Valley Fever (Coccidioidomycosis)

Tutorial
for
Primary Care Professionals

Prepared by the

VALLEY FEVER CENTER FOR EXCELLENCE

University of Arizona

Tucson, AZ

Preface

In the south and central deserts of Arizona and the central valley of California, Valley Fever should be a familiar phrase to clinicians and patients alike. Certain medical and surgical specialists practicing in these areas are particularly likely to be aware of the less frequent but more serious complications of the disease. However, despite their significant impact on regional pubic health and individuals' lives, a very large majority of these infections are managed by primary care clinicians either without an accurate diagnosis or with sub-optimal care. In January 1996, the Valley Fever Center for Excellence established a hotline which physicians and others with questions about Valley Fever could call for information. From the questions received through the hotline, it became apparent that many details about the causes and responses to Valley Fever were not fully understood. One area particularly important was the importance of early diagnosis and proper management of the initial respiratory infection. Early diagnosis of Valley Fever by primary care professionals can improve patient care by reducing patient anxiety, unneeded diagnostic tests, and unwarranted use of antibacterial agents. Moreover, serious complications requiring treatment might be identified sooner. We hope to improve this situation with this revised edition of the Valley Fever Tutorial for Primary Care Professionals.

The purposes of this monograph are two-fold. First, it is intended to be a syllabus to accompany a medical education program on the primary care aspects of coccidioidomycosis organized by the Valley Fever Center for Excellence. Slide presentations from the most recent CME program can be found at the Valley Fever Center for Excellence Website (http://www.vfce.arizona.edu). While this syllabus does not follow the presentation structure of the CME program, it covers much of the same information. 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 at (520) 626-6517 or through its website at http://www.vfce.arizona.edu. Second, this publication is designed to be a reference for the office shelf. The information contained within is not intended to be an exhaustive review of the disease. The content was selected for its relevance and usefulness to busy family practitioners, internists, emergency room personnel, and others dealing with patients in a primary care setting, especially within regions endemic for *Coccidioides* species.

I hope you find this information helpful. The Valley Fever Center for Excellence needs financial support to continue its work. Should you wish to make a tax-deductible contribution you can do so by sending a check payable to the University of Arizona Foundation to:

The Valley Fever Center for Excellence
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or online at

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June 2009

SECTION 1: OVERVIEW OF COCCIDIOIDOMYCOSIS

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 in the following year. First thought to be a protozoan infection, its true fungal nature was determined in 1900. Initially, this infection was considered rare and fatal. However, by 1935, it had been linked to the common illness known as San Joaquin Valley Fever and by the 1940's its existence within southern Arizona was well appreciated. No effective therapies were available for any form of coccidioidomycosis until the late 1950's when intravenous amphotericin B was first introduced. In the 1970's, azole antifungal therapies were first used which led to the current availability of several orally active compounds of this class including fluconazole and itraconazole.

Caused by a fungus (*Coccidioides* spp.)

Valley Fever is also referred to as: Coccidioidomycosis, Cocci, Desert Rheumatism, and San Joaquin Valley Fever

Infection results from inhaling a spore

Severity varies:
- mild (60%)
- moderate (30%)
- severe (10%)

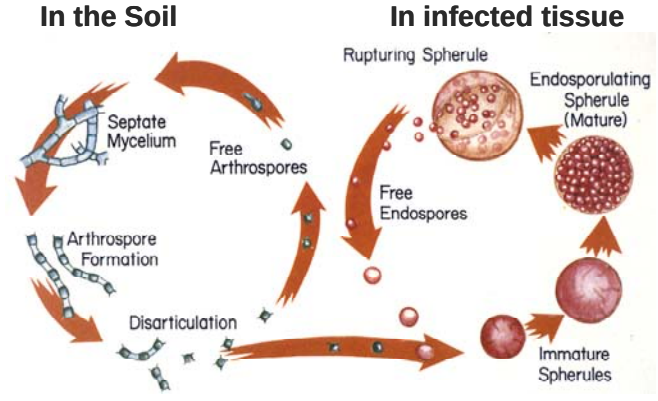


Figure 1. Life cycle of Coccidioides spp.

