% or less result in the spread of the infection through the bloodstream beyond the chest (dissemination). Dissemination most frequently involves skin, bones, joints, or the meninges, but virtually any other organ or tissue in the body can become infected. These complications often require consultation with specialists in Pulmonary Medicine or Infectious Diseases and may produce extensive morbidity. A survey of death certificates identify an average of 140 deaths annually in the United States. A recent public health investigation in Arizona found that death certificates might underreport Valley fever as a cause of death by seven-fold.[4]

**Table 2. Spectrum of Coccidioidomycosis.**

- Two-thirds of infections are mild, do not come to medical attention.
- One-third seek medical attention:
  - The most common symptoms are:
    - » Fever, fatigue, cough, chest pain, headache, skin rash, joint aches.
  - The recovery often takes many weeks to many months in otherwise healthy people.
- The complications are:
  - Acute respiratory failure.
  - Residual lung nodules (~5%).
  - Lung cavitation (~5%).
  - Infections beyond the lungs (dissemination, 1% or less).

## Current therapies

Most patients with recent Valley fever infections resolve without treatment as a consequence of cellular immunity. When amphotericin B was the only available antifungal drug, its toxicity often outweighed treatment. With the advent of oral azole drugs such as fluconazole, treatment of uncomplicated initial infections is now a feasible option. Even so, the value of azole treatment for these infections is uncertain, and opinions among experts differ on whether or not to routinely treat all patients with uncomplicated illnesses.[5] In a small number of patients, coccidioidal infection produces a very severe pneumonia, and in others, it spreads to other parts of the body. Such complications dictate the need for treatment, and even so the infection may remain difficult to control.

A majority of complicated infections follow a subacute or chronic progression, and initial therapy usually involves oral administration of oral azole antifungals, such as fluconazole or itraconazole. Amphotericin B is effective only if administered parenterally, and its use is often associated with significant side effects and toxicities. Despite these drawbacks, in rapidly progressive infections, amphotericin B is often the preferred initial treatment. Typically, treatment is continued for many months to years.[5]

When therapy is discontinued after the apparent successful control of complicated disease, a relapse of infection occurs in approximately one-third of patients. Therefore, some patients may need lifelong therapy to maintain control. Chief among these are patients with deficiencies in cellular immunity or those with coccidioidal meningitis.

## Value of early diagnosis

A primary reason for diagnosing early coccidioidal infections is simply that it provides patients with answers to why they are feeling so poorly. By giving an illness a specific name, it removes the patient's fear of the unknown. This is especially true for older patients, where the concern exists that an undiagnosed respiratory illness may represent cancer. A myriad of physical, mental, and emotional consequences are associated with an incorrect or suspected diagnosis of cancer. For patients of all ages, an accurate diagnosis allows for reassurance in most cases and appropriate prognostic patient education. Diagnosis has always been a major contribution by clinicians, and the value of diagnosis to patients' sense of well-being and satisfaction cannot be over-estimated.

**Table 3. The Value of Early Diagnosis.**

- Allays patient anxiety by:
  - Giving a name to the illness.
  - Dispelling the fear of cancer.
  - Providing patient education and prognosis.
- Decreases the need for invasive and expensive tests.
- Removes the temptation for empiric therapy.
- Allows for earlier detection of complications.

In addition, early diagnosis of Valley fever reduces or eliminates the need to search for another diagnosis. The symptoms associated with Valley fever that take weeks or even months to resolve often prompt concerned clinicians to subject their patients to a variety of blood tests, chest X-rays, CT scans, PET scans, bronchoscopy, percutaneous fine-needle aspiration, and even thoracotomies. These procedures have attendant costs, discomfort, and potential risks, which would be unnecessary once the diagnosis of coccidioidomycosis is established.

A third benefit of diagnosing coccidioidal infections early is the reduction of empiric use of antibacterial drugs. In a recent retrospective study, 43% patients experienced at least a one-month delay and received on average four outpatient prescriptions or inpatient orders for antibacterial drugs prior to their Valley fever diagnosis [Donovan, submitted for publication].

In addition to the cost of antibiotics, this strategy has the potential to cause adverse events for the patient and increase antibiotic resistance in the community. A less frequent but potentially more serious problem is the use of corticosteroids for the cutaneous or rheumatologic complaints that may accompany primary coccidioidal infection. The immunosuppressive effects of corticosteroids may impede host defenses, and their use in patients with early coccidioidal infections may prevent the normal immunologic control.

Finally, for the relatively small number of patients who either are at risk for or already manifest Valley fever complications, prompt recognition of the true diagnosis should result in earlier appropriate management and consequently less tissue destruction and residual morbidity.

# SECTION 2:
## PRIMARY CARE MANAGEMENT OF COCCIDIOIDOMYCOSIS

## Overview

This section describes an approach for recognizing a new infection, evaluating its impact on the patient, and subsequently managing the illness depending upon its level of complications. We have developed an acronym (C-O-C-C-I) for this approach based on five important steps described in detail here. A pocket-sized overall flow diagram for this process is provided as an appendix.

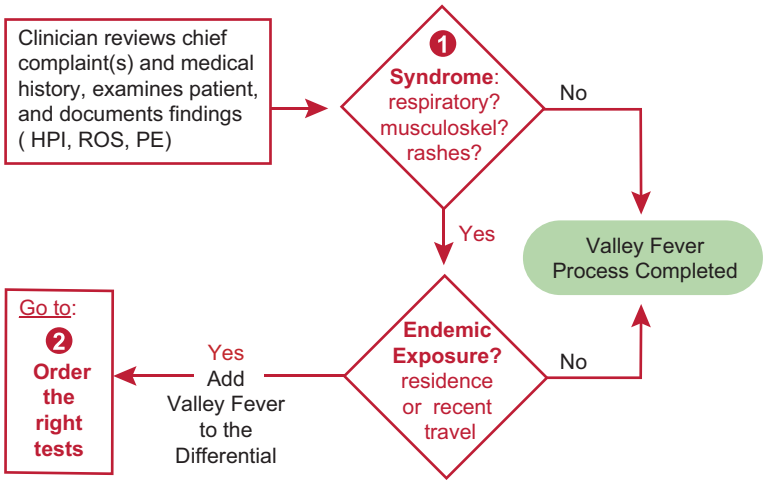
## Spectrum of clinical manifestations of Valley Fever

The incubation period of coccidioidal infection ranges from one to four weeks,

**To Recognize and Treat Coccidioidomycosis**

**C** onsider the diagnosis
**O** rder the right tests
**C** heck for risk factors
**C** heck for complications
**I** nitiate management

## 1 Consider the diagnosis




after which a variety of manifestations develop. The most common symptoms are fatigue, night sweats, and pulmonary symptoms (cough, pleuritic chest pain, and dyspnea). Although difficult to quantify, fatigue is often the most prominent symptom. Stories like “I went to bed and didn’t wake up for 15 hours” or “I got up for breakfast and then was exhausted” are common.

