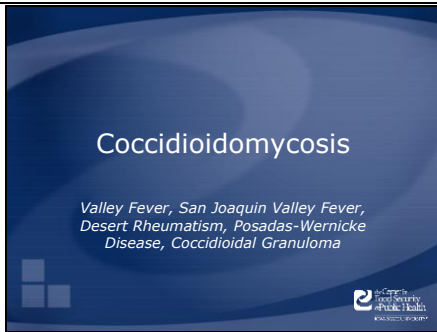


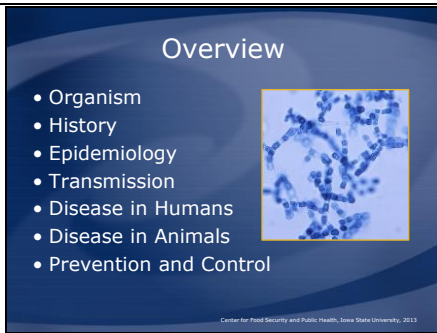
S
l
i
d
e

1



S
l
i
d
e

2



In today's presentation we will cover information regarding the organism that causes coccidioidomycosis and its epidemiology. We will also talk about the history of the disease, how it is transmitted, species that it affects (including humans), and clinical and necropsy signs observed. Finally, we will address prevention and control measures, as well as actions to take if avian coccidioidomycosis is suspected. [Photo: This photomicrograph revealed the presence of, thin, septate, hyaline or glass-like hyphae, from which numerous, thick-walled *Coccidioides immitis* arthroconidia have sprouted. The average arthrospore measures 3.0 x 4.5µm, and is barrel-shaped. Source: Dr. Lucille K. Georg/CDC Public Health Image Library]

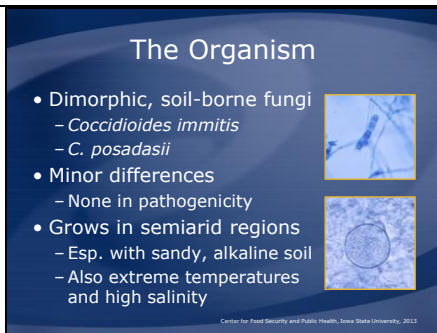
S
l
i
d
e

3



S
l
i
d
e

4



Coccidioidomycosis is caused by the dimorphic, soil-borne, fungi *Coccidioides immitis* and *C. posadasii*. *Coccidioides immitis* (typically found in California) and *Coccidioides posadasii* (typically found outside California). *C. immitis* and *C. posadasii* differ in some characteristics such as their tolerance to heat and salt, but no differences in their pathogenicity have been recognized. *C. immitis* and *C. posadasii* are soil saprophytes (an organism, especially a fungus or bacterium, that grows on and derives its nourishment from dead or decaying organic matter) that grow in semiarid regions with sandy, alkaline soils. In their mycelial (mold) form, these organisms can grow under environmental extremes, including alkaline conditions, extreme temperatures and high salinity, that other organisms cannot tolerate; however, they compete poorly with other soil fungi and bacteria outside their usual niche. [Photo: (Top) Magnified 500X, this photomicrograph revealed the presence of thin, septate, hyaline or glass-like hyphae, from which numerous, thick-walled *Coccidioides immitis* arthroconidia have sprouted. The average arthrospore measures 3.0 x 4.5µm, and is barrel-shaped. (Bottom) This photomicrograph revealed the presence of a round, thick-walled, spherule-staged *Coccidioides immitis* fungal organism. Source: Lucille Georg/CDC Public Health Image Library]

S
l
i
d
e
5

Life Cycle

- Two asexual reproductive structures
 - Arthroconidia
 - Grows in environment
 - Infectious to humans/animals
 - Spherules with endospores
 - In the body

The diagram illustrates the life cycle of *Coccidioides* spp. It shows two main stages: environmental and host. In the environment, arthroconidia (arthrospores) are produced and can germinate into a growing arthroconidium. In the host, an infective propagule enters the body, forming a spherule. Inside the spherule, endospores develop and eventually separate, forming a separated spherule. The spherule eventually ruptures, releasing endospores, which can then form a new spherule or separate spherule.

Center for Food Security and Public Health, Iowa State University, 2013

Coccidioides spp. are propagated by two asexual reproductive structures – arthroconidia (arthrospores) and endospores. Arthroconidia are produced by the mold form growing in the environment, and are dispersed by the wind. They germinate to form new mycelia if the environmental conditions are appropriate. Arthroconidia are also infectious for humans and animals, which are accidental hosts. Mature arthroconidia are extremely resistant to adverse conditions, and can survive for months or years in the soil and dust. Inside the body (usually in the lungs), arthroconidia become spherules. As each spherule enlarges, endospores develop inside it. The spherule eventually ruptures and releases the endospores, which develop into new spherules. Endospores can also spread to other parts of the body in the blood or lymph, causing disseminated disease. If they reach the environment, endospores can form a new mold. [Photo: Life cycle of *Coccidioides*. Source: Sauabh Patil/Wikimedia Commons]

S
l
i
d
e
6

HISTORY

S
l
i
d
e
7

History

- Discovered in Argentina, 1892
 - Soldier, cutaneous lesions
- Additional research in areas of endemicity
 - San Joaquin Valley
 - Migrants from the Midwest
 - WW II military recruits, prisoners of war, Japanese held in internment camps
- Cases continue to occur in U.S.

The map shows the state of California with the San Joaquin Valley highlighted in a darker shade, indicating it as an area of endemicity for *Coccidioides*.

Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis was discovered in Argentina in 1892, in a soldier with cutaneous lesions. The disease, which is commonly known as Valley Fever, was further described in the 1930s in people who migrated to the San Joaquin Valley from the Midwest—particularly those escaping the “Dust Bowl” in Texas and Oklahoma. The disease was also studied in people affected by World War II, such as military recruits, prisoners of war, and persons of Japanese descent who were moved to camps and other areas of endemicity. Coccidioidomycosis is notifiable in 15 states, and continues to be a public health problem in endemic areas such as Arizona and California. (Source: <http://cid.oxfordjournals.org/content/44/9/1202.full>) [Photo: Map showing the location of San Joaquin Valley in California. Source: California.gov]

S
l
i
d
e
8

EPIDEMIOLOGY

S
I
d
e
g

Geographic Distribution

- Western hemisphere
 - U.S.
 - Mexico
 - Central and South America
- Endemic in southwestern U.S.
 - Arizona
 - New Mexico
 - West Texas
 - Central and Southern California

Center for Food Security and Public Health, Iowa State University, 2012

Coccidioides spp. occur in the Western Hemisphere, at latitudes between 40°N and 40°S, from California to Argentina. The distribution of these organisms is patchy. They are endemic in the southwestern U.S., including Arizona (where the incidence in humans is particularly high), parts of New Mexico, Texas (west of El Paso), and the central and southern portions of California, especially the San Joaquin Valley. The endemic area extends into Mexico, and foci of infection have been detected in Central and South American countries including Argentina, Colombia, Guatemala, Honduras, Venezuela, Paraguay and Brazil. *C. immitis* seems to be restricted to California, but it might exist in some adjacent areas of Baja California (Mexico) and Arizona. *C. posadasii* is found in the remaining regions. Whether the ranges of these two organisms overlap is not known.

S
I
d
e
1
0

Endemic Areas in the U.S.

Center for Food Security and Public Health, Iowa State University, 2012

This CDC map of the United States shows geographic variation in the prevalence of coccidioidin sensitivity in young adults. In areas of endemicity, the percent of reactors is highest. [Photo: Map shows areas in the U.S. that are endemic for Coccidioidomycosis. Source: CDC Coccidioidomycosis in the US Southwest at <http://www.cdc.gov/fungal/pdf/cocci-fact-sheet-sw-us-508c.pdf>]

S
I
d
e
1
1

Risk Factors for Infection

- Dust exposure a risk factor
- Occupational groups at risk
 - Farmers, construction workers
- Weather-related peaks
 - Wet followed by dry, windy periods
 - Earthquakes, windstorms

Center for Food Security and Public Health, Iowa State University, 2012

Individuals exposed to large amounts of dust have higher infection rates. Occupational risk groups include farmers, construction workers and archaeologists. Coccidioidomycosis is seasonal, and its incidence peaks at different times in different areas, depending on the weather patterns. The number of cases increases when a wet period, followed by a dry and windy season, results in increased growth of the fungus followed by windborne dispersion of the arthrospores. Major epidemics occur intermittently, and have been associated with large earthquakes and windstorms. The incidence of coccidioidomycosis appears to be increasing in the U.S. In Arizona, the number of new cases per 100,000 population grew from approximately 12 in 1995 to 58 in 2005.

S
I
d
e
1
2

Risk Factors for Infection

- Immunocompromised persons at risk
 - HIV-1 patients with decreased CD4 T cell counts
 - Organ transplant patients
 - Lymphoma patients
 - People receiving long-term corticosteroids
 - Pregnant women
 - Elderly

Center for Food Security and Public Health, Iowa State University, 2012

Immunocompromised persons are particularly susceptible to coccidioidomycosis. In endemic areas, this disease is common among patients who are infected with HIV and have decreased CD4 T cell counts. In the only published prospective study, which was conducted in the 1980s, almost 25% of HIV infected patients developed symptomatic coccidioidomycosis within approximately 3.5 years of monitoring. Better control of the HIV virus with antiretroviral drugs appears to have decreased the severity and incidence of coccidioidomycosis since that time. Other groups at increased risk for serious illness include organ transplant patients, lymphoma patients, people who are receiving long-term corticosteroids, pregnant women, especially in the third trimester, and the elderly. Host genes, especially MHC class II genes, seem to be important in the risk of dissemination, and an African or Asian (especially Filipino) background increases the risk of severe illness.

S
l
i
d
e

1
3

Morbidity and Mortality: Humans

- Southwest U.S.
 - Prevalence 10-70%
- Illness severity
 - 60% cases asymptomatic to mild
 - 40% cases become ill
 - 90% infections limited to lungs
- Case fatality rate
 - Varies with location of organism and treatment

Center for Food Security and Public Health, Iowa State University, 2013

Depending on the region, 10-70% of the population in the southwestern U.S. has been infected by this organism. The severity of the illness is highly variable. In 60% of cases, the infection is asymptomatic or so mild that it is not recognized; the remaining 40% become mildly to severely ill. About 90% of patients have infections limited to the lungs and recover without sequelae. The case fatality rate for disseminated coccidioidomycosis varies with the location of the organisms and the treatment. Meningitis occurs in 30-50% of patients with untreated disseminated disease, and it is almost invariably fatal without prolonged or lifelong therapy. People who have recovered from coccidioidomycosis are resistant to reinfection.

S
l
i
d
e

1
4

Number of US Valley Fever Cases, 1995-2011

Center for Food Security and Public Health, Iowa State University, 2013

An estimated 150,000 more cases go undiagnosed every year. More than 70% of cases occur in Arizona and 25% occur in California.

[Photo: Histogram of human cases of Coccidioidomycosis (Valley Fever) in the U.S. from 1995-2011. Source: CDC Coccidioidomycosis in the US Southwest at <http://www.cdc.gov/fungal/pdf/cocci-fact-sheet-sw-us-508c.pdf>]

S
l
i
d
e

1
5

Geographic Distribution of Coccidioidomycosis in persons >65 years of age, U.S., 1999-2008

Baddley JW, Winthrop KL, Patkar NM et al. Geographic Distribution of Endemic Fungal Infections among Older Persons, United States. Emerging Infectious Diseases. 2011;17(9). Center for Food Security and Public Health, Iowa State University, 2013.

