Coccidioidomycosis

Coccidiomycosis,
Valley Fever,
San Joaquin Valley Fever,
Desert Rheumatism,
Posadas-Wernicke Disease,
Coccidioidal Granuloma

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Importance

Coccidioidomycosis is a fungal disease, almost always acquired from the environment, that can affect many species of mammals and some reptiles. This fungus is endemic in the soil in parts of the Americas, particularly the southwestern United States, Mexico, and some regions of Central and South America. Its distribution is patchy, but in some "hot spots," up to 70% of the human population may have been infected. Most infections in people are relatively mild or asymptomatic, but severe or fatal illness also occurs, especially in the elderly or immunocompromised. Among animals, coccidioidomycosis seems to be particularly common in dogs, which have a spectrum of illness similar to humans, and South American camelids, but clinical cases have also been reported in many other species, including both domestic animals and captive or free-living wildlife.

Etiology

Coccidioidomycosis is caused by the dimorphic, soil-borne, ascomycete fungi *Coccidioides immitis* and *C. posadasii* (formerly known as the "California" and "non-California" populations of *C. immitis*). *C. immitis* and *C. posadasii* differ in some characteristics such as their *in vitro* tolerance to heat and salt, but they cause the same illnesses and do not seem to differ in virulence.

Species Affected

Coccidioides spp. infections have been reported in many mammals, as well as some snakes and lizards. Clinical cases have predominantly been described in dogs, South American camelids, nonhuman primates, and various nonnative species kept in zoos in endemic regions. They are also seen occasionally in cats and horses. Overt disease has rarely been documented in cattle, sheep or pigs, although lung lesions may be found at slaughter. Sporadic clinical cases or subclinical lesions have been reported in diverse free-living wildlife, including cougars (*Puma concolor*), coyotes (*Canis latrans*), nine-banded armadillos (*Dasypus novemcinctus*), some desert rodents, sea otters (*Enhydra lutris*), a bottlenose dolphin, a koala (*Phascolarctos cinereus*) and bats. Many cases in free-living wildlife are probably missed.

Coccidioides spp. do not seem to affect birds, though one report identified an apparent outbreak of coccidioidomycosis in moribund and dead chickens in Nigeria, based on the organism's morphology alone. Whether a fungus that resembles *Coccidioides* might exist in parts of Africa (see additional information in Geographic Distribution), or rare infections in birds might have been overlooked is currently unclear.

Zoonotic potential

C. immitis and *C. posadasii* both affect humans.

Geographic Distribution

Coccidioides spp. are endemic in parts of the Western Hemisphere where the environment is conducive to their survival, but their distribution is patchy even in these regions. In the U.S., they are mainly found in southwestern states including Arizona, central and southern California (especially the San Joaquin Valley), New Mexico, Texas and Utah, but they have also been identified in Washington state. They are common in parts of Mexico, and foci of infection have been detected in some Central and South American countries including Argentina, Bolivia, Brazil, Colombia, Guatemala, Honduras, Paraguay and Venezuela. Although there are no recent reports of *Coccidioides* in Nicaragua, a dog from Nicaragua was imported to Norway with coccidioidomycosis in the 1950s.

The two organisms that cause coccidioidomycosis tend to occur in different locations. *C. posadasii* is the sole or major organism in most of the Americas, while *C. immitis* has a more limited distribution. The latter organism is responsible for nearly all cases in California, though *C. posadasii* is seen occasionally in South American camelids (whether these animals were infected in California is unclear). *C. immitis* has also been reported in Washington state, Utah (together with *C. posadasii*), Baja California (Mexico) and Colombia, and it might occur in parts of Arizona adjacent to California.

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There is no definitive evidence that *Coccidioides* is endemic anywhere outside the Americas; however, what appear to be locally acquired human cases suggest that these organisms might exist in China, particularly in eastern regions near the coast. There are also two reports of *Coccidioides*-like organisms in Africa, both identified by morphology alone. In one instance, organisms were reported in sick chickens in Nigeria. In the other, a fatal illness in a young boy from Sudan was diagnosed as coccidioidomycosis, though the organism could not be confirmed as *Coccidioides* in samples sent outside the country for fungal identification. Whether the African reports are of *Coccidioides* or another fungus is still unclear.