When a cough is present, it frequently is not particularly productive of large amounts of sputum. Fever is present in nearly half of patients. A headache occurs in approximately one-fifth of the patients with early infection. Fortunately, as a transient symptom, this does not represent meningitis. Weight loss of as much as 5% to 10% is also common with newly acquired coccidioidal infections. As this description indicates, the clinical presentation of pulmonary Valley fever

overlaps substantially with the presentation of many other types of respiratory illnesses.

Skin manifestations include a diffuse nonpruritic maculopapular eruption which has been noted to occur in 16% of males and 7% of females, especially children and young adults. It is so transient and so inconsequential that it often goes undetected. More obvious are *Erythema nodosum* (seven to eight times more frequent in women than men) and *Erythema multiforme*. These two rashes are not specific for coccidioidomycosis. However, when found in patients with endemic exposure to *Coccidioides* spp., Valley fever is frequently responsible.

Another common symptom is diffuse and migratory arthralgia, present in 22% of patients. Typically, the complaints are symmetrical. Joints may be mildly inflamed and painful but typically do not exhibit an effusion. The triad of fever, *Erythema nodosum*, and diffuse arthralgias has produced the synonym of "desert rheumatism" for the disease. All of these manifestations are thought to be immunologically mediated and not the consequence of viable fungal cells in either the skin, muscles, or the joints of patients who suffer these complaints.

Chest radiographs often, but not always, disclose abnormalities associated with the early infection. Pulmonary infiltrates are usually one-sided and are typically patchy and not as consolidated as seen with bacterial infections. Often there is associated ipsilateral hilar adenopathy. Parapneumonic pleural effusions may also occur as part of a primary infection. Although disease of one lung is the rule, the process can occasionally be bilateral (Table 4).

**Table 4. The Clinical Manifestations of Valley Fever.**

**Symptoms**

- Fatigue
- Night sweats
- Cough
- Chest pain
- Dyspnea
- Hemoptysis
- Headache
- Arthralgias

**Signs**

- Fever
- Weight loss
- Erythema nodosum
- Erythema multiforme

**Chest radiographs**

- Pulmonary infiltrates
- Hilar adenopathy
- Pleural effusions

Routine laboratory findings commonly do not show specific abnormalities. Peripheral blood leukocyte counts are usually normal or only slightly elevated. Eosinophilia is sometimes present and occasionally to strikingly high levels. Erythrocyte sedimentation rate and C-reactive protein are often elevated. However, recent studies indicate that serum procalcitonin levels may be normal.[6] If corroborated, this test might be a useful way to distinguish coccidioidal from bacterial pneumonia.

Attempts to use clinical presentation and routine laboratory results as an indicator of coccidioidal infection thus far have been unsuccessful. In one study, several patient findings were significantly associated with coccidioidal infection, as compared to patients with other causes of acute respiratory problems.[7] However, the predictive value of these abnormalities was very limited and not of practical help in identifying most infections.

## Selecting patients for evaluation

Since the signs, symptoms, and routine laboratory abnormalities are nonspecific, virtually any patient evaluated for a variety of complaints, especially those related to the respiratory system, could arguably be evaluated for coccidioidomycosis. The more patients who are tested for Valley fever, the more infections are likely to be diagnosed. This was the case in one study of college students.

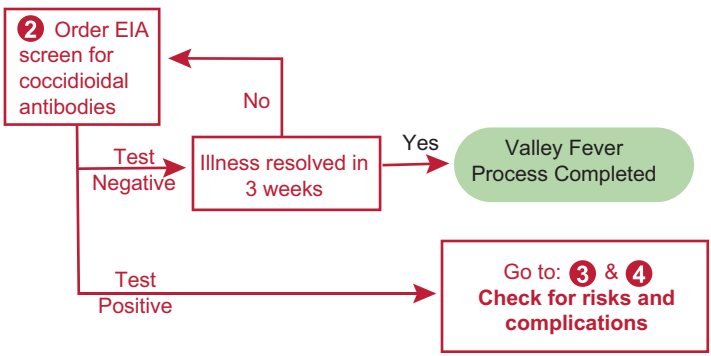
On the other hand, despite the prevalence of Valley fever within the endemic patient population, many other acute illnesses also exist. Thus, by increasing provider sensitivity and the number of tests ordered to diagnose Valley fever, the overall proportion of tests that are diagnostic might decrease.

A critical step for clinicians in a busy practice is to establish routine indications for ordering the appropriate tests. Several indications for Valley fever testing are proposed. These were are selected for simplicity and application to common situations (Table 5). These recommendations may be modified if new information emerges from studies now underway.

**Table 5. In patients who reside in or have traveled to endemic regions, consider testing for coccidioidomycosis if any of the following indications are present:**

- Respiratory symptoms and at least one of the following:
  - More than 1 office visit
  - Chest X-ray ordered
  - Antibiotic prescribed
- Two of the following for more than one week:
  - Fever
  - Fatigue
  - Arthralgia
- Unexplained peripheral blood eosinophilia
- Skin lesions of:
  - *Erythema nodosum*
  - *Erythema multiforme*

## 2 Order the right tests



## Detection of anticoccidioidal antibodies in serum

### Serologic tests

For diagnosing primary infections, serologic tests are the most commonly employed laboratory approach. Of the variety of tests available, some are highly specific for an active infection, while a few have occasional false-positive results.[8]

Specific tests are typically selected by the director of the clinical laboratory. Factors involved in such selection include the cost and rapidity of obtaining results, the availability of tests from specific reference laboratories that provide other testing services, and the sensitivity and specificity of the tests. Moreover, tests available to a specific provider may change over time because of renegotiated contracts and other factors. These considerations have complicated the ordering and interpretation of coccidioidal serologic testing. Because of this, the following two general principles are useful in the primary care setting:

First, in most circumstances, a positive serologic test for coccidioidal antibodies is highly presumptive of a current coccidioidal infection. Therefore, a report of any positive serologic test should always be reviewed by someone familiar with test interpretation. Second, a negative serologic test never excludes the presence of a coccidioidal infection. For this reason, in evaluating a possible coccidioidal infection, one or even two repeated serologic tests will increase the sensitivity for diagnosis. If repeated testing over the course of two months fails to produce a serologic diagnosis, further serologic testing is likely to be unrewarding.

> “A positive serologic test for coccidioidal antibodies is highly presumptive of a coccidioidal infection. Therefore, any positive serologic result should always be reviewed by someone familiar with test interpretation.”

"A negative serologic test should never exclude a coccidioidal infection. In evaluating a possible coccidioidal infection, repeated serologic tests will increase the sensitivity for diagnosis."