[Photo: Geographic distribution of coccidioidomycosis in persons >65 years of age, United States, 1999-2008. Values are number of cases/100,000 persons-years. Source: Geographic Distribution of Endemic Fungal Infections among Older Persons, United States. John W. Baddley, Kevin L. Winthrop, Nivedita M. Patkar, Elizabeth Delzell, Timothy Beukelman, Fenglong Xie, Lang Chen, and Jeffrey R. Curtis. Emerging Infectious Diseases. 2011;17(9). Available at: <http://wwwnc.cdc.gov/eid/article/17/9/10-1987-f2.htm>]

S
l
i
d
e

1
6

TRANSMISSION

S
l
i
d
e

1
7

Transmission

- Humans, animals= accidental hosts
- Routes of transmission
 - Inhalation
 - Inoculation (penetrating objects)
 - Dust-covered fomites
- Communicability
 - Direct transmission between people or animals very rare

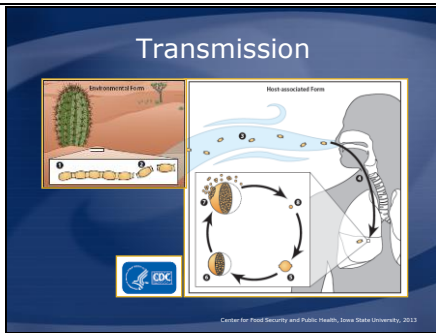
Center for Food Security and Public Health, Iowa State University, 2013

Coccidioides arthroconidia are infectious for humans and animals, which are accidental hosts. In the vast majority of cases, people or animals are infected by inhalation. Aerosolization of arthroconidia increases when contaminated soil is disturbed by humans (as in an archaeological dig or construction site) or by natural causes such as earthquakes or dust storms. Epidemics can occur when heavy rains, which promote the growth of mycelia, are followed by drought and winds. Arthroconidia can also be inoculated directly into skin, bone or other tissues by penetrating objects, but this seems to be uncommon. Dust-covered fomites have been suspected in cases that occur outside the endemic area, when there is no history of travel to these regions.

Coccidioidomycosis is ordinarily not transmitted directly between people or animals; however, there are exceptions. One person was infected during the necropsy of a horse, and another was apparently infected through broken skin while embalming a person. Recently, localized coccidioidomycosis was reported in a veterinary assistant who had been bitten by a cat. In all three cases, the infection was acquired from a person or animal with disseminated disease. *Coccidioides* spp. can be transmitted in transplanted organs. In mares, it is possible that coccidioidal abortion results from ascending infections via the vagina.

S
l
i
d
e

1
8



As previously described, in the environment, *Coccidioides* sp. exists as a mold (1) with septate hyphae. The hyphae fragment into arthroconidia (2), which measure only 2-4 μm in diameter and are easily aerosolized when disturbed (3). Arthroconidia are inhaled by a susceptible host (4) and settle into the lungs. The new environment signals a morphologic change, and the arthroconidia become spherules (5). Spherules divide internally until they are filled with endospores (6). When a spherule ruptures (7) the endospores are released and disseminate within surrounding tissue. Endospores are then able to develop into new spherules (6) and repeat the cycle.

[Photos: Biology/Transmission of Coccidioidomycosis. Source: Centers for Disease Control and Prevention at <http://www.cdc.gov/fungal/coccidioidomycosis/causes.html>]

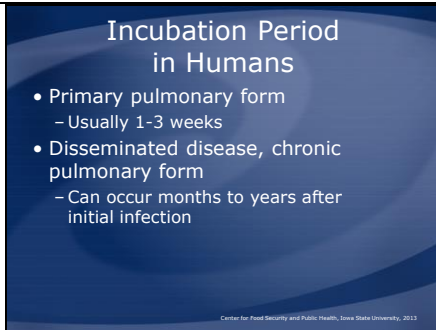
S
l
i
d
e

1
9



S
l
i
d
e

2
0




The incubation period for primary pulmonary or cutaneous coccidioidomycosis is usually one to three weeks. Disseminated disease or chronic pulmonary coccidioidomycosis can occur months or years after the initial infection.

S
l
i
d
e
2
1

Primary Pulmonary Coccidioidomycosis

- Acute disease form
 - Most asymptomatic or mild
- Symptomatic disease
 - Often flu-like
 - May resemble pneumonia
 - Skin lesions
 - 10-50% of patients with pulmonary disease



Center for Food Security and Public Health, Iowa State University, 2013


Acute infections in the lungs (primary pulmonary coccidioidomycosis) can be asymptomatic or so mild that they are unrecognized. In symptomatic cases, the illness is often flu-like, with fever, fatigue, malaise, headache, sore throat, coughing and/or pleuritic chest pain. Overt signs of pneumonia may also be seen. Approximately 10-50% of patients with pulmonary disease develop skin lesions. An erythematous, macular rash may occur in the early stages, and hypersensitivity reactions can cause erythema nodosum or erythema multiforme. Erythema nodosum, which is characterized by tender, reddened nodules on the lower extremities, usually suggests that the prognosis is good.

[Photo: Erythema nodosum lesions on skin of back due to hypersensitivity to antigens of *Coccidioides immitis*. Source: CDC Public Health Image Library.]

S
l
i
d
e
2
2

Primary Pulmonary Coccidioidomycosis

- Severe disease more common if immunosuppressed
- Mild cases often self-limited
- Pulmonary nodules may persist
 - Incidental finding on chest x-rays
 - Distinguish from other conditions



Center for Food Security and Public Health, Iowa State University, 2013

Severe respiratory disease, with high fever, dyspnea and hypoxemia, is uncommon in healthy people, but more frequent in individuals who are immunocompromised. It may progress to acute respiratory distress syndrome or respiratory failure. Milder cases of primary pulmonary coccidioidomycosis are self-limited and often resolve within a few weeks, although the fatigue may persist for weeks or months. A condition that mimics septic shock has also been reported, and has a high mortality rate. Nodules, which are often solitary, or thin-walled cavities may persist after the resolution of pulmonary disease. They are usually an incidental finding on chest x-rays, but must be distinguished from neoplasia and tuberculosis or other granulomatous conditions.