Transmission and Life Cycle

C. immitis and *C. posadasii* are soil saprophytes usually found in semiarid regions with sandy, dry soils and relatively warm winters. These organisms have been reported to tolerate air temperatures from -40°C (-40°F) to 49°C (120°F) and soil temperatures from -6.5°C (20°F) to 60.5°C (141°F). They can grow under environmental extremes, including alkaline conditions, extreme heat and high salinity, that other organisms cannot tolerate; however, they compete poorly with other fungi and bacteria outside their usual niche. They can survive for up to 6 weeks in seawater or salt water under laboratory conditions, and outbreaks have been reported in marine mammals.

In the environment, *Coccidioides* grows as a mycelium (mold) and is propagated by arthroconidia. Mycelial growth is optimal when moisture levels and organic matter are high. *Coccidioides* spp. are generally thought to grow directly in the soil; however, their environmental niche is still incompletely understood, and some authors have revived a controversial hypothesis that infected small animals, particularly burrowing rodents, may play an important role when the organisms they carry contaminate the soil or produce arthroconidia in tissues after the animal's death. Arthroconidia are dispersed by the wind, and can germinate to form new mycelia if the environmental conditions are right. They are also infectious for humans and animals. Their aerosolization increases when contaminated soil is disturbed by humans (as in an archaeological dig or construction site) or natural causes such as earthquakes or dust storms. Arthroconidia are extremely resistant to adverse conditions and can survive for months or years in soil and dust. Dust-covered fomites have been suspected in some cases that occur outside endemic areas.

Animals and humans usually become infected when they inhale arthroconidia; however, these structures can also be inoculated directly into skin, bone or other tissues by penetrating objects, and they might cause ascending infections via the vagina in some mares with localized uterine infections. After entering the body, arthroconidia are transformed into spherules, which enlarge and form endospores. Mature spherules containing endospores (sporangia) eventually rupture, and the released endospores develop into new spherules. Endospores occasionally spread to other parts of the body in blood or lymph. Because endospores are large, transplacental transmission of *Coccidioides* is thought to be unlikely unless the placenta is disrupted, e.g., in placentitis; thus, most congenital infections have been attributed to contact with fungi in the vagina during birth. Nevertheless, transplacental transmission has been suspected in a few cases, and was recently demonstrated in a human infant delivered by C-section. Fungal hyphae and arthroconidia are not ordinarily found inside living animal tissues; however, they have, on rare occasions, been seen in cavitations or solid coccidiomas in the lungs, and, in at least one case, in the skin of a person with primary cutaneous coccidioidomycosis.

Coccidioides spp. can be acquired in transplanted organs, but horizontal transmission is otherwise thought to be extremely rare. The few published reports of such events include a person who became infected during the necropsy of a horse, probably by inhaling endospores; another who was apparently infected through broken skin while embalming a person; and a veterinary assistant who developed localized coccidioidomycosis at the site of a cat bite. In all three cases, the infection was acquired from a person or animal with disseminated disease. If they reach the environment (e.g., on fomites contaminated with organic matter, such as wound dressings), endospores can form a new mold.

Disinfection

Disinfectants reported to be effective against one or more stages of *Coccidioides* include sodium hypochlorite (bleach), alcohols, peracetic acid, iodophors, hydrogen peroxide (≥6%), phenolics and some quaternary ammonium compounds. The environmental forms of the organism, particularly arthroconidia, are more difficult to inactivate than spherules and endospores. In one study, 10% bleach or 70% alcohol were effective against *C. immitis* arthroconidia with contact times of 1-2 minutes, though longer times might be needed when the concentration of the organism is particularly high. The phenolic disinfectant Vesphene® IIse was not as effective: while viable arthroconidia were significantly reduced after 5 minutes, complete inactivation was estimated to require more than 20 minutes.

C. immitis and *C. posadasii* arthroconidia can also be inactivated by heating at 80°C (176°F) for 5 minutes or 65-75°C (149-167°F) for 10 minutes, while mycelia were susceptible to 30 minutes at temperatures between 65°C and 75°C. As an additional margin of safety, the authors of this study suggest heat treating arthroconidia at 80°C for 10 minutes or mycelia at this temperature for 30 minutes. Autoclaving (moist heat of 121°C/ 250°F for a minimum of 15 minutes) is also effective.