### Enzyme-linked immunoassays (EIA)

EIA tests for coccidioidal antibodies are available commercially and are the most sensitive for coccidioidal infection in common use. For many, this is the best screening test for Valley fever.[9] The test kits allow for the specific detection of IgM or IgG antibodies. However, these results are not interchangeable with immunodiffusion IgM or IgG test results discussed next. Moreover, false-positive results have been noted with the IgM EIA test. How frequently this occurs is not a settled issue.[6-8]

### Immunodiffusion tests (ID)

ID tests are also available commercially. The ID test for IgM antibodies react with a polysaccharide antigen from the fungal cell wall. The ID IgG test reacts with a specific extracellular chitinase. These two tests are also called the IDTP and IDCF tests because they were originally designed to qualitatively mimic the "tube precipitin" and the "complement fixing" antibody tests, respectively.[10] Since the antigens used in the EIA tests are proprietary to the tests' manufacturers, ID tests do not necessarily correlate with EIA results. ID tests, if positive, are considered confirmatory of EIA test results. However, because ID tests are generally less sensitive than EIA results, patients in whom the ID tests are negative may still be considered to have coccidioidomycosis with a compatible clinical syndrome and positive EIA results.

### Complement fixing (CF) antibodies

When patient serum that contains CF antibodies is mixed with coccidioidal antigen, an immune complex forms which consumes complement. This event is detected by the subsequent addition of tanned red blood cells, which normally lyse in the presence of fresh complement but remain intact if the complement is depleted. Because of the complexity of this test, it has not been marketed as a kit and is only available from reference laboratories, each of which configure the test with that lab's own quality control. Although this test was originally developed and is still performed with complex extracts of *Coccidioides* spp.,

it is now known that the antigen involved in this reaction is the same chitinase involved in the ID IgG test. CF antibodies can be detected in other body fluids and their detection in the cerebrospinal fluid is an especially important aid to the diagnosis of coccidioidal meningitis.

CF test results are expressed as titers, such as 1:4 or 1:64, indicating the greatest dilution of serum at which complement consumption is still detected. Higher CF titers are more frequently associated with extensive coccidioidal infection, and rising CF antibody concentrations are of concern. Thus, serial determinations of CF titers are of prognostic as well as diagnostic value.[11] The use and limitations of CF test results for that purpose are discussed in the "Initiate Management" section.

### Latex tests

Latex tests for coccidioidal antibodies are also commercially available. They are attractive to clinical laboratories because of their ease of use and rapidity of obtaining a result. However, there are significant numbers of false-positive reactions, and therefore a positive latex test is not as reliable as any of the other tests described in this section.

## Mycology cultures for diagnosis

### Cultures for *Coccidioides* spp.

Isolating *Coccidioides* spp. from sputum or another clinical specimen is definitive evidence of a coccidioidal infection. Despite this, early infections are usually not diagnosed by culture. The reasons why cultures are not routinely obtained in the ambulatory care setting are related to several factors.

First, fungal cultures are an unusual request in the ambulatory care setting. Although it would be valuable if this were to change, requesting fungal cultures on a sputum specimen currently may be disruptive to workflow. Another consideration is that patients with coccidioidal pneumonia may not be able to produce a specimen for culture. While this problem can usually be circumvented, it takes extra steps. Finally, there is a potential risk to laboratory personnel of isolating *Coccidioides* spp.

Laboratories handling fungal cultures should be thoroughly versed in safe-handling of such specimens and culture medium, and small outpatient

laboratories may not be so equipped or trained. None of these considerations are absolute barriers to obtaining culture confirmation. Since negative serologies do not exclude the diagnosis of coccidioidomycosis, cultures may be the only way to obtain a timely diagnosis in some patients. As a general rule, the more serious the illness, the more likely fungal cultures should be considered as an essential part of the diagnostic evaluation.

**Handling of specimens for fungal culture**

Sputum or other clinical specimens should be collected in a sterile container. This may be done in the clinic at no risk to personnel, since the infection is not transmitted from the primary specimen. Patients with scant sputum can be asked to take a specimen cup home with them and collect a specimen early in the morning (when sputum is usually more readily retrievable) and then return the cup.

Such specimens can be stored refrigerated until transfer to the medical facility. For more serious problems, other respiratory secretions (bronchoscopic aspirates) and tissue specimens (skin or bone biopsies) can be submitted for culture.

**Laboratory evaluation of sputum or other respiratory specimens**

Direct examination of secretions can be performed immediately or after the addition of potassium hydroxide. Although culture results are more sensitive than direct examination, identification of spherules in this way is diagnostic and very rapid. *Coccidioides* spp. cannot be detected by Gram staining. However, spherules can be seen with cytology stains such as are performed on bronchoscopy specimens, by hematoxylin and eosin stains of tissue sections, and with other specialized stains.

*Coccidioides* spp. are not particularly fastidious and grow well on most mycologic and bacteriologic media. Furthermore, growth usually develops within four to seven days of incubation. Some clinical laboratories within the coccidioidal endemic region have used these characteristics to advantage by holding all routine bacteriologic sputum cultures for a week before discarding the plates, since some patients who are thought to have bacterial pneumonia will actually yield *Coccidioides* spp.

When growth occurs, it is typically as a white (nonpigmented) mold. However, there are many exceptions to this general appearance, and the morphologic appearance is not reliable in determining if the fungus is or is not *Coccidioides* spp.

Once growth is evident on culture medium, care should be taken not to open the culture container except in an appropriate biocontainment cabinet. Cultures at this stage are infectious and can cause disease in persons exposed to them unless the cultures are properly handled. Since the morphologic appearance of *Coccidioides* spp. is not sufficient to determine the species, additional laboratory testing must be carried out for specific identification.

The most common way for microbiologists to perform additional testing is to detect a specific DNA sequence using a commercially available DNA probe. Smaller laboratories often refer the culture to a reference laboratory where species identification is completed.

As of December 2012, *Coccidioides* spp. are no longer designated select agents by the Centers for Disease Control and Prevention (CDC).

**Skin testing**

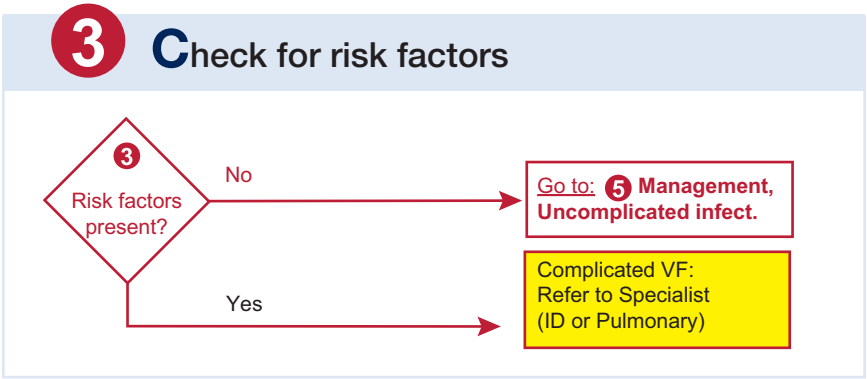
Dermal hypersensitivity to coccidioidal antigens is highly specific for past coccidioidal infection, and if used in patients when they are healthy, it can index patients as to whether they are at risk of future illness due to Valley fever.

For example, persons who demonstrate a reactive skin test are very likely to be immune for life and have little chance of future coccidioidal problems. On the other hand, for those who do not react, Valley fever remains a possible etiology in a future illness. However, because skin test results remain positive after infection in most persons for life, it may not relate to the current illness. In addition, some of the most serious infections may be associated with selective anergy, and the skin test may not demonstrate reactivity.

Therefore, as useful as skin test results are for indexing risk in patients while healthy, important limitations exist when used as a screening procedure for recent or current infection. If Valley fever is diagnosed by other means, skin testing may have prognostic significance, as patients with progressive infections often fail to develop dermal reactivity to coccidioidal antigens. Since the 1990s, there was no coccidioidal skin test commercially available. However, a company (Nielsen BioSciences, San Diego, CA) has redeveloped a spherule-based skin test antigen

(SPHERUSOL®) and has received approval from the FDA to market it as a test of immunity in patients who already have a diagnosis of Valley fever.[12]

Results of a skin test are measured at 48 hours after the antigen is injected intradermally. Induration of greater than 5 mm is considered reactive. Erythema at the injection site is not of diagnostic value. Coccidioidal skin testing does not influence coccidioidal serology results.




## The first step postdiagnosis

Once a diagnosis of coccidioidal infection is established, the next step is to review any possible risk factors that might make the patient particularly susceptible to complications. This is usually accomplished during a complete history and physical examination.

### Immunosuppression

By far the most clearly demonstrable risk of complications from a coccidioidal infection is the coexistence of major immunosuppressive conditions that adversely affect cellular immunity. These would include immunosuppression to prevent rejection of organ transplants, AIDS in HIV-infected persons, and anti–tumor necrosis factor therapy for rheumatologic conditions. For example, the risk of infections extending beyond the lungs in renal transplant recipients can be as high as 75%.[13] This risk is much greater than the risk of a similar complication in the general population.

Immunosuppressive conditions that affect humoral immunity appear to have relatively little or no risk for complications of coccidioidal infection. Similarly, splenectomy, hypocomplementemia, or neutrophil dysfunction syndromes are not major risk factors for this disease.

### Diabetes mellitus

Patients with diabetes appear to have an increased risk of pulmonary complications.[14] While many of such patients resolve their initial infection without residual problems, a disproportionate number seem to develop symptoms related to pulmonary cavities and chronic pneumonia. There is little or no evidence that this group of patients is at increased risk for developing extrapulmonary dissemination.

### Pregnancy

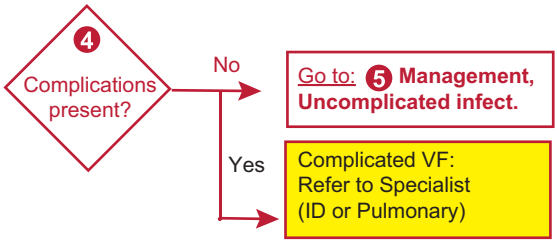
Women who are newly diagnosed with Valley fever during pregnancy are at particular risk of serious infection.[15] Those at highest risk are women diagnosed during the third trimester or immediately postpartum. Such infections may be life-threatening and should be regarded as complicated management problems.

### Other risk factors

There are additional factors that should be considered relevant to the risk of complications from coccidioidal infection. Complications are more frequent in men than in women and in adults than in children. Life-threatening infections are more common in the elderly. Recent evidence suggests this is related in part to accumulated comorbidities in aging persons rather than age itself.[16]

In addition, there appears to be an increased risk of disseminated infection among African Americans, Filipinos, and perhaps other racial groups. Racial predilection for complications is somewhat conjectural since the exact definitions of racial groups are in dispute and carefully controlled epidemiologic studies are not available. Even if racial differences exist (as most authorities believe), the increase in risk may be only four-fold above that of the population as a whole.[17]

## 4 Check for complications evident by physical exam or imaging




## Assessing complications

Even in the absence of the risk factors just discussed, it is important to assess patients with coccidioidal infections for complications because they can also occur in patients without apparent reason.

Complications from initial coccidioidal infections are divided into those that occur in the chest or beyond (extrathoracic dissemination). These two types of complications usually do not overlap. When complications are present, they produce localized symptoms and signs of chronic or subacute inflammation. As a result, a careful review of symptoms and physical examination are usually a sufficiently sensitive initial screen.

In patients not treated with antifungal drugs for the initial infection, complications usually are manifest in the first weeks or months and nearly always manifest within the first year. If a new focal complaint develops in association with a recent coccidioidal infection, its possible relationship to the infection should be considered. For example, in general practice, low back pain is a common symptom, and mild discomfort is often managed symptomatically before extensive diagnostic studies are undertaken. However, if this symptom were to occur in a patient within weeks or months of developing coccidioidal pneumonia, it may be useful to recommend a radionuclide scan or other imaging procedure to determine if the new symptom is due to infection in the lumbar vertebrae. This

is done to detect complications early, before serious tissue destruction occurs. Similarly, persistent or progressive headaches, skin lesions, or joint effusions in the context of a recently diagnosed coccidioidal pneumonia might warrant more detailed investigation with lumbar puncture, biopsy, or aspiration, respectively.

### Persistent or slowly resolving pneumonia

Most pulmonary infections are subacute in nature. Without treatment, symptoms usually improve within the first month but may not completely resolve for several months. In some patients, the course of illness is even more protracted. There is no consensus regarding how protracted illness must be before it is considered as slowly resolving. However, in studies of new therapies for coccidioidomycosis, entry criteria often specify that pulmonary disease must have been present for at least three months. In clinical practice, shorter periods of illness may be more reasonable.

### Pulmonary cavitation

Cavities form in approximately 5% of patients with coccidioidal pneumonia. Half of these cavities are thought to disappear within the first two years. Many cavities cause no symptoms. Others cause discomfort, cough, hemoptysis, and occasionally constitutional symptoms of fatigue, night sweats, and weight loss. Occasionally, a coccidioidal cavity will rupture into the pleural space. This usually has an abrupt onset and consequently leads to prompt evaluation. Given the peripheral nature of many coccidioidal cavities, this event is surprisingly uncommon.

### Chronic fibrocavitary pneumonia

A few patients experience repeated development of pneumonia over a period of many years. Sometimes, this includes different lobes of the lung.

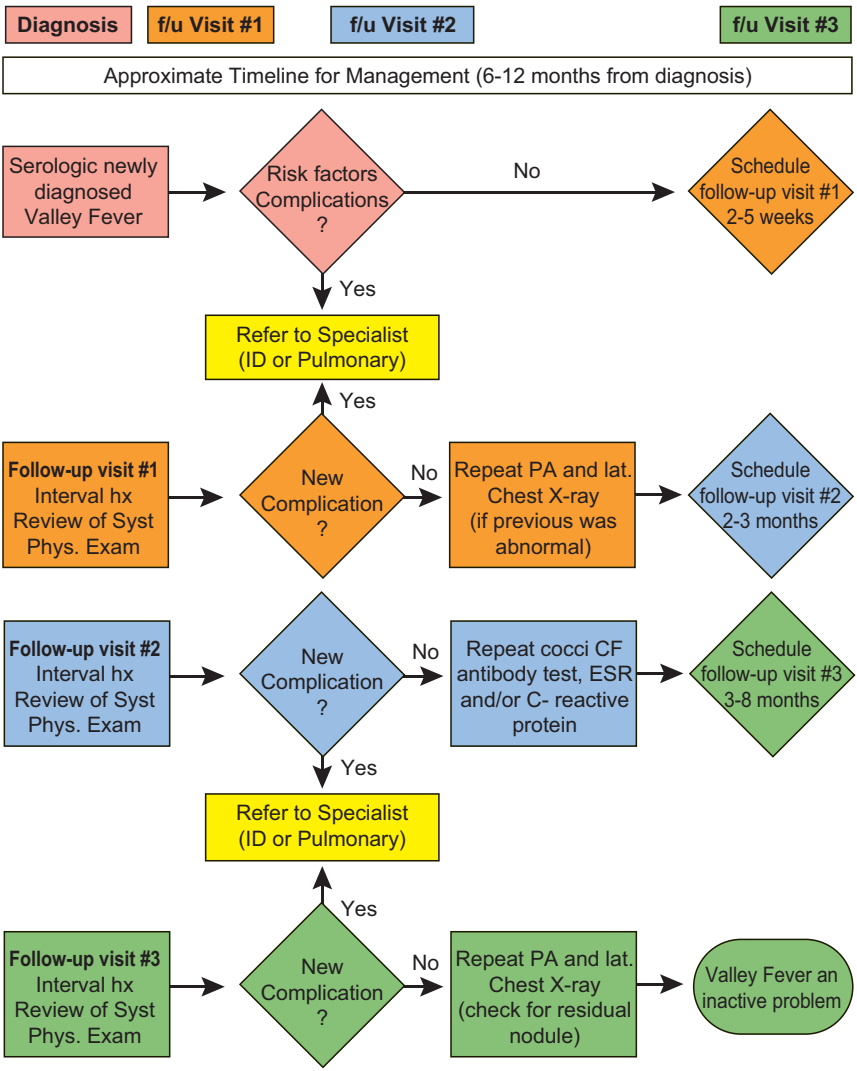
### Diffuse fulminant pneumonia

In some patients, coccidioidal pneumonia is very severe, causing hypoxia and requiring respiratory support to prevent respiratory collapse. This is obviously a major complication and is handled very differently than most infections.

### Extrathoracic dissemination

When infection spreads beyond the lungs, it usually does so within the first several months after the initial infection and nearly always within the first year. In this way, coccidioidal infections differ from tuberculosis, which commonly returns decades after the initial infection.[18] An important exception to this rule is in the intervening development of major degrees of immunosuppression of the nature discussed previously. The most common sites of dissemination are skin, joints, bones, and the meninges. However, virtually any part of the body can be affected.

# 5 Initiate management



## Strategies for uncomplicated early infections

Once a diagnosis of coccidioidal infection is established and a thorough evaluation for enhanced risk and evidence of complications has been accomplished, a rational management strategy can be formulated.

Patients who do not have risk factors, symptoms, or physical findings suggestive of progressive infection can be classified as having early uncomplicated infections. In general, a majority of patients will fall into this category and might be safely managed by primary care practitioners. The remainder may benefit from consultation with a specialist in Infectious Diseases or Pulmonary Medicine to aid in developing a treatment plan. Management of complicated coccidioidal infections is beyond the scope of this monograph, but comprehensive treatment guidelines are available.

General guidelines for managing patients with uncomplicated infections are outlined in Figure 2 and a more detailed flow diagram is included as an appendix.

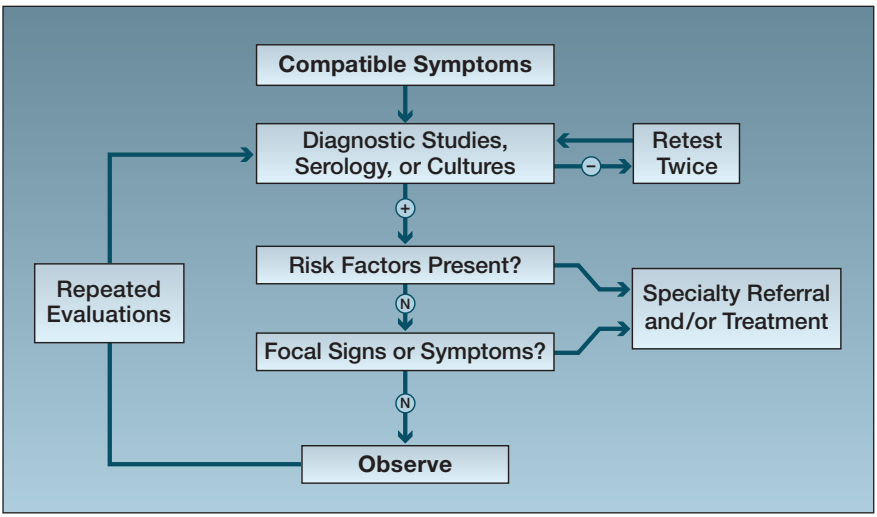



Figure 2. Managing uncomplicated coccidioidomycosis.

### Health education and recommendations to the patient and family

Very commonly, establishing a diagnosis will be of great help to the patient because it clearly identifies the nature of the illness and allows the health care provider the opportunity to explain what may happen in the future. A general review of how patients contract Valley fever, the typical symptoms, the need for therapy, or the lack of the need for therapy, may be helpful to put the patient's experience in a more general and knowledgeable context.

Patient information leaflets have been prepared to facilitate this process and are available from the Valley Fever Center for Excellence.

Explaining that the illness usually improves slowly over a period of weeks to even months will be useful in allowing patients to align their expectations with the natural history of the illness. The patient can be advised that he or she cannot transmit the infection to others and therefore poses no risk to others.

Although the prognosis is generally favorable for most patients, it is important to explain to patients some of the infrequent but possible complications, both pulmonary and extrapulmonary. Worsening respiratory symptoms should prompt reevaluation, and new focal symptoms outside of the chest should be noted and, if they persist, be brought to the attention of the treating clinician. Explaining the need for follow-up to the patient even as the infection resolves without therapy should improve adherence to follow-up care.

### Frequency of follow-up health care visits

Continued follow-up is, in fact, at the core of the management of uncomplicated coccidioidal infections. This is needed to confirm that the illness remains uncomplicated and that more specific interventions are not necessary.
In addition, residual pulmonary abnormalities may remain, which should be documented for future reference so that they are not unnecessarily reevaluated as a new problem years later. In rare instances, coccidioidal infections and lung neoplasms have coexisted, and this possibility should be considered during the follow-up period.

The interval between medical visits varies according to the severity of the symptoms and the course of infection up to the point of diagnosis. If symptoms are still worsening, follow-up visits or telephone contact might be appropriate within days to a week later, since continued worsening may prompt reevaluation and the initiation of antifungal therapy.

On the other hand, if there is clear evidence of improvement, then a return visit might be appropriate in two to four weeks. After the first two or three visits, the intervals between visits typically range from one to several months. By two years, an uncomplicated coccidioidal infection can be considered resolved.

**Monitoring the course of infection**

Several clinical and laboratory findings are helpful to assess the course of infection. Generally, systemic signs of fever, night sweats, and weight loss are the first to abate as a coccidioidal infection improves. The respiratory symptoms of chest pain, cough, and sputum production may be more protracted.

Not infrequently, fatigue and an inability to resume normal activities are some of the last symptoms to resolve. Since this is commonly a chronic process, patients may fail to see changes in these symptoms from day to day, and only when asked to compare their current state with one week or one month earlier do they become cognizant of improvements. Often, having the patient keep a journal with entries every other week is a helpful tool to document progress.

Laboratory tests can also be helpful in providing objective evidence of improvement. Erythrocyte sedimentation rate, often elevated with early coccidioidal infections, is an inexpensive measure of systemic inflammation and can be used to monitor progress. Typically, this would not be measured any more often than on a weekly basis. In addition, the CF or IDCF antibody concentration is expected to decrease as a coccidioidal infection resolves, and it is important to demonstrate this response. If these results do not normalize as expected, concern should be raised that complications may be developing and that further diagnostic studies may be in order. Repeated serologic testing should seldom be any more frequent than every two weeks and usually ranges from one to several months between tests.

A suggested plan for follow-up timing for review of systems (ROS), physical examination, coccidioidal CF tests, and chest radiographs is shown in Table 6.

Chest radiographs should be repeated to demonstrate either resolution of all pulmonary abnormalities or to document what residual abnormalities persist. Early in the course of infection, the interval may be as frequent as several days until symptoms or radiographic findings demonstrate that abnormalities are stable or improving. Subsequent chest radiographs should be obtained either every several weeks or every several months. Often, two views of the chest are sufficient to monitor progress, and the increased sensitivity of CT scans is not usually needed as the patient improves.

### Physical therapy reconditioning as an approach to persistent fatigue

Not infrequently, patients who resolve all evidence of active infection continue to be disabled because of profound fatigue. For example, in a study from the University of Arizona that compared the impact of Valley fever to mononucleosis, twice as many students with Valley fever dropped out for a semester.[19] It is very possible that this persistent symptom is a consequence of patients becoming deconditioned as a consequence of the fatigue that Valley fever first produces. If that is true, then referral to a physical therapist to assist the patient with a reconditioning program might be very helpful to hasten recovery. The Valley Fever Center for Excellence has initiated this practice, and the preliminary results have been encouraging.

**Table 6. Suggested Plan for Follow-up Visits.**

| Visit | Time From Diagnosis | ROS, Phys Exam | Coccidioidal Serology | Chest X-ray (PA and Lat.) |
|---|---|---|---|---|
| 1 | 2-5 weeks | X | | X |
| 2 | 2-3 months | X | X | |
| 3 | 3-6 months | X | | |
| 4 | 12 months | X | | X |

## Antifungal therapy

For early uncomplicated coccidioidal infections, most patients can be managed without antifungal therapy. There are currently five commercially available oral antifungal drugs with activity for treating coccidioidal infections: ketoconazole, fluconazole, itraconazole, voriconazole, and posaconazole. Published reports have demonstrated activity of all of these agents in treatment of complicated coccidioidal infections, but there are no randomized trials demonstrating that any of these drugs shorten the course of early uncomplicated infections or prevent later complications. Two observational studies also provide no evidence for a beneficial effect in the pharmacologic treatment of early coccidioidal pneumonia.[20, 21]

Given this uncertainty, the decision whether to initiate antifungal drug therapy for uncomplicated coccidioidal pneumonia is highly individualized. This issue is addressed further in the Infectious Diseases Society of America (IDSA) Practice Guidelines.[5] Treatment with fluconazole or itraconazole for such patients typically involves doses ranging from 200 to 400 mg per day, with treatment durations ranging from several to many months.

Treatment of complicated infections is beyond the scope of this monograph but is also addressed in the IDSA Practice Guidelines. The length of treatment for such patients ranges from one year to the entire course of the patient's lifetime, depending upon the location of the infection and underlying risk factors.

The cost of therapy is substantial. Drug costs alone range from $2,000 to $20,000 per year, depending upon the specific drug and the daily dose prescribed.

# SECTION 3:
## ADDITIONAL INFORMATION

## History

The first patient recognized with what is now known as coccidioidomycosis was an Argentinean soldier in 1893. The first North American patient was recognized by a San Francisco surgeon the following year. First thought to be a protozoan infection, its true fungal nature was determined in 1900.

Initially, coccidioidomycosis was considered rare and fatal, but that understanding has changed dramatically. By 1935, it had been linked to the common illness known as San Joaquin Valley Fever, a self-limited illness, which usually conferred resistance to acquiring second infections. This quickly led to an appreciation of the various syndromes and the range of severities that infection produces (Table 1). By the 1940s, its existence within southern Arizona was well appreciated, and in the 1950's a survey of dermal hypersensitivity to a coccidioidal antigen gave a more comprehensive estimate of its distribution within the western United States.

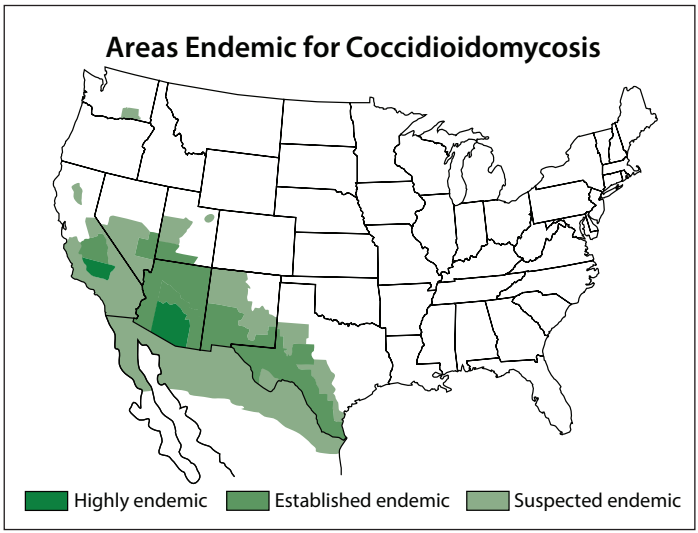



Figure 3. Endemic areas for coccidioidomycosis in the United States (provided by CDC).