[Photo: This chest x-ray shows the effects of a fungal infection, coccidioidomycosis. In the middle of the left lung (seen on the right side of the picture) there are multiple, thin-walled cavities (seen as light areas) with a diameter of 2 to 4 centimeters. To the side of these light areas are patchy light areas with irregular and poorly defined borders. Source: Medline Plus at <http://www.nlm.nih.gov/medlineplus/ency/imagepages/1600.htm>]

S
l
i
d
e
2
3

Progressive Pulmonary Coccidioidomycosis

- Clinical signs do not resolve
 - Chronic and progressive disease
- Lesions
 - Nodular or cavitory in lungs
 - Cavitory lung disease with fibrosis
 - Miliary pulmonary dissemination
- Disease usually limited to respiratory tract

Center for Food Security and Public Health, Iowa State University, 2013

In progressive pulmonary coccidioidomycosis, the clinical signs do not resolve, but develop into chronic and progressive disease. Nodular or cavitory lesions, cavitory lung disease with fibrosis, or miliary pulmonary dissemination may be seen. Even when the lungs are extensively involved, the disease usually remains limited to the respiratory tract.

S
l
i
d
e
2
4

Disseminated Coccidioidomycosis

- Small percentage of cases
- Often acute
 - Can be rapidly fatal without treatment
- May also progress slowly
 - Periods of remission and recurrence
- Tissues affected
 - Skin, regional lymph nodes, bones, joints, visceral organs, testes
 - Clinical signs vary

Center for Food Security and Public Health, Iowa State University, 2012

Disseminated coccidioidomycosis occurs in a small percentage of cases, and may develop weeks, months or years after the primary infection. It is usually acute, and can be rapidly fatal without treatment, but it may also progress more slowly with periods of remission and recurrence. The skin, regional lymph nodes, bones and joints are most often affected in humans, but virtually any tissue or organ including the visceral organs and testes may be involved. The clinical signs vary with the affected tissues. A wide variety of lesions may be seen when the fungus disseminates to the skin. The head, neck and chest are most often involved. The lymph nodes and musculoskeletal system can also be affected.

S
l
i
d
e
2
5

Disseminated Coccidioidomycosis: Coccidioidal Meningitis

- Symptoms
 - Fever, headache, cognitive impairment
 - Inflammation can lead to vasculitis, stroke, or hydrocephalus
- Untreated cases
 - Death almost always within 2 years
- Other possible outcomes
 - Encephalitis, mass-occupying lesions, brain abscesses, aneurysms

Center for Food Security and Public Health, Iowa State University, 2012

In people, dissemination to the central nervous system (CNS) usually results in coccidioidal meningitis. The symptoms may include fever, headache and signs of meningeal irritation. Cognitive impairment or personality changes are possible, and inflammation can result in complications of vasculitis, stroke or hydrocephalus. Untreated cases of coccidioidal meningitis almost always end in death within two years. Less often, dissemination to the CNS may result in encephalitis, mass-occupying lesions, brain abscesses or aneurysms.

S
l
i
d
e
2
6

Primary Cutaneous Coccidioidomycosis

- Rare
 - Caused by direct skin inoculation
- Lesions
 - Chancriform ulcerated nodule/plaque
 - Can spread along lymphatics and cause regional lymphadenopathy
- Often heals spontaneously if immunocompetent

Center for Food Security and Public Health, Iowa State University, 2012

Primary cutaneous coccidioidomycosis, the result of direct inoculation into the skin, is rare. The initial lesion may be a chancriform ulcerated nodule or plaque. The infection spreads along the lymphatic vessels, and may be accompanied by regional lymphadenopathy. The lesions often heal spontaneously within a few weeks if the person is immunocompetent. Osteomyelitis can be caused by direct inoculation of the bone from a penetrating object.

S
l
i
d
e
2
7

Coccidioidomycosis in the Immunosuppressed

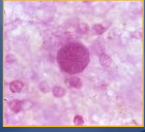
- More susceptible to infection
- Previous infections can be reactivated
- Symptoms of disease
 - Fatal pulmonary disease most common
 - Other sites may be affected if organism disseminates

Center for Food Security and Public Health, Iowa State University, 2012

Coccidioidomycosis is more likely to be serious in immunocompromised patients, especially those who have defective cell-mediated immune responses. A previous infection can also be reactivated if a person becomes immunosuppressed. HIV-1 patients with low CD4 T cell counts are at risk for disseminated or severe coccidioidomycosis. Overwhelming pulmonary disease, which is frequently fatal, is common in this group. If the organism disseminates, it may be found in multiple sites. In addition to the skin, bones, lymph nodes and meninges, other tissues such as the spleen, genitourinary system, thyroid gland, pancreas, adrenal glands, brain and transplanted organ may be involved.

Diagnosis in Humans: Direct Observation

- Visualization of organism
 - Respiratory secretions
 - Pleural fluid
 - Tissues, exudates
- Spherules
 - Most 20-80 μm
 - Contain endospores
- Multiple stains effective




Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis can be diagnosed by visualizing the organism in respiratory secretions, pleural fluid, tissues or exudates. Organisms are rarely found in cerebrospinal fluid (CSF) in cases of meningitis. In the body, *Coccidioides* spp. form spherules, double-walled structures that vary widely in abundance and size. Most spherules are 20-80 μm in diameter, but some can be as large as 200 μm . They contain endospores, small, 2-5 μm globular structures that develop into new spherules when they are released. Spherules containing endospores are diagnostic, while spherules without endospores are presumptive evidence for coccidioidomycosis. Multiple stains can be used.