Infections in Animals

Incubation Period

Primary pulmonary infections usually become symptomatic 1-4 weeks after exposure, while disseminated disease can occur months to years after the animal was infected.

Clinical Signs

Mammals

The outcomes of exposure to *Coccidioides* range from asymptomatic infections to severe, life-threatening illnesses. Coccidioidomycosis is primarily a respiratory disease in mammals, but organisms in the respiratory tract occasionally disseminate to other parts of the body. Direct inoculation into other sites, though uncommon, can result in skin lesions, osteomyelitis or other localized conditions without pulmonary involvement.

Pulmonary coccidioidomycosis is asymptomatic in many or most cases, and resembles other respiratory diseases when it becomes symptomatic. Most clinical cases have been described in dogs. Affected dogs often have a chronic cough, which can be either dry, or moist and productive. There may also be nonspecific signs of illness including fever (in some but not all cases), anorexia and weight loss. Signs of pneumonia are possible. Lung nodules or other lesions may be found on x-ray in asymptomatically infected dogs as well as those that are sick. Cats with pulmonary coccidioidomycosis can have similar signs; however, coughing is reported to be less common, and lung lesions without respiratory signs seem to be frequent. Clinical cases have rarely been reported in cattle, sheep or pigs, though lesions suggestive of self-limited pulmonary infections may be found in the lungs and thoracic lymph nodes at slaughter. Erythema nodosum, a cutaneous hypersensitivity reaction that sometimes accompanies pulmonary infections in humans, has not been reported in any animal species.

Disseminated coccidioidomycosis can affect nearly any tissue or organ including the bones, joints, lymph nodes, skin, subcutaneous tissues, CNS, visceral organs (e.g., heart, liver, spleen, pancreas, kidney, gastrointestinal tract, peritoneum), reproductive organs (testes, prostate gland, uterus, mammary gland) and eye. The clinical signs vary with the site, and may be accompanied by persistent or fluctuating fever, depression, anorexia, regional lymphadenopathy, weight loss and other nonspecific signs. Protein-losing nephropathy from immune complex glomerulonephritis has been reported in some cases in dogs. Some animals with disseminated disease have nonspecific signs alone.

In dogs, disseminated coccidioidomycosis often affects the bones, especially those of the appendicular skeleton, and typically presents with lameness and pain. Involvement of the vertebrae can result in neurological signs such as ataxia, paresis or paralysis, as well as back or neck pain. Draining skin nodules or tracts are sometimes be found over sites of bone involvement. The bones do not seem to be involved as often in cats; however, skin lesions are common. Skin lesions in all species may appear as nodules, masses, ulcers, crusts, plaques, abscesses or chronic draining tracts, as well as non-healing dermatitis (e.g., regional erythema or papules and pustules). Nodular lesions are the most common cutaneous form in dogs and cats. Coccidioidomycosis can also affect the mucous membranes, and localized, recurrent nasal granulomas have been seen in some horses.

Dissemination of *Coccidioides* to the CNS often results in a single granuloma in the cerebrum, brainstem and/or spinal cord in dogs and cats, but recent studies have also found a significant number of dogs with diffuse meningoencephalitis. Seizures are common in dogs with CNS granulomas. Other neurological signs may include locomotor defects (ataxia, paresis, paralysis), cranial nerve deficits, and changes in mentation and/or behavior. CNS signs are reported to be more variable in cats. Organisms in the eye have caused anterior uveitis, iritis, fungal granulomas, chorioretinitis, endophthalmitis, periocular swelling and subpalpebral conjunctival inflammatory masses. Retinal detachment and blindness are possible.

Reproductive involvement has mostly been described in horses, llamas and alpacas, and can include abortions with or without respiratory signs, mastitis and the birth of offspring with disseminated disease.

Reptiles

Only a few cases have been described in reptiles. Pulmonary coccidioidomycosis, with additional lesions in the thyroid and pancreas, was seen in a Sonoran gopher snake (*Pituophis melanoleucus affinis*), and a Gila monster (*Heloderma suspectum*) at a zoo had a focal pulmonary granuloma. Incidental lesions included intestinal coccidioidomycosis, characterized by small intestinal granulomas, in a red coachwhip snake (*Masticophis flagellum piceus*) with vertebral neoplasia; pulmonary lesions in a Gila monster; and kidney lesions in a Texas indigo snake (*Drymarchon corais erebennus*). Intracoelomic inoculation of *C. immitis* into various species of lizards sometimes caused systemic infections; at other times, the organism only replicated at the inoculation site.