Mycology

The fungal species that cause Valley Fever are in the Genus *Coccidioides immitis* and *C. posadasii* (Figure 1). In the past, all strains were designated as *C. immitis* but recent genetic analysis has shown that strains segregate into two distinct groups. Strains now designated *C. immitis* in most cases originate from infections contracted in California and those designated *C. posadasii* from infections contracted elsewhere. At the present time, most clinical laboratories do not determine species for new isolates in which case designation as simple *Coccidioides* spp. is technically more accurate.

In the soil *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, alternating cells undergo autolysis, lose their internal contents, and their walls become extremely brittle. The remaining barrel-shaped single cells (known as arthroconidia) are then easily disrupted. The size of each arthroconidium is approximately 3-5 µm. This is small enough to both remain suspended in air and be inhaled deep into the lungs which establishes an infection. At that point, an arthroconidium transforms into a spherical shape and enlarges, frequently to as much as 75 µm in diameter. Inside the growing spherule, the cell wall invaginates to repeatedly transect the 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.

Epidemiology

The endemic regions of *Coccidioides* spp. roughly correspond to the “lower Sonoran life zone,” which are areas of low rain fall, high summer temperatures, and moderate winter temperatures. Regions that fit that description are found in the southern deserts of Arizona (including Maricopa, Pinal, and Pima counties), the central valley and southern portions of California (including Kern, Tulare, and San Louis Obispo counties), the

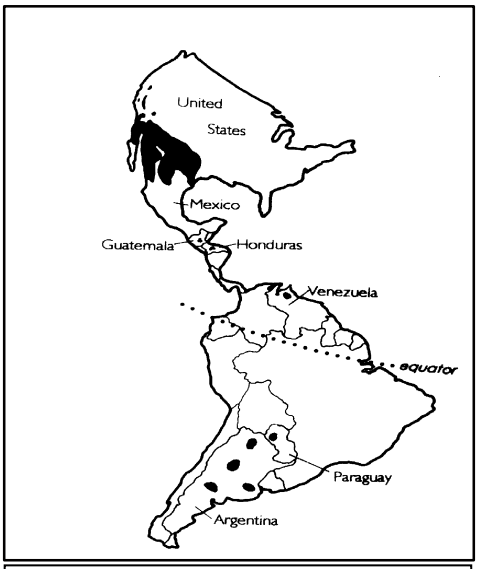


Figure 2. Shaded areas indicate the distribution of coccidioidomycosis in the western hemisphere.

southern tip of Nevada, southern Utah, southern New Mexico, western Texas (especially along the Rio Grande), and northern and Pacific coastal areas of Mexico (Figure 2). Some areas have been identified in Central and South America as well.

Even within endemic regions, the distribution in the soil is not uniform and in fact most acreage appears not to contain the fungus. Thus, while occasionally disruption of soil produces increased risk of exposure, such activity often does not. Conversely, windy conditions, which typically involve large areas of the desert, may more likely result in arthroconidia becoming airborne and distributed across urban and rural areas alike. The implication is that exposure to *Coccidioides* spp. is more associated with living in or visiting endemic areas *per se* than it is with engaging in activities associated with heavy dust exposure.

Since infection occurs after inhaling arthroconidia that have developed in the soil, virtually all infections originate in an endemic region. Very rarely, dirt which contains arthroconidia carried from the endemic region has been the source of infection elsewhere. **Infection resulting from respiratory exposure to an infected patient has never been reported, and patients with Valley Fever need not be isolated from others.** Peak infection rates occur during the driest periods of the year. In Arizona this is the early summer and late fall whereas in California it is a single season lasting throughout the summer.

Spectrum of disease

The majority 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 a community acquired pneumonia. For most such patients, it is not possible without specific laboratory testing to distinguish Valley Fever pneumonia from that caused by other etiological agents. Whether diagnosed or not, most infections are controlled by induction of immunity although the associated illness may last for many weeks to many months. Approximately 5 - 10% of infections result in pulmonary sequelae and 1% or less result in spread of infection outside of the lungs to cause lesions in the skin, bones, joints, meninges, or virtually any other organ or tissue in the body. These complications produce a great deal of chronic morbidity and cause 50 to 100 deaths annually in the United States.

Spectrum of Coccidioidomycosis

60% of infections mild, with little or no symptoms

Those seeking medical attention
- -Most common symptoms:
  Fever, fatigue, cough, chest pain, headache, skin rash, joint aches
- -Average recovery is weeks to many months in otherwise healthy people

Complications
- -Residual lung nodules (~5%)
- -Lung cavitation (~5%)
- -Infections beyond the lungs (1% or less)

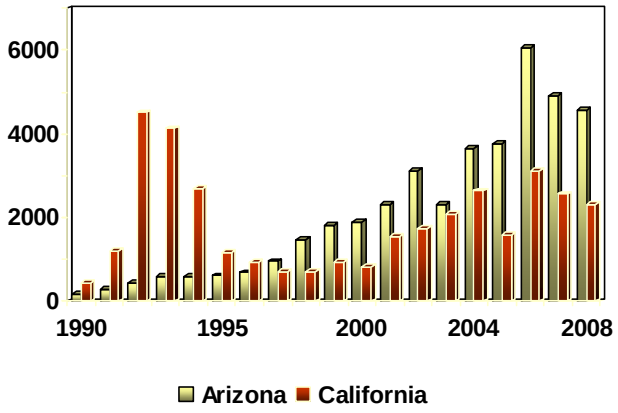
Current therapies

Many patients with Valley Fever pneumonia require no treatment and the illness resolves as a consequence of acquired immunity. However, in some patients coccidioidal pneumonia is acutely very severe. In others, it produces various progressive pulmonary syndromes or leads to spread of infection to other parts of the body. Such complications dictate the need for treatment and despite this may be difficult to control. A large majority of such infections follow a subacute or chronic progression, and initial therapy typically involves oral administration of azole antifungals such as fluconazole or itraconazole. Typically, treatment is continued for many months to years. When therapy is discontinued after the apparent successful control of disease, a relapse of infection occurs in approximately one-third of patients. Thus, some patients may need lifelong therapy for control. Chief among these are patients with deficiencies in cellular immunity or those with

coccidioidal meningitis. Amphotericin B is effective only if administered parenterally and usually is associated with significant side-effects and toxicities. Despite these drawbacks, in rapidly progressive infections, amphotericin B is often the preferred initial treatment.

SECTION 2: THE IMPORTANCE OF VALLEY FEVER IN PRIMARY CARE

Figure3.



Coccidioidomycosis is a reportable disease at the national level and reporting is required in Arizona and California where cases annually number in the thousands (Figure 3). That Arizona has approximately twice as many infections as California corresponds proportionally to the population sizes in the most intensely endemic regions of the two states (table 1).

In 2007, the Arizona Department of Health Services conducted a telephone survey of nearly 500 persons, approximately 10% of those reported being newly diagnosed with Valley Fever that year. From these interviews, it was found that over half were ill for more than six months, 75% were unable to do usual daily activities for over 3 months, and 75% of workers missed an average of one month of employment. Also found were significant delays in diagnosis. For example, patients waited 44 days before seeking care for their illness. Once care was sought, there was an additional average delay of 5 months involving 3 or more clinic visits before the correct diagnosis was made. The impact on the health care system was substantial since over half of patients sought their care from emergency rooms, 40% of those were hospitalized one or more nights, and 25% of the patients required 10 or more visits to clinicians to manage their illness. From Arizona hospital records, there were over 1,700 admissions resulting from Valley Fever infections in 2007 costing approximately $86 million. The full report can be accessed at http://www.azdhs.gov/phs/oids/epi/pdf/VF_Annual_Report_2007.pdf.

As significant as these findings are, other analyses indicate that many times the number of reported infections goes unrecognized. In one study conducted in Phoenix, Arizona, only 3% to 13% of patients with community acquired pneumonia were tested for Valley Fever [1]. In contrast, when Tucson patients with a clinical diagnosis of community acquired pneumonia were prospectively tested for Valley Fever, 29% were found to be positive [2]. These and other less direct measurements [3] all indicate that approximately 50,000 patients annually seek medical care for Valley Fever pneumonia. Since most coccidioidal infections can only be diagnosed by specific laboratory testing, the lack of clinicians testing for Valley Fever could easily account for the under reporting of illness by as much as 90%.

Table 1. Populations (in millions of persons) of selected counties within regions highly endemic for coccidioidomycosis.

	Year		
State	**1970**	**1990**	**2007**
Totals	2.5	4.5	7.3
Arizona	1.5	2.9	5.1
Maricopa (Phoenix)	1.0	2.1	3.8
Pima (Tucson)	0.4	0.7	1.0
Pinal	0.1	0.1	0.3
California	0.6	1.0	1.5
San Louis Obispo	0.1	0.2	0.3
Kern (Bakersfield)	0.3	0.5	0.8
Tulare	0.2	0.3	0.4
Texas			
El Paso (El Paso)	0.4	0.6	0.7

Sources: US Bureau of the Census

Undiagnosed infections are almost certainly not as serious as those that are recognized. Nonetheless, there are several very important reasons why diagnosis, especially in the primary care setting, should be pursued.

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. Diagnosis has always been a major contribution of physicians, and even though the modern medical profession has many interventions at its disposal, the value of diagnosis to patient satisfaction should not be under estimated. This is especially true for older patients, where the concern that 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 all ages, an accurate diagnosis allows for reassurance in most cases and appropriate prognostic patient education.

Additionally, 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 diagnostic 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 complications which might be avoided if coccidioidomycosis were known to have been responsible.

A third benefit of diagnosing coccidioidal infections early is the reduction or elimination of empiric therapy for bacterial infection. Patients with persistent respiratory complaints often receive empiric antibiotics in an ambulatory practice. In one study, 81% of patients with Valley Fever pneumonia received at least one course and 31% received multiple courses of antibacterial treatment for their illness [2]. 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 anti-inflammatory effects of corticosteroids may impede host defenses, and their use in patients with early coccidioidal infections may cause adverse effects.

Finally, by establishing a diagnosis of coccidioidomycosis early, complications (should they arise) may be more quickly recognized and treated. As discussed below, complications of coccidioidal infection usually manifest within months of the initial infection. For this reason, symptoms which are associated with or develop in the weeks following a new coccidioidal infection may indicate extrapulmonary spread. A more detailed evaluation of new symptoms at this stage might identify earlier a need for treatment and reduce tissue destruction and consequent morbidity.

In summary, the posture health care professionals take with respect to early diagnosis of coccidioidal infections is critical to all further discussion about the proper management of this infection in the primary care setting. Historically, the approach in general has been passive, leaving diagnosis and treatment to only the most severely ill. Providing an accurate, early diagnosis can decrease patient anxiety, eliminate unwarranted diagnostic testing, and unnecessary exposure to antibiotics. It also allows for earlier identification and treatment of complications. The Arizona Department of Health Services has recommended that physicians whose patients have endemic exposure for Valley Fever be tested for this possibility should they develop signs and symptoms of pneumonia. The Valley Fever Center for Excellence endorses that recommendation as reflected in this manual. The following sections, then, describe general strategies for primary care professionals to identify and manage this important disease.

Value of Early Diagnosis

- Allay patient anxiety by:
  - ✓ Giving their illness a name
  - ✓ 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

SECTION 3: PRIMARY CARE MANAGEMENT OF COCCIDIOIDOMYCOSIS

The following sections outline an approach for recognizing new infections, assessing their impact on patients, and subsequently managing their illness depending upon its level of complication. We have developed an acronym *(***COCCI)** for this approach. These five topics will be discussed in this section.