[Photo: This photomicrograph revealed some of the histopathologic characteristics found within a pus specimen, which was prepared using periodic acid-Schiff (PAS), and which had been harvested from a skin lesion in a case of cutaneous coccidioidomycosis. This particular specimen shows a chlamydo-spore, or immature spherule of a *Coccidioides immitis* fungal organism. As the reproductive structure, this spherule contains the organism's endospores. Source: CDC Public Health Image Library]

Diagnosis in Humans: Culture

- Body fluids, exudates, tissues
- Selective and non-selective media
- Colony morphology
 - Floccose, white or buff, variable texture
- Arthroconidia
 - Barrel-shaped
 - 2-4 μm wide
 - Multinucleated



Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis can also be diagnosed by culturing affected body fluids, exudates or tissue specimens. *C. immitis* and *C. posadasii* can grow on most fungal media; selective and non-selective media should be used. Mold colonies can usually be detected within 4-5 days. When they first appear, the colonies are often gray and membranous and may be difficult to recognize. Older colonies are usually floccose and variable in texture. They become white or buff, but can develop other colors as they age. The hyphae are hyaline and septate. Arthroconidia are not found in young colonies, but develop as the colony ages, and can be used for presumptive identification. They tend to be barrel-shaped and are approximately 2 to 4 μm in width, thick-walled and usually multinucleated. When combined with serology, or with the detection of endospores inside spherules on direct microscopy, the presence of arthroconidia is diagnostic.

[Photo: Sabouraud's dextrose agar culture of *Coccidioides immitis* with chloramphenicol and cycloheximide after 2 wks. Source: CDC Public Health Image Library]

Diagnosis in Humans: Serology

- Assays
 - ELISA
 - Immunodiffusion
 - Complement fixation
- IgG titer correlated with severity
- Limitations
 - Early cases may be seronegative
 - Immunocompromised patients may have poor immune responses

Center for Food Security and Public Health, Iowa State University, 2013

Serological assays include enzyme-linked immunosorbent assays (ELISA) and immunodiffusion, which can detect both IgM and IgG, and complement fixation, which detects IgG. A quantitative complement fixation or quantitative immunodiffusion test can be used to monitor changes in IgG titers. Specific IgM can usually be detected within 1-3 weeks after infection. Specific IgG can be found starting 2-3 weeks after exposure, but in some patients it can take several months to develop. Early cases may be seronegative, and immunocompromised patients may have poor immune responses. IgG titers are usually correlated with the severity of the infection in humans, and high or increasing titers may suggest dissemination. The detection of antibodies in CSF is often the only way to diagnose coccidioidal meningitis, because organisms are rarely found in this condition.

S
l
i
d
e

3
1

**Diagnosis in Humans:
Additional Tests**

- Coccidioidin/spherulin skin test
 - Epidemiological studies
 - Reagents no longer available
- PCR
 - Assays in development

Center for Food Security and Public Health, Iowa State University, 2013

The coccidioidin or spherulin skin test was used extensively in epidemiologic studies at one time, but the reagents are no longer available in the U.S. This test indicates past as well as current infections. Polymerase chain reaction (PCR) assays are in development.

S
l
i
d
e

3
2

Treatment in Humans

- Options
 - Antifungal drugs
 - Surgical excision/debridement
- Some cases may resolve without treatment
- Lifetime treatment may be necessary
 - E.g., HIV-1 infected patients with low CD4 cell counts

Center for Food Security and Public Health, Iowa State University, 2013

Options for treatment range from observation to antifungal drugs, depending on the severity of the disease and risk factors for dissemination. Azoles such as fluconazole, itraconazole and ketoconazole, as well as amphotericin B, may be used. Surgical excision or debridement may occasionally be employed in disseminated cases or enlarging pulmonary cavitory lesions. Treatment may not be necessary for patients with primary coccidioidomycosis, as most cases resolve on their own and antifungal drugs can have side effects. However, some physicians recommend treatment in all symptomatic cases to decrease the duration or intensity of the illness. In some cases (such as meningitis or an infection in an HIV-1 infected patient with a low CD4 cell count), lifetime treatment may be needed to prevent relapses.

S
l
i
d
e

3
3



DISEASE IN ANIMALS

S
l
i
d
e

3
4

Species Affected

- Clinical cases common
 - Dogs, llamas
 - Non-human primates
- Disease less common
 - Cats
 - Horses
- Disease rare
 - Cattle, sheep, pigs

Center for Food Security and Public Health, Iowa State University, 2013

Coccidioides spp. infections have been reported in many domesticated, captive exotic or wild mammals, as well as in some reptiles. Clinical cases are relatively common in dogs, llamas, nonhuman primates, and many nonnative species kept in zoos in endemic regions. They are also seen in cats and horses. Overt disease has rarely been documented in cattle, sheep or pigs, although lung lesions may be found at slaughter. Among wild animals, severe or fatal illness has been seen in sea otters, a bottlenose dolphin and cougars, and lesions have been reported in other species including coyotes, nine-banded armadillos (*Dasypus novemcinctus*) and desert rodents. *Coccidioides* spp. do not seem to affect birds. [Photo: (Top) German Shepherd. Source: Public Domain, www.pixabay.com; (Bottom) Llama. Source: JohannDreo/WikimediaCommons]

S
I
d
e
3
5

Incubation in Animals

- Primary pulmonary infection
 - Usually symptomatic within 1-4 weeks
- Disseminated disease
 - Months to years after initial exposure
- Illness similar to human disease
 - Primarily respiratory disease
 - Dissemination to any tissue/organ occurs (varies by species)

Center for Food Security and Public Health, Iowa State University, 2012

Primary pulmonary infections usually become symptomatic one to four weeks after exposure, while disseminated disease can occur months to years later. *Coccidioides* spp. infections in animals vary from asymptomatic to severe and fatal. As in humans, coccidioidomycosis is primarily a respiratory disease, but in some cases, the organisms disseminate to other tissues. The most common sites of dissemination vary with the species, but nearly any tissue or organ can be affected. Dissemination may or may not be accompanied by signs of systemic illness.