## Geographic Risks

Historically much of the endemic regions for *Coccidioides* spp. roughly correspond to the "lower Sonoran life zone," which are areas of low rainfall, high summer temperatures, and moderate winter temperatures. Endemic regions that fit that description are found in the southern deserts of Arizona (including Maricopa, Pima, and Pinal counties), the Central Valley and southern portions of California (including Fresno, Kern, and Kings counties), the southern tip of Nevada, southern Utah, southern New Mexico, western Texas (especially along the Rio Grande), and the northern and Pacific coastal areas of Mexico, and parts of Central and South America. However, *Coccidioides* spp. has been isolated outside those areas, such as the California foothills near Redding, a site in Dinosaur National Monument, northeastern Utah, and recently, as far north as Southcentral Washington State. (Figures 3-4). The geographic risk is much broader than previously recognized and anyone who resides in or reports travel history to areas where Coccidioides exists is at risk.


Figure 4. Endemic areas for coccidioidomycosis in the Western Hemisphere (provided by CDC).

## Epidemiology

Coccidioidomycosis is a nationally notifiable disease and, since 2009, more than 10,000 cases have been reported in most years, but preliminary estimates suggest that 6 to 14 times as many symptomatic infections may occur. The most highly endemic areas include southern Arizona and California's Central Valley and central coast, and approximately 95% of reported cases are from Arizona and California (Figure 5). However, the disease is reportable in 27 states, and any provider should check with their local health department on reporting procedures. Because many cases occur in travelers to endemic areas who return to states where the disease is uncommon, clinicians in non-endemic areas also need to be aware of the risk of coccidioidomycosis and ask patients with compatible symptoms to see if they had traveled to an endemic area.

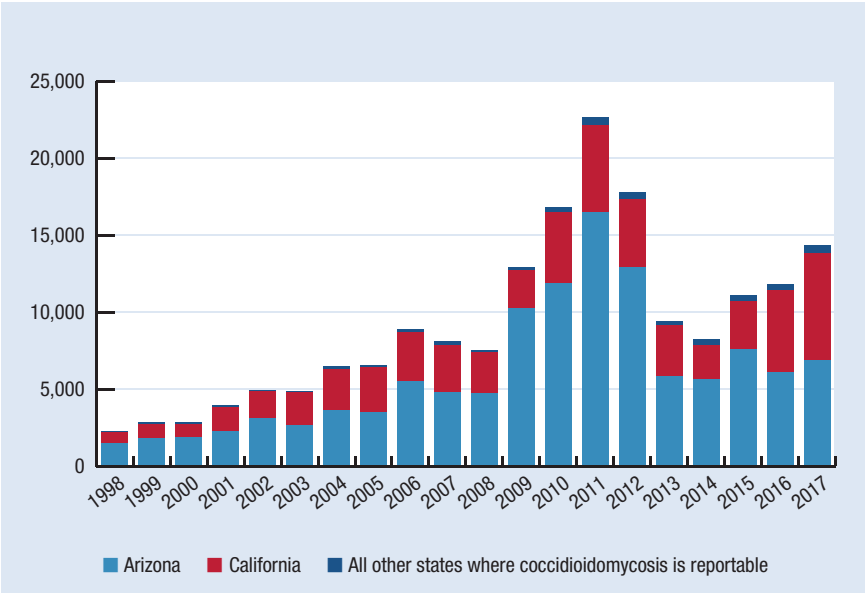



Figure 5. Annual number of cases of coccidioidomycosis reported in the United States, 1998 through 2017.

This fungal disease can affect people of any age, but it's more common in adults, and more men are affected than women. Certain groups of people are at higher risk for developing the severe forms of coccidioidomycosis, including African Americans and Filipinos, people who have weakened immune systems (e.g., patients with HIV/AIDS, organ transplant, or on corticosteroids or TNF-inhibitors), pregnant women, and persons with diabetes.

The morbidity of this disease represents a substantial burden on patients and healthcare. In both endemic areas and non-endemic areas alike, patients experience considerable diagnostic delays. Studies in both settings have found a median of approximately one month between seeking care and receiving a correct diagnosis. These patients seek care numerous times, often receive multiple antibacterial treatments, and more than 40% are hospitalized for their illness.[22, 23] Additional and early consideration of coccidioidomycosis will likely improve outcomes in these patients.

Infections are reported year round but rates increase in some of the driest periods of the year. The vast majority of infections occur sporadically in people, but dusty conditions caused by soil disruption have been associated with point source outbreaks. Even within endemic regions, the distribution of the fungus in the soil environment is not uniform, but aerosolized dust can be whipped up by strong winds and dispersed into neighboring urban areas. Since infection primarily occurs after inhaling an arthroconidium that has developed in the soil, virtually all infections originate in an endemic region. Very rarely, dirt which contains arthroconidia is carried on fomites from the endemic region to other parts of the country, even internationally. However, infections are not transmitted directly from an infected patient to another person, and patients with Valley fever need not be isolated from others.

## CONCLUSION

Valley fever represents a substantial public health problem, the true burden of which likely remains under-recognized. The clinical presentation of this disease is often non-specific, and increased awareness among clinicians, particularly those involved in primary care, about the disease is essential in order to ensure that patients with Valley fever receive a timely and accurate diagnosis. Clinicians should maintain a high clinical suspicion for Valley fever in patients who live in the endemic region or who have traveled to these areas. Although only a small proportion of patients with Valley fever develop pulmonary complications or extrathoracic dissemination, it is important to identify these complications as early as possible. For the other patients, most coccidioidal infections are uncomplicated. The five steps—**C**onsider the diagnosis, **O**rder the right tests, **C**heck for risk factors, **C**heck for complications, and **I**nitiate management (**COCCI**)—are a simple way for generalists to identify those with complications and to manage uncomplicated infections without specialty referral.

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## APPENDIX

THE UNIVERSITY OF ARIZONA COLLEGE OF MEDICINE TUCSON
Valley Fever Center for Excellence

Banner Health

# Recognition, Evaluation and Management of *Coccidioidomycosis* (Valley Fever)

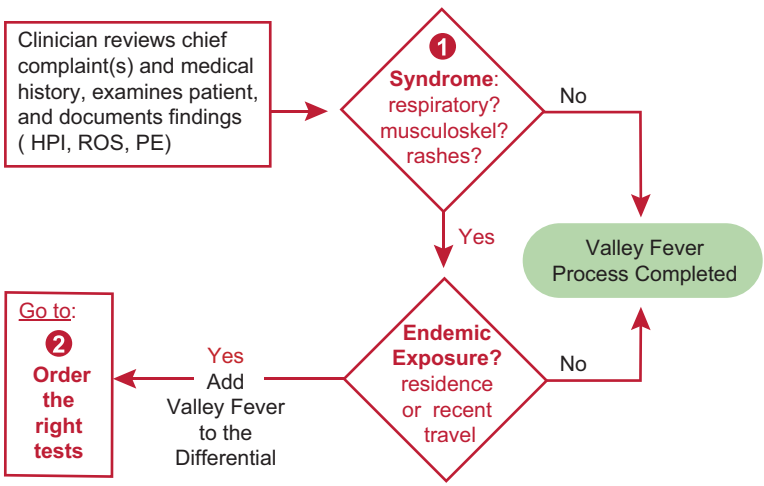
## Just Remember C-O-C-C-I

### RECOGNITION

**C**

### ❶ Consider the diagnosis

**Respiratory:** Previous visit, needs X-ray or antibacterial Rx?
**Musc/Skel:** More than one week, associated with fever or fatigue.
**Rashes:** *E. nodosum* or *E. multiforme*