CONSIDER THE DIAGNOSIS OF VALLEY FEVER

Spectrum of clinical manifestations for Valley Fever. The incubation period of coccidioidal infection ranges from 7 to 21 days after which a variety of manifestations develop. The most common symptoms are fatigue, night sweats, and pulmonary symptoms (cough, chest pain, dyspnea, and hemoptysis). 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%-10% is also common with coccidioidal infections. It is apparent from this that the clinical presentation overlaps substantially with the presentation of many other types of respiratory illnesses.

Clinical Manifestations of VF	
Symptoms	Signs
Fatigue	Fever
Night sweats	Weight loss
Cough	*Erythema nodosum*
Chest pain	*Erythema multiforme*
Dyspnea	
Hemoptysis	Chest radiographs
Headache	Pulmonary infiltrates
Arthralgias	Hilar adenopathy
	Pleural effusions

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 seemingly inconsequential that it is often missed. More notable 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 from endemic exposure to *Coccidioides* spp., Valley Fever is frequently responsible.

C onsider the diagnosis
O rder the right tests
C heck for risk factors
C heck for complications
Initiate management

Another symptom is diffuse and migratory arthralgia (22% of patients). Joints may be mildly inflamed and painful but typically do not exhibit an effusion. The triad of fever, *E. 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 or the joints.

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. Peripneumonic pleural effusions may

When to Order Tests for Valley Fever

Skin lesions of:
- *E. nodosum*
- *E. multiforme*

Two of the following for more than two weeks:
- Fever
- Fatigue
- Arthralgia

Unexplained peripheral blood eosinophilia

Respiratory symptoms and:
- More than one office visit
- Chest X-ray ordered
- Antibiotic prescribed

also occur as part of a primary infection. Although disease of one lung is the rule, the process can occasionally be bilateral.

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 rates and C reactive protein are often elevated.

Attempts to use clinical presentation and routine laboratory results as an indicator of coccidioidal infection have been uniformly unsuccessful. In one study, several patient findings were significantly associated with coccidioidal infection as compared to patients with other causes of acute respiratory problems [4]. 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 that are tested for Valley Fever, the more infections are likely to be found. 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 diagnosis Valley Fever, the overall proportion of tests that are diagnostic will decrease.

A critical step for clinicians in a busy practice is to establish routine indications for ordering the appropriate tests. In the table on the previous page, several indications are proposed which are selected for simplicity and application to common situations.

ORDER THE RIGHT TESTS

Detection of anti-coccidioidal antibodies in serum. 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 a significant frequency of false-positive results. Specific tests are typically selected by the director of the clinical laboratory. Factors involved in such selection include cost, 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. This has complicated the 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 significant coccidioidal infection. Therefore, a report of a 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. If repeated testing over the course of two months fails to produce a serologic diagnosis, further serologic testing is likely to be unrewarding.

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Tube precipitin (TP) antibodies. Antibodies of this type were originally detected by the presence of a precipitin button that formed at the bottom of a test tube after overnight incubation of patient serum mixed with coccidioidal antigen. Because IgM is most adept at forming such immune precipitins and because these reactions were detected early after onset of infection, this test is now often referred to as the "IgM test." The antigen responsible for this reaction is a polysaccharide from the fungal cell wall. Up to 90% of patients will have TP antibodies detected at some time within the first three weeks of symptoms and this will decline to less than 5% 7 months after the onset of a self-limited illness.

Complement fixing (CF) antibodies. When patient serum 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 complement but remain intact if the complement is depleted. Since IgG is the

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immunoglobulin class usually involved in such immune complexes, this test is often referred to as the "IgG test." Although this test was originally developed using various complex extracts of *C. immitis*, it is now known that the antigen involved in this reaction is a chitinase, a protein enzyme important for the structure of the fungal cell wall. In early coccidioidal infections, CF antibodies are detected somewhat later and for longer periods than TP antibodies. 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. Another difference between CF and TP antibodies is that CF 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. In general, higher titers reflect more extensive coccidioidal infection and rising CF antibody concentrations are associated with worsening disease. Thus serial determinations of CF antibody concentrations are of prognostic as well as diagnostic value.

Immunodiffusion tests (IDTP, IDCF). Antibodies that were detected by the original TP or CF tests can be detected by an alternative procedure known as the immunodiffusion (IDTP and IDCF tests, respectively). Although the conduct of the IDTP and IDCF tests are quite similar, each uses a different antigen in order to measure different types of antibodies. As with the original tests, the IDTP is reported by some laboratories as the "**IgM test**" and the IDCF as the "**IgG test**" result. Both tests have been found to be at least as sensitive as their original counterparts. Moreover, immuno-diffusion tests are amenable to being manufactured and distributed as commercially prepared kits, thus allowing the tests to be performed in labs not fully dedicated to a mycology specialty.

Enzyme-linked immunoassays (EIA). An EIA test for coccidioidal antibodies is available commercially. The test kit allows for the specific detection for IgM or IgG antibodies. However, these results are not interchangeable with the "**IgM test**" or "**IgG test**" results mentioned above. Positive EIA results are highly sensitive for coccidioidal infection. However, occasionally false positive results are noted especially with the IgM EIA test.

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.

Cultures for *Coccidioides* spp. Isolating *Coccidioides* spp. from a sputum or other 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 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, currently requesting fungal cultures on a sputum specimen may be disruptive to work flow. 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. 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.

Evaluation by the laboratory. Direct examination of secretions can be carried out 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 a bacterial pneumonia will actually yield *Coccidioides* spp. When growth occurs, it is typically as a white (non-pigmented) mould. 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 bio-containment 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 do this is detection of a specific DNA sequence using a commercially available DNA probe. Smaller laboratories often opt to refer the culture to a reference laboratory where species identification is completed.

Coccidioides spp. are designated select agents by the CDC and as such are strictly regulated by law once isolates are identified.

Skin testing. Dermal hypersensitivity to coccidioidal antigens is highly specific for coccidioidal infection. However, since skin tests 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 epidemiologic studies, important limitations exist when used as a screening procedure for recent infection. In patients known to have Valley Fever, skin testing may have prognostic significance since patients with well controlled infection usually display positive skin tests whereas those with progressive infections often fail to develop dermal reactivity to coccidioidal antigens. For over a decade skin testing antigens have not been commercially available. However, this situation may change.

Interpretation. Results of skin tests are measured both 24 and 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.

CHECK FOR RISK FACTORS

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 co-existence of major immunosuppressing conditions that adversely affect cellular immunity. This would include immunosuppression to prevent rejection of organ transplants, AIDS syndrome in HIV-infected persons, 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%. This is much greater than the risk of a similar complication in the general population.

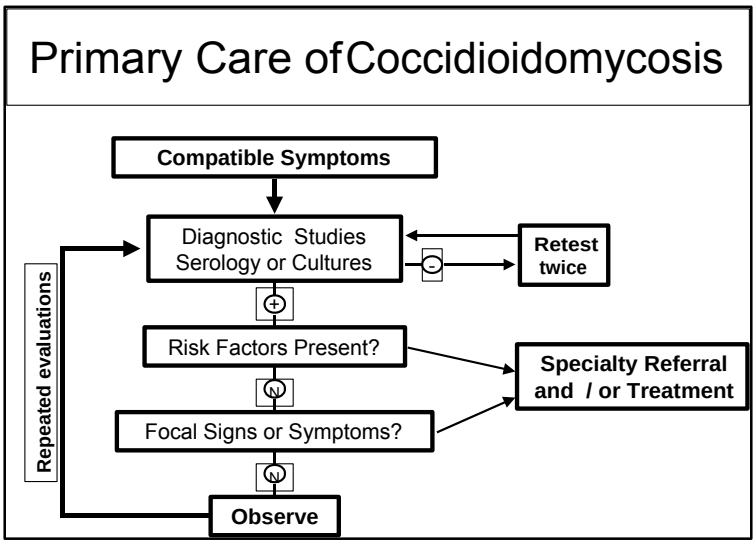
Immunosuppressing conditions that affect humoral immunity appear to have relatively little risk for complications of coccidioidal infection. Similarly, splenectomy, hypocomplementemia, or neutrophil dysfunction syndromes are not major risk factors for this disease.

Diabetes mellitus. Diabetic patients appear to have an increased risk of pulmonary complications [5]. While many diabetics 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 infections.

Pregnancy. Women who contract Valley Fever during pregnancy are at particular risk of serious infection. Those at highest risk for serious infection 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 which 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 to accumulated co-morbidities in aging persons rather than age itself [6]. Also, 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 two-fold or three-fold above that of the population as a whole. Finally, certain occupational exposures may increase risk of infection. However, exactly which occupations and what the proportions of the increase over ambient risk are not currently well defined.



Check for Progressive Pulmonary Syndromes or Disseminated Disease

Even in the absence of the risk factors previously 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 and those that involve parts of the body outside of the lungs (extrapulmonary dissemination). These two types of complications usually do not overlap. Most complications 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.

Most complications manifest within the first year or two after the initial infection. If a new 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 develop in a patient within weeks or months of developing coccidioidal pneumonia, it may be useful to recommend a radionuclide scan 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 biopsy, aspiration, or lumbar puncture, 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. Of these, half will 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.

Extrapulmonary 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 two years. In this way, coccidioidal infections differ from tuberculosis which commonly returns decades after the initial infection. An important exception to this rule is in the intercurrent development of major degrees of immunosuppression of the nature discussed above. The most common sites of dissemination are skin, joints, bones and the meninges. However, virtually any part of the body can be affected.

INSTITUTE 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 (illustrated in the flow diagram). 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 sizable 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, pulmonary diseases, neurology, or other disciplines to aid in developing a treatment plan. Management of complicated coccidioidal infections is beyond the scope of this manual but comprehensive treatment guidelines are available. The following are some guidelines for managing patients with uncomplicated infections.

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 practitioner 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 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 medical attention. With this description, the need for follow-up as the infection resolves even though therapy is not begun becomes clearer to the patient, and this should improve compliance.

Frequency of follow-up health care visits. At the core of management of uncomplicated coccidioidal infections is continued follow-up. This is needed to confirm that the illness remains uncomplicated and that more specific interventions are unnecessary. In addition, residual pulmonary abnormalities may remain, which should be documented for future reference so that they need not be unnecessarily reevaluated as a new problem years later. In rare instances, coccidioidal infections and lung neoplasms have co-existed and this 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 for instituting 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.

Monitors of 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. 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 their improved course. Often having the patient keep a journal with entries every other week is a helpful tool to document progress.

Laboratory studies 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 improvement. Typically this would not be measured any more frequently than weekly. Also, the CF or IDCF antibody concentration is expected to decrease as a coccidioidal infection resolves and it is important to demonstrate this. If these results do not normalize as expected, then concern should be raised that complications may be developing and possibly further diagnostic studies would 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.

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 abnormalities to be stable or improving. Subsequent chest radiographs should be obtained every several weeks to every several months. Often two views of the chest are sufficient to monitor progress and the increased sensitivity of CT scans are not usually needed as the patient improves.

Antifungal therapy. For early uncomplicated coccidioidal infections, most patients can be managed without antifungal therapy. There are currently three commercially available oral antifungal drugs available with activity for treating coccidioidal infections: ketoconazole, fluconazole, and itraconazole. 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. A recent observational study also provides no evidence for a beneficial drug effect in the treatment of early coccidioidal pneumonia [7]. 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 IDSA practice guidelines [8]. Length of treatment for such patients typically ranges from several to many months.

Treatment of complicated infections is beyond the scope of this syllabus but is also addressed in the practice guidelines [8]. Lengths of treatment for such patients' ranges from a year to life-time, depending upon the location of the infection and underlying risk factors involved. 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.

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