S
I
d
e
3
6

Disease in Dogs

- Infection may be subclinical
- Clinical disease
 - Primary pulmonary most common
 - Chronic cough
 - Weight loss
 - Solitary lung nodules
 - Disseminated disease
 - Bones (appendicular skeleton)
 - CNS (granulomatous)



Center for Food Security and Public Health, Iowa State University, 2012

Many dogs may be infected subclinically. Primary pulmonary infection is the most common form in dogs that become ill. Affected animals often have a chronic cough, which may be dry, or moist and productive. Weight loss and anorexia are common. Lung lesions, including solitary nodules similar to those found in humans, can be seen in some asymptomatic dogs. *Coccidioides* spp. disseminates most often to the bones, especially those of the appendicular skeleton, and causes lameness and pain. Other reported sites of dissemination include the lymph nodes, skin, subcutaneous tissues, CNS, heart, liver, spleen, kidney, eyes, testes and prostate gland. In dogs, CNS invasion in dogs is usually characterized by granulomatous lesions rather than meningitis, and seizures are the most common sign. [Photo: (Top) X-ray of coccidioidomycosis in dog lung and chest cavity. (Bottom) Coccidioidomycosis in bone of dog. Source: The University of Arizona, Valley Fever Center for Excellence at <https://www.vfce.arizona.edu/valleyfeverinpets/vfid-symp.aspx>]

S
I
d
e
3
7

Morbidity and Mortality: Dogs

- Infection common in endemic areas
 - 70% infections subclinical
 - Young dogs most affected
 - Outdoor exposure a risk factor
 - Disease occurs in 20% of symptomatic dogs

Center for Food Security and Public Health, Iowa State University, 2012

Coccidioides spp. infections seem to be common among dogs in endemic areas. Approximately 70% of these infections are estimated to be subclinical. Infections are more common in young adult dogs and those that spend more time outdoors. Disease is estimated to occur in 20% of symptomatic dogs, but higher percentages have been reported in some studies. There are no long-term studies to determine whether recrudescence occurs in asymptotically infected dogs.

S
I
d
e
3
8

Disease in Cats

- Clinical disease
 - Skin lesions most common
 - Non-healing dermatitis
 - Ulcers, masses, abscesses
 - Regional lymphadenopathy
 - Other non-specific signs
- Sites of dissemination
 - Similar to dogs
 - Clinical signs variable

Center for Food Security and Public Health, Iowa State University, 2012

In cats, skin lesions seem to be the most common presenting sign. They may appear as non-healing dermatitis, ulcers, masses, abscesses or chronic draining tracts. Regional lymphadenopathy is possible, and non-specific signs such as fever, lethargy, weight loss and anorexia are common. Severe weight loss can be the only sign in some cats. Many cats have lung lesions without these signs. Other sites of dissemination are similar to the dog, although the bones do not seem to be involved as often. As in dogs, dissemination to the CNS usually causes granulomas; however, the clinical signs are more variable in cats, and may include incoordination, seizures, hyperesthesia, and changes in behavior. Ocular disease can also be seen.

S
l
i
d
e
3
9

Morbidity and Mortality: Cats

- Few reported cases
 - May be resistant compared to dogs
- Recognized clinical cases often serious
 - Middle-aged cats
- No link to immunosuppression
 - FIV, FeLV



Center for Food Security and Public Health, Iowa State University, 2013

Fewer cases of coccidioidomycosis have been reported in cats than dogs, and it is possible that they are more resistant to disease. However, clinical cases that are recognized in cats are often serious. Illness seems to be most common in middle-aged cats. In one study, there was no apparent link to feline leukemia virus or feline immunodeficiency virus infection.

[Photo: Cat. Source: Christing Majul/Flicker Creative Commons]

S
l
i
d
e
4
0

Disease in Horses

- Most reported cases disseminated
- Pulmonary disease
- Other signs
 - Osteomyelitis
 - Mastitis
 - Abortion
 - Cutaneous/soft tissue
 - Weight loss



Center for Food Security and Public Health, Iowa State University, 2013


Relatively few cases of coccidioidomycosis in horses have been published, and most have been of disseminated disease. However, the spectrum of illness includes pulmonary disease, with or without pleural or pericardial effusion, as well as osteomyelitis, mastitis, abortion, disseminated infection, and cutaneous or soft tissue lesions such as abscesses. In one study, chronic weight loss was the most common sign in horses. Abortions seem to occur with or without respiratory signs, and some authors have suggested that they might be a form of localized disease. Primary cutaneous infections might also occur in horses.

[Photo: Horse. Source: USDA]

S
l
i
d
e
4
1

Disease in Other Species

- Llamas
 - Particularly susceptible
 - Disseminated disease
- Other species
 - Cattle, sheep, pigs
 - Overt illness rare
 - Lesions suggestive of self-limited pulmonary infection seen at slaughter



Center for Food Security and Public Health, Iowa State University, 2013

Llamas seem to be particularly susceptible to coccidioidomycosis, and disseminated disease has been reported in this species. Overt illness has rarely been reported in cattle, sheep or pigs, but lesions suggestive of self-limited pulmonary infections can be seen in the lungs and thoracic lymph nodes at slaughter.

[Photo: Llama. Source: Gavin Schaefer/Wikimedia Commons]

S
l
i
d
e
4
2

Morbidity and Mortality: Horses, Ruminants, Pigs

- Horses
 - 4% healthy horses seropositive in endemic regions
- Cattle
 - Lesions detected at slaughter
 - 5-15% in Arizona, 2.5% in Mexico
 - 14% seropositive in Mexico
- Swine
 - 12% seropositive in Mexico


Center for Food Security and Public Health, Iowa State University, 2013

Little is known about the prevalence of coccidioidomycosis in horses. A recent survey found that only 4% of healthy horses in endemic regions were seropositive. Clinical cases are rarely seen in cattle, sheep or pigs, but asymptomatic infections may be common. Lesions have been reported in 5-15% of cattle slaughtered in some parts of Arizona, and in 2.5% of cattle slaughtered in Mexico. In some endemic regions of Mexico, 12% of the swine and 13% of the cattle were seropositive, and approximately 7% of cattle tested positive with the coccidioidin skin test.

S
l
i
d
e
4
3

Disease in Other Animals

- Asymptomatic lesions occur in wide variety of species
 - Captive exotic animals
 - Canids
 - Felids
 - Bats
 - Wallabies
 - Kangaroos
 - Tapirs
 - Non-human primates



Center for Food Security and Public Health, Iowa State University, 2013

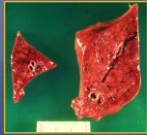
Asymptomatic lesions or clinical signs can occur in a wide variety of other species. Fatal coccidioidomycosis has been reported in captive exotic animals including canids, felids, bats, wallabies, kangaroos, tapirs, Przewalski's horses and many species of nonhuman primates, as well as in wild cougars. Disseminated coccidioidomycosis was also documented in several southern sea otters (*Enhydra lutris nereis*) that were found moribund or dead in coastal waters of California, and in an emaciated, sick bottlenose dolphin in this region. In wild coyotes, lesions were reported as an incidental finding.

[Photo: Wallaby, kidney. The kidney is distorted by multiple variably-sized firm pale raised nodules (granulomas). Source: Dr. C. Andreasen, Iowa State University, College of Veterinary Medicine, Department of Veterinary Pathology]

S
I
i
d
e
4
4

Post Mortem Lesions

- Lungs
 - Variable foci of inflammation
 - Discrete nodules
 - Firm, grayish cut surface
 - Mineralized foci
- Effusions
 - Slightly cloudy, tinged red
- Lymph nodes
 - Firm, swollen



Center for Food Security and Public Health, Iowa State University, 2013


Gross lesions may be either disseminated or limited to the lungs, mediastinum and thoracic lymph nodes. The lungs are often involved, even in disseminated disease where the primary complaint is not respiratory. The lesions are characterized by foci of inflammation, which may be red to yellow, gray or white; miliary or nodular; and firm, caseous or liquefactive. Discrete nodules of variable size with a firm, grayish cut surface are often found. Mineralized foci may also be present. Effusions caused by *Coccidioides* spp. are slightly cloudy, and are frequently tinged with red. If the heart is involved, the pericardium may be thickened and fibrotic, and it can be adhered to the epicardium. Affected lymph nodes are firm and swollen. Varying placental lesions have been reported in horses that aborted.

[Photo: Dog, lung. Cross section of lung reveals multifocal to coalescing pale firm areas (granulomas). Source: Armed Forces Institute of Pathology/CFSPH]

S
I
i
d
e
4
5

Diagnosis in Animals

- Multiple tests may be required
 - Cytology
 - Histopathology
 - Culture
 - Serology
 - Radiographs
 - Other advanced imaging
- Trial with antifungal drugs



Center for Food Security and Public Health, Iowa State University, 2013

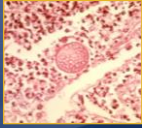
Establishing a diagnosis of coccidioidomycosis may be challenging in animals, and multiple tests including cytology, histopathology, culture and serology may be necessary. Adjunct tests such as radiographs can be helpful. Pulmonary lesions and hilar lymphadenopathy may be identified in small animals with respiratory disease, while animals with bone disease have lytic and proliferative lesions, with periosteal new bone formation. Advanced imaging studies may be useful in some cases. A trial with antifungal drugs is sometimes used to establish a presumptive diagnosis when other methods fail or are unacceptably invasive (e.g., a granuloma in the brain).

[Photo: This photograph depicted a slant culture growing *Coccidioides immitis* fungal organisms on a medium of glucose Phytone™, yeast extract, while contained within a 25 X 150mm test tube. Source: Lucille Georg/CDC Public Health Image Library]

S
l
i
d
e
4
6

Diagnosis in Animals: Direct Observation

- Visualization of parasite
 - Tissues, exudates, transtracheal or bronchoalveolar lavage fluids, lymph nodes, pleural fluids
- Spherules
 - Double-walled
 - Most 20-80 μm
 - Contain endospores
- Multiple stains effective



Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis can be diagnosed by visualizing the parasites in tissues, exudates, transtracheal or bronchoalveolar lavage fluids, lymph nodes and pleural fluid. In the body, *Coccidioides* spp. form spherules, double-walled structures that vary widely in abundance and size. Most spherules are 20-80 μm in diameter, but some can be as large as 200 μm . They contain endospores, small, 2-5 μm globular structures that develop into new spherules when they are released. Spherules containing endospores are diagnostic, while spherules without endospores are presumptive evidence for coccidioidomycosis. In rare cases, the organisms may form hyphae in tissues or air spaces in the lung. As in humans, multiple stains can be used.

[Photo: Histopathology of coccidioidomycosis of lung - mature spherule with endospores of *Coccidioides immitis*. Source: CDC Public Health Image Library]

S
l
i
d
e
4
7

Diagnosis in Animals: Culture

- Body fluids, exudates, tissues
- In-house culture not advised
- Selective and non-selective media
- Colony morphology
 - Older colonies
 - Floccose, white or buff, variable texture
- Arthroconidia
 - Barrel-shaped, 2-4 μm wide, multinucleated

Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis can also be diagnosed by culturing affected body fluids, exudates or tissue specimens. In-house fungal culture is not advisable, because the arthroconidia from mature cultures are readily aerosolized and inhaled. Several types of media can be used. As in humans, colonies can usually be detected within 4-5 days. Young colonies are often gray and membranous, becoming white or buff, floccose, and variable in texture as they age. The hyphae are hyaline and septate. Arthroconidia, which develop with age, tend to be barrel-shaped and are 2 to 4 μm in width, thick-walled and usually multinucleated. When combined with the presence of spherules containing endospores on direct microscopy, the presence of arthroconidia is diagnostic. Genetic probes to confirm the organism's identity are used routinely in human laboratories, but veterinary laboratories will usually only report the presence of arthroconidia.

S
l
i
d
e
4
8

Diagnosis in Animals: Serology

- Techniques and interpretation not well established in animals
- Assays
 - AGID (most used)
 - ELISA
 - Latex particle agglutination
- IgM: 2-5 weeks; IgG: 8-12 weeks
- IgG titer not linked to severity

Center for Food Security and Public Health, Iowa State University, 2013

Serology can be useful, but the techniques and their interpretation are not as well established in animals as humans. Agar gel immunodiffusion (AGID) assays for IgG and IgM are the most frequently used serological tests. ELISAs to detect IgM and IgG and the latex particle agglutination (LA) test for IgM are more sensitive than AGID, but can have false-positive results. In dogs and cats, positive results in these tests should be confirmed with AGID. In infected dogs, IgM can usually be detected within 2 to 5 weeks, and IgG develops approximately 8 to 12 weeks after infection. Unlike humans, the magnitude of the IgG titer does not seem to correlate with the severity of the disease in dogs, and titers in symptomatic and subclinically infected animals overlap. Serology may be a weak diagnostic tool in cats. In horses, limited studies suggest that even low titers may indicate active infections in horses if there are clinical signs.

S
l
i
d
e
4
9

Treatment in Animals

- Antifungal drugs
 - Common practice
 - Regimen can be problematic
 - Adverse effects
 - Long term treatment required
 - Useful drugs
 - Amphotericin B, Ketoconazole, Itraconazole, Fluconazole

Center for Food Security and Public Health, Iowa State University, 2013

Dogs and cats with clinical coccidioidomycosis are usually treated with antifungal drugs. It is not known how many animals with primary respiratory disease would recover on their own, but significant numbers of dogs developed disseminated disease before oral antifungals became available. For this reason, treatment became common practice. There is some debate about this practice, since these drugs can have adverse effects and must often be given for months.

Antifungal drugs that have been used in dogs and cats include amphotericin B and azole drugs such as ketoconazole, itraconazole and fluconazole. There are a few reports of successful treatment of horses with conditions such as pulmonary coccidioidomycosis or vertebral osteomyelitis. Most animals are treated for at least 6-12 months. In disseminated disease, treatment is often continued for one to several years. Relapses can be seen.


S
l
i
d
e
5
0

PREVENTION AND CONTROL

S
l
i
d
e
5
1

Prevention in Humans

- Difficult to prevent in endemic areas
- Dust control
 - Pave dirt roads
 - Seed lawns
 - Dampen dust with oil
- Prophylactic drug treatment
- Screen transplant patients
- No vaccine available



Center for Food Security and Public Health, Iowa State University, 2013

Coccidioidomycosis is difficult to prevent in endemic areas; however, reducing exposure to airborne dust may be helpful. Dust control measures such as paving dirt roads, seeding lawns and dampening dust with oil have been reported to decrease the number of cases in military personnel. People at risk for severe disease may, in some cases, be given prophylactic drug treatment. Transplant programs in endemic areas conduct screening programs for coccidioidomycosis. If the recipient or donor has been infected, prophylaxis or treatment may be recommended. Although vaccines are in development, no vaccine is currently available. [Photo: Agricultural dusts. Sourc: OSHA]

S
l
i
d
e
5
2

Prevention in Humans

- Transmission via animal and humans very rare
 - Still, follow ordinary safety precautions
- Fomites
 - Clean and disinfect
 - Destroy if cannot be decontaminated
- Laboratory
 - Do not culture in-house
 - BSL2 or 3 required


Center for Food Security and Public Health, Iowa State University, 2013

Coccidioides spp. are not normally acquired from other people or from animals. However, there are rare reports of cases transmitted in an animal bite or after contact with tissues at necropsy, and ordinary safety precautions should not be neglected. Contaminated objects that could support the growth of the mycelial form should be decontaminated or destroyed promptly, before arthrospores can form. Clinical specimens in the endemic area should be sent to a diagnostic laboratory; in-house fungal culture is not advisable because arthroconidia from mature cultures are readily aerosolized and inhaled. Plates that are more than 3-5 days old are more likely to have arthroconidia, and are more dangerous. Biosafety level 2 practices with negative air pressure and a class II biological safety cabinet have been recommended for laboratories working with *Coccidioides* spp., but some sources suggest biosafety level 3 for all fungal laboratories

S
I
d
e
5
3

Prevention in Animals

- Limit animal's exposure to large concentrations of arthroconidia
 - Desert soils
 - Areas of soil disturbance
 - Dust storms following rain
 - Other dusty conditions
- No vaccine available



Center for Food Security and Public Health, Iowa State University, 2013


Prevention is difficult in endemic areas, but it might be helpful to limit the animal's exposure to large concentrations of arthroconidia, such as those in desert soils, areas of soil disturbance and dusty conditions. Dust storms after a rainy season may contain especially high concentrations of aerosolized spores. No vaccine is available.

[Photo: Horses in dust. Source: RobThomes-Flickr Creative Commons]

S
I
d
e
5
4

Disinfection

- Halogens
 - Iodine
 - Chlorine
 - Hypochlorite/bleach
- Phenolics
- Quaternary ammonium compounds
- Moist heat
 - 121°C for a minimum of 15 minutes



Center for Food Security and Public Health, Iowa State University, 2013

Although fungal agents are highly resistant to most disinfectants, halogens (such as iodine, and chlorine in the form of hypochlorite [bleach]), phenolics (such as Tek-Trol), and quaternary ammonium compounds (Di-Quat 10-S and Roccal-D Plus) have proven effective against *Coccidioides* spp. Arthroconidia are resistant to dry heat, but they can be inactivated by moist heat (121°C for a minimum of 15 minutes).

[Photo: Disinfection supplies. Source: Danelle Bickett-Weddle, Iowa State University/CFSPH]

S
I
d
e
5
5

Additional Resources

- Center for Food Security and Public Health
 - www.cfsph.iastate.edu
- Centers for Disease Control and Prevention
 - <http://www.cdc.gov/fungal/coccidioidomycosis/>
- Valley Fever Center for Excellence, University of Arizona
 - <https://www.vfce.arizona.edu/Default.aspx>

Center for Food Security and Public Health, Iowa State University, 2013

S
I
d
e
5
6

Acknowledgments

Development of this presentation was made possible through grants provided to the Center for Food Security and Public Health at Iowa State University, College of Veterinary Medicine from the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, the Iowa Homeland Security and Emergency Management Division, and the Multi-State Partnership for Security in Agriculture.

Authors: Kerry Leedom Larson, DVM, MPH, PhD, DACVPM; Anna Rovid Spickler, DVM, PhD
Reviewer: Glenda Dvorak, DVM, MPH, DACVPM

Last updated: June 2013