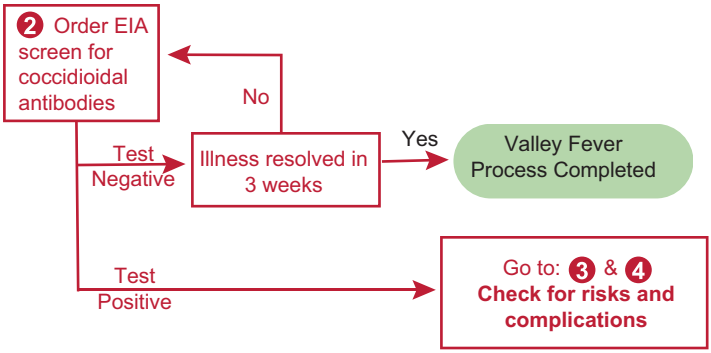


## RECOGNITION *continued*

**O**

### ❷ Order the right tests

EIA screen for coccidioidal antibodies with reflex to immunodiffusion and quantitative CF.




## EVALUATION

**C**

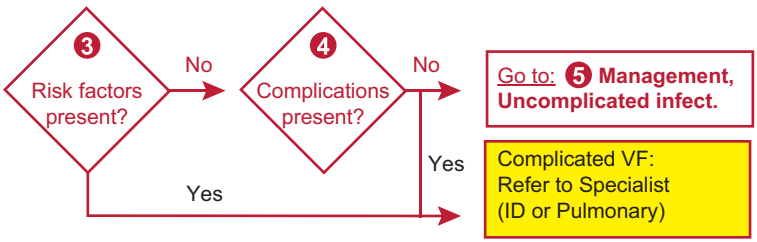
### ❸ Check for Risk Factors

Immunosuppression (HIV, organ recipient, Rheum/GI/Derm response modifier Rx, renal failure)
Diabetes, major cardiac or pulmonary comorbidities, pregnancy

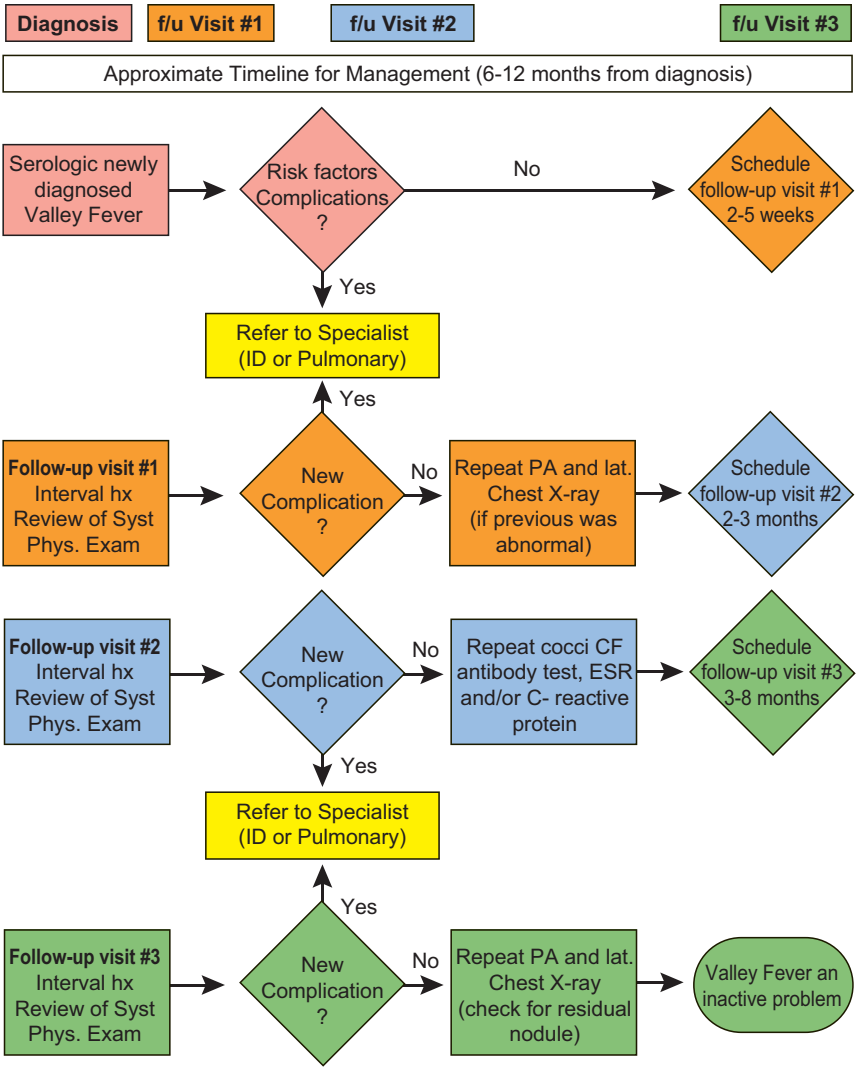
**C**

### ❹ Check for complications evident by physical exam or imaging

Focal ulceration or skin/soft tissue inflammation.
Asymmetric skeletal pain, joint effusions.
Progressive or unusual headache.



# I ❺ Initiate Management, Uncomplicated VF



## Health education for the patient and family:

General review of what is Valley fever: How you get it, typical symptoms, overall prognosis, need for follow-up

Patient leaflets

## Purpose of follow-up visits:

Monitor resolution of weight loss, fever, night-sweats, respiratory signs and symptoms, rashes and musculskeletal complaints.

Repeat ESR and/or C-reactive protein until normalized.

Look for new signs or symptoms of focal inflammation suggestive of developing dissemination (uncommon but very serious).

Repeat serology and chest X-rays

## Antifungal Therapy:

Highly individualized because of the lack of clinical studies. See Tutorial booklet for a discussion

If used, typically fluconazole 400 mg/day for 3-6 months.

## Residual fatigue syndrome:

Very common, often for many weeks or even many months but eventually self-resolving. Recent evidence suggest it is due to an oxygen-utilization deficit, measured as a reduced VO2 peak during cardio-pulmonary exercise testing (CPET).

Management

Explain that this is common and not a symptom of a progressive destructive process

Treat with reconditioning plan, possibly with referral to physical therapy

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