Post Mortem Lesions

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Gross lesions in primary pulmonary coccidioidomycosis are limited to the lungs, mediastinum and thoracic lymph nodes, while disseminated disease can affect tissues and organs throughout the body. The lungs are often involved even when the primary complaint is not respiratory. Gross lesions are characterized by foci of inflammation, which may be red to yellow, gray, white or tan; miliary or nodular; and firm, caseous or liquefactive. In many cases, there are discrete nodules of variable size with a firm, grayish cut surface. Mineralized foci may also be present. If the heart is involved, the pericardium may be thickened and fibrotic, and it may be adhered to the epicardium. Effusions caused by C*occidioides* spp. are slightly cloudy and often tinged with red. Nodules have been found in the placenta of some horses after abortions; however, in at least one case, the placenta was edematous and congested but contained no visible nodules.

Diagnostic Tests

Establishing a diagnosis of coccidioidomycosis can be challenging in some animals, and multiple tests including cytology, histopathology, culture and serology may be

necessary. PCR tests for the direct detection of organisms in clinical samples are starting to be employed in human laboratories, and may also be useful for animals, if available. Research on antigen detection tests is limited, but a few studies found that the currently available human assays were relatively insensitive in dogs. Radiographs are often helpful, and advanced imaging studies (e.g., MRI for CNS masses) may be employed in some cases. A trial with antifungal drugs is sometimes used to support a presumptive diagnosis when other methods fail or are unacceptably invasive.

Cytology of exudates, bronchoalveolar lavage fluids, lymph node aspirates or pleural fluid may sometimes reveal organisms in live animals, while histopathology is useful in biopsy samples or tissues taken postmortem. Various preparations including calcofluor white fluorescent stain, potassium hydroxide (KOH) wet mounts, Grocott-methenamine silver, periodic acid-Schiff and hematoxylin-eosin stains can be used to visualize *Coccidioides*. Organisms are also found occasionally with Giemsa, Papanicolau or mucicarmine staining, but they do not usually stain with Gram stains. *Coccidioides* spherules are double-walled structures that vary widely in abundance. They are generally around 20-80 µm in diameter, but may occasionally be as large as 200 µm. Some spherules may contain endospores, which are 2-5 µm globular structures. Free endospores can occasionally be the predominant form in a specimen, and may be confused with yeasts such as *Histoplasma*.

Culture of affected body fluids, exudates or tissue specimens is generally done in specialized laboratories; in-house fungal culture is not advisable, as the arthroconidia from mature cultures are readily aerosolized and inhaled. *C. immitis* and *C. posadasii* can grow on most fungal media as well as many media used to isolate bacteria. Because they do not compete well with other fungi or bacteria, samples with mixed flora should be plated onto selective as well as nonselective media. *Coccidioides* colonies are often gray and membranous when they first appear, but they become floccose, white or buff, and variable in texture. Other colors may be seen as they age. Arthroconidia, which are produced only in older cultures, are typically barrel-shaped, approximately 2-4 µm in width, thick-walled and multinucleated. Genetic assays to confirm the organism's identity are used routinely in human laboratories, but veterinary laboratories have traditionally only reported the presence of arthroconidia. When combined with cytologic evidence of spherules containing endospores, the presence of arthroconidia is considered diagnostic. Spherules without endospores are considered presumptive evidence for *Coccidioides*. *C. immitis* and *C. posadasii* colonies can be distinguished by PCR, but this is usually unnecessary.

Serology can be useful in animals, though studies on whether seropositive animals have active disease, and at what titers, are sometimes contradictory. Titers may not be detectable until several weeks after infection, and there are occasional reports of dogs and cats that do not seem to develop antibodies despite having active disease. Agar gel immunodiffusion (AGID) assays for IgG and IgM are the most frequently used serological tests. ELISAs to detect IgM and IgG and a latex particle agglutination test for IgM are also available. A lateral flow assay licensed for humans appears to be a promising rapid test in dogs. Cross-reactivity to other fungal agents, such as *Histoplasma*, may be an issue in some tests.

Treatment

Dogs and cats with clinical coccidioidomycosis are usually treated with antifungal drugs. It is unclear how many animals with primary respiratory disease would recover on their own, but significant numbers of dogs developed disseminated disease before antifungal agents became available. The most commonly used drugs in animals are amphotericin B and azoles such as ketoconazole, itraconazole, fluconazole and posaconazole. Other protocols, including combination treatment with an azole and terbinafine, have been tried in a few cases. In most cases, animals are treated for several months, and sometimes for a year or more. At least some cases of CNS disease are reported to respond without the need for lifetime treatment.

Control

Disease reporting

Veterinarians who encounter or suspect coccidioidomycosis should follow their national and/or local guidelines for disease reporting. State authorities should be consulted in the U.S., where coccidioidomycosis in animals is not necessarily reportable even where reporting of human cases is mandatory.

Prevention

Prevention is difficult in endemic areas, but it might be helpful to limit animals' exposure to dusty conditions and areas where large concentrations of arthroconidia might be present, such as desert soils and areas of soil disturbance. Dust storms after a rainy season may contain particularly high concentrations of organisms. Clinical cases also seem to be common in dogs taken on armadillo hunts.

Morbidity and Mortality

There is limited information about coccidioidomycosis in animals. Much of it comes from research and case reports in dogs. Risk factors associated with coccidioidomycosis in dogs include spending time outdoors and being in close contact with the soil during activities such as digging or armadillo hunts. Many dogs seem to become infected as young adults. One prospective study in an endemic area found a cumulative probability of infection of 28% by 2 years of age, while the cumulative probability of clinical signs was 6%. Another study suggested that approximately 4% of the canine population in three endemic counties in Arizona develops coccidioidomycosis each year.

As in humans, most pulmonary infections in animals are probably mild or asymptomatic and resolve without treatment. Estimates in dogs suggest that approximately 70% of infections are subclinical, a rate comparable to humans.

Likewise, lesions have been reported in 5-15% of cattle slaughtered in some parts of Arizona and 2.5% of cattle slaughtered in Mexico, though clinical cases are rarely reported in this species. About 12% of swine and 13% of cattle were seropositive in some regions of Mexico, and approximately 7% of cattle tested positive with the coccidioidin skin test. One study from an endemic region found antibodies in 4% of healthy horses, and these titers decreased or disappeared over 2-6 months without any animals becoming ill. While immunosuppression is thought to be associated with increased susceptibility to illness, a study in cats found no association between this disease and FIV or FeLV infection status.

In clinical cases, the prognosis varies with the form of the disease and the treatment. Pulmonary infections often have a good outcome, while disseminated disease is more serious. There seems to be a disproportionate number of disseminated cases in dogs compared to humans. While infections are limited to the lungs in at least 99% of healthy people, some estimates suggest that 20% or more of symptomatic dogs have disseminated disease. Similarly, many of the small number of reported cases in cats, which often affected middle-aged animals, were serious and disseminated. It might be that dogs and cats are more susceptible to coccidioidomycosis and/or exposed to higher doses of arthroconidia than humans. However it is also possible that pulmonary infections that resolve without intervention in animals are underdiagnosed. The prognosis in disseminated disease varies with the organ(s) affected. CNS disease is generally the most serious form. It is reported to respond to treatment in many dogs if diagnosed early, though relapses are possible.

Little information is available on the prognosis in other species. One study of horses reported that disseminated disease or pulmonary disease with thoracic effusion were fatal in approximately 90% of cases. Horses with pulmonary signs and no thoracic effusion were less severely affected, and two of six animals were treated successfully with antifungal drugs. The survival rate was higher in horses with cutaneous lesions, mammary abscesses, or infections of soft tissues with no evidence of lung involvement. No deaths occurred in untreated mares with coccidioidal abortion, and at least one of these animals later had healthy foals.

Infections in Humans

Incubation Period

The incubation period for primary pulmonary or cutaneous coccidioidomycosis is usually 1-3 weeks, though it can be longer. Disseminated disease can occur months or years after infection.

Clinical Signs

Pulmonary coccidioidomycosis

Acute lung infections are the most common form of coccidioidomycosis in people. Many infections are asymptomatic or so mild that they remain unrecognized. The symptoms in clinical cases are usually flu-like, and may include fever, night sweats, fatigue, malaise, headache, sore throat, coughing and/or pleuritic chest pain. Overt signs of pneumonia, as well as pleural effusion, are also possible. Severe respiratory disease, with high fever, dyspnea and hypoxemia, is uncommon in healthy people, but more frequent in immunocompromised individuals. It may progress to life-threatening acute respiratory distress syndrome or respiratory failure. In addition, there are occasional cases where the clinical signs do not resolve, but develop into chronic and progressive pulmonary disease with nodular or cavitary lesions, cavitary lung disease with fibrosis, or miliary pulmonary dissemination.

Pulmonary disease is sometimes accompanied by skin lesions caused by hypersensitivity reactions to the organism. They can include an erythematous, macular rash or urticaria, particularly in the early stages, and erythema nodosum or erythema multiforme. Erythema nodosum, which is characterized by tender, reddened nodules mainly on the lower extremities, seems to be a sign of a strong immune response, and usually suggests that the prognosis is good. The skin lesions that accompany pulmonary disease do not usually contain any organisms.

The vast majority of uncomplicated pulmonary cases are self-limited, and milder cases often resolve within a few weeks, but fatigue may persist for weeks or months. Residual pulmonary sequelae are reported to occur in approximately 5-7% of cases, and can include nodules (which are often solitary) and/ or thin-walled cavities. Nodules and cavities are usually an incidental finding on chest x-rays and are often asymptomatic; however, some patients may have coughing, chest pain and/or hemoptysis, and secondary bacterial infections are possible. It is also possible, though rare, for a cavity near the pleura to rupture and cause hydropneumothorax. Cavities may persist for years, though approximately half are estimated to eventually resolve on their own.

Disseminated coccidioidomycosis

Disseminated coccidioidomycosis affects up to 1% of healthy people and a greater percentage of those who are immunocompromised It may develop weeks, months or years after the primary infection, but typically occurs within the first few months. It is often acute, and some forms can be rapidly fatal without treatment, but it sometimes progresses 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 various visceral organs, the peritoneum, bone marrow, genitourinary tract and eye may be involved. Generalized spread and septic shock are also possible.

The clinical signs depend on the tissues affected. Skin lesions (which contain organisms) may include nodules, papules, pustules, furuncles, verrucous (wart-like) plaques, abscesses, granulomatous lesions or ulcerations. These lesions are often found on the head, neck and/or chest. Dissemination to the musculoskeletal system can result in osteomyelitis, septic arthritis and/or synovitis. Arthritis

usually affects only one joint, often a weight-bearing joint such as the knees, but it can be migratory. Subcutaneous abscesses and sinus tracts can develop near the affected bones and joints. Infected lymph nodes may become necrotic and ulcerate or drain. Ocular involvement is uncommon but can have diverse presentations including lacrimal gland fossa mass, chorioretinitis, iridocyclitis or endophthalmitis. Ocular disease has been reported in some people who have no evidence of systemic disease.

Dissemination to the CNS is especially serious, and usually presents as coccidioidal meningitis in humans. However, encephalitis, mass-occupying lesions, brain abscesses or aneurysms have also been seen. Common symptoms of coccidioidal meningitis include headache, fever and signs of meningeal irritation. There may also be cognitive impairment, changes in consciousness or personality, and focal neurological signs. CNS inflammation can result in complications of vasculitis, stroke or hydrocephalus. Untreated coccidioidal meningitis is usually fatal within two years.

Primary cutaneous coccidioidomycosis and other localized diseases

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 Dissemination to other sites is possible.

Diagnostic Tests

Coccidioidomycosis can sometimes be diagnosed by visualizing the parasite in respiratory secretions (sputum, bronchoalveolar lavage fluid), pleural fluid, tissues, skin scrapings (KOH or calcofluor stain) or exudates, or by culturing these samples, as in animals. PCR to detect nucleic acids directly in clinical samples may be available in some laboratories. Enzyme immunoassays that identify antigens in serum, urine or CSF could be useful, though they have mainly been evaluated in immunocompromised patients or those with severe disseminated disease. Organisms can be difficult to detect in cerebrospinal fluid (CSF) in cases of meningitis: they are rarely found by cytology, and culture is diagnostic in less than a third of cases. Many of these cases are diagnosed by finding antibodies to *Coccidioides* in the CSF.

In humans with coccidioidomycosis, serