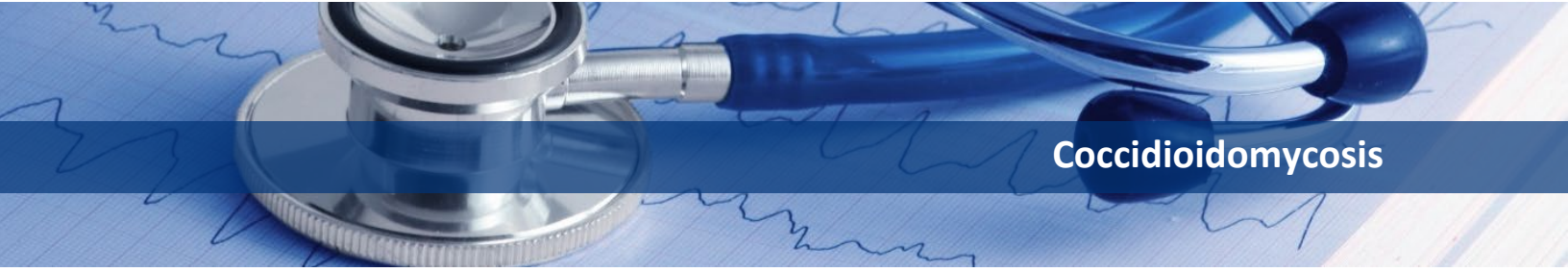

Coccidioidomycosis

Coccidioidomycosis, also known as “cocci” or “Valley fever”, is a mycotic disease caused by the fungus *Coccidioides*[1]. It was first discovered in 1892 in an Argentinean soldier with disseminated disease[2]. Two years later, another patient with disseminated infection was reported in the San Joaquin Valley in California, where it received the name “Valley fever”[2]. It was initially classified as a protozoan infection, but re-classified as a fungus in 1900[2]. The fungus is present in the top 2–8 inches of warm, dry soils at lower elevations of the southwestern United States, as well as parts of Mexico and Central and South America[3].

In the United States, *Coccidioides* spp. is endemic in Arizona, California, Utah, Nevada, and western Texas[3]. Recently, the fungus was also found in south-central Washington state[4]. These areas have an arid or semi-arid climate with scant rainfall, high summer temperatures and few freezes, conditions ideal for the growth of *Coccidioides* spp[2].

Around 150,000 people are believed to be infected with Valley fever every year in the United States[1]. The majority of reported Valley fever cases nationwide occur in Arizona (approximately 65%), followed by California[5]. Even in these states, *Coccidioides* spp. is not ubiquitous, with most of the soil being free of the fungus[2]. About 94% of reported cases in Arizona reside in Maricopa, Pima, or Pinal County[6]. In the last decade, the incidence in Arizona has decreased from 185.9 per 100,000 population in 2010 to 144.1 per 100,000 population in 2019. Each year, there are roughly 750 hospitalizations of Arizona residents with a primary diagnosis of Valley fever and over $50 million in total hospitalization charges[6].

In Arizona and other endemic areas, Valley fever is a significant burden on patients and the healthcare system. According to an ADHS enhanced surveillance investigation of cases reported during 2007–2008 (n=493), more than half of the patients were symptomatic for more than five months, 74% of employed patients missed a median of 14 workdays, and 75% of the affected individuals were unable to do daily activities at some point during their illness[8]. The analysis also found that there were delays in diagnosis, with a median of 55 days between the onset of symptoms and diagnosis. Patients sought healthcare a median of 11 days after symptom onset, and there was a median of 23 days from first seeking healthcare before diagnosis of Valley fever. Forty-six percent of the interviewed patients sought medical attention in an emergency room at least once during the course of illness, and 26% saw a healthcare provider more than 10 times. Early diagnosis of Valley fever may provide a number of benefits including reduction in the utilization of unnecessary antimicrobial drugs, allayed patient anxiety, and improved clinical management[8].

A. Agent:

Coccidioides spp. is an aerobic fungus. There are two species: *C.* posadasii (which is found in Arizona), and *C. immitis*. Although genetically distinct, the two species are morphologically identical and disease manifestation is indistinguishable[2]. Most clinical laboratories do not determine species for isolates. Therefore, a simple case designation of *Coccidioides* spp. is accurate.

Coccidioides* Life Cycle*:
In the soil, *Coccidioides* spp. occurs in the mycelial phase as septate hyphae[3]. Eventually, the hyphae break apart into arthroconidia. These arthroconidia are small (diameter of 2–4 µm) and thus can remain suspended in the air after being dispersed[4]. These suspended arthroconidia can then be inhaled into the terminal bronchioles of the lungs to cause infection. At this point, arthroconidia transform into spherules that divide internally to produce endospores. When spherules rupture, they release and spread endospores to nearby tissue. Each endospore can then develop into another spherule and repeat the cycle.

B. Clinical Description:
Valley fever produces mild or no symptoms in 60% of infected persons[9]. In the 40% who do become symptomatic, the most common manifestations are fever, cough, fatigue, chest pain, shortness of breath, chills, muscle and joint aches, and rash (erythema nodosum or erythema multiforme). It is usually a self-limiting disease resolving without any treatment and therefore often goes unreported. Resolved infection results in durable, lifelong immunity and there is no evidence that reinfection can occur in immunocompetent persons[10]. Some studies have indicated that 15–30% of community-acquired pneumonia in the hyper-endemic population centers of southern Arizona is caused by Valley fever[11–12]. Pulmonary lesions manifest as nodules, cavitation, or consolidation and can be misdiagnosed as lung cancer.

Rarely, in less than 1% of cases, the infection becomes disseminated involving the skin, bones, joints, meninges, viscera, serous areas or the lymph nodes[10]. Risk factors for dissemination include:

- People who have weakened immune systems (e.g., due to HIV/AIDS[13], organ transplantation[14], corticosteroids or TNF-inhibitors[15]),
- People who are Black[16] or Filipino[17–18],
- Pregnant women[19]— especially during the third trimester or immediately after giving birth.

Mortality attributed to Valley fever accounts for less than 200 deaths per year in the United States[20].

C. Reservoirs:
Soil in endemic areas; the fungus has been found at a higher frequency in and around rodent burrows[21].

D. Mode of Transmission:
There is no person-to-person or zoonotic (animal-to-person) transmission. Thus, Valley fever is not contagious; it is, however, infectious. The most common mode of transmission is by inhalation of airborne arthroconidia. Transmission via fomites has also been reported[21]. Rarely, transmission has also occurred in organ transplantation and inhalation of arthroconidia in viscero-cutaneous fistula. Cutaneous or traumatic inoculation rarely occurs[10].

E. Incubation Period:
The incubation period ranges from 1–4 weeks for primary infection; disseminated infection can occur years after primary infection[21].

F. Period of Communicability:

There is no person-to-person or zoonotic (animal-to-person) transmission[21].

G. Susceptibility:
Anyone who has not previously been infected and resides in or travels through an endemic area is susceptible to infection[2]. Other mammals (e.g., dogs, horses, cats, cattle, sheep, llamas, rodents) and some reptiles are also susceptible.

H. Treatment:
People with severe or disseminated infections may warrant treatment with antifungals such as azoles (e.g., fluconazole, itraconazole) and amphotericin B[1].

For more on clinical management of Valley fever see:

- 2016 Infectious Disease Society of America Practice Guidelines for the Treatment of Coccidioidomycosis
- Valley Fever: Timely Diagnosis, Early Assessment, and Proper Management: CME, 2016.
- Treatment for Early, Uncomplicated Coccidioidomycosis: What Is Success?

Disease Management

I. Clinical Description for Case Definition[22]:
Infection may be asymptomatic or may produce an acute or chronic disease. Although the disease initially resembles an influenza-like illness or pneumonia-like febrile illness primarily involving the pulmonary system, dissemination can occur to multiple organ systems. An illness typically characterized by one or more of the following:

- Influenza-like signs and symptoms, including fever, chest pain, cough, myalgia, arthralgia, headache
- Pneumonia or other pulmonary lesion, diagnosed by chest X-ray
- Rashes, including erythema nodosum or erythema multiforme
- Involvement of bones, joints, or skin by dissemination
- Meningitis
- Involvement of viscera and lymph nodes

J. Laboratory Criteria for Diagnosis[22]:
Laboratory-confirmed coccidioidomycosis requires at least one of the following:

- Cultural OR histopathologic evidence of presence of *Coccidioides* species.
- Demonstration of Coccidioides-specific nucleic acid or proteins in a clinical specimen or isolate using a molecular assay (e.g., PCR, DNA Probe, MALDI-TOF).
- Detection of coccidioidal antibodies in serum, CSF, or other body fluids using:
    - Enzyme immunoassay (may be abbreviated as EIA or ELISA)
    - Immunodiffusion (may be abbreviated as ID, IMD, IMDF, IDTP, IDCF, etc.)
    - Complement fixation (CF)
    - Lateral flow assay (LFA)
    - Tube precipitin
    - Latex agglutination
- Detection of Coccidioides species antigen in serum, CSF, or other body fluids.

- Coccidioidal skin test conversion from negative to positive after the onset of clinical signs and symptoms.

A single positive laboratory, irrespective of time it was reported, is sufficient to classify as a confirmed case.

Case Classification	
Confirmed	A case that is laboratory confirmed.

K. Classification of Import Status:
N/A

L. Laboratory Testing:
The Arizona State Public Health Laboratory does not perform testing for Valley fever. The following laboratory methods are used by commercial and hospital laboratories:

- Enzyme-Linked Immunosorbent Assay (EIA/ ELISA) - IgM or IgG
- Immunodiffusion - IgM or IgG
- Complement Fixation (CF) - IgG
- Fungal Culture
- Histopathology
- Polymerase Chain Reaction (PCR)
- Latex Agglutination - IgM or IgG
- Tube Precipitin - IgM
- Antigen
- Lateral Flow Assay (LFA)
- Mass Spectrometry (e.g., MALDI-TOF)

M. Assessing Laboratory Results:
Serological tests are the most commonly used laboratory method for the diagnosis of Valley fever. IgM antibodies are the most sensitive serological marker of early infection[23]. IgM is positive within the first week in 50% of primary infections and in 90% of primary infections by 3 weeks[10,23]. These antibodies are detectable in only 5% of patients within 6 months of the onset of a self-limited disease. However, IgM may persist and/or reappear in chronic cavitations or systemic reinfection associated with ventriculo-peritoneal shunt placement[23].

IgG antibodies are positive in 85–90% of patients by 3 months after infection and persist for about 6–8 months, although in some cases, it can persist for years[23]. IgG titers by complement fixation are a useful quantitative measure of the extent and progression of the disease. Most patients with titers of 1:16 or less do not have disseminated disease. High titers (1:32 or higher) are found in severe extra-pulmonary or disseminated disease. Low or negative titers may be found in mild or asymptomatic disease or in immunosuppressed patients[10,23]. IgG titers in the serum and CSF can be followed by complement fixation to monitor the effectiveness of the treatment and to assess the risk of relapse.

EIA and Immunodiffusion[24]: The two most common techniques among all the laboratory methods used for acute diagnosis. Positive EIA results are highly sensitive for infection; however false-positive results may occur with the IgM EIA test. Immunodiffusion tests have low sensitivity and high specificity.
Complement Fixation[24]: Used in the follow-up of the disease. Rising CF antibody concentrations are associated with worsening disease. Thus, serial CF antibody concentrations are used for prognostic purposes.
Tube Precipitin[24]: An IgM antibody test with up to 90% of patients having detectable antibodies by this method within 3 weeks of symptoms onset. After 7 months, this decreases to less than 5% for self-limited disease.
Latex Agglutination[24]: Has a high rate of false-positive results; therefore a positive test is not as reliable as other tests.

Fungal Culture[24]: The most definitive method of diagnosis of *Coccidioides* spp. from clinical specimens. Can take up to 3 weeks to complete and is not as sensitive as serological tests.
PCR[24]: Can be used in the identification of *Coccidioides* spp. from clinical specimens. However, it is still experimental and used by only a limited number of clinical laboratories.

Interpreting Lab Results	
Positive results	Reactive, F band present, abnormal *Coccidioides* identified/ isolated/undifferentiated, confirmed by DNA probe
Negative results	Non-reactive, indeterminate or equivocal

Interpreting Titer Results		
Titer	**Complement Fixation**	**Immunodiffusion**
1:2 or less, CSF	Positive	Positive
1:2, serum or unknown	Positive	Positive
1:4 or greater, all specimen types	Positive	Positive

N. Outbreak Definition:
An increase in cases in time or place that is greater than expected.

Investigation Guidelines

O. Time Frame[25]:
Providers must submit a report to the Local Health Department within 5 working days after a case or suspect case is diagnosed, treated, or detected. Laboratories must submit a report to ADHS within 5 working days after obtaining a positive test result. Laboratories must submit an isolate or specimen, as applicable, only by request. Local health agencies must submit a report to ADHS after conducting an epidemiological investigation of an outbreak.

P. Forms:
N/A

Q. Investigation Steps:
For a local health agency[25]:

A.A.C. R9-6-322. Coccidioidomycosis (Valley Fever)
Outbreak control measures: A local health agency shall:

1. Conduct an epidemiologic investigation of each reported outbreak of coccidioidomycosis; and
2. For each outbreak of coccidioidomycosis, submit to the Department the information required under R9-6-206(E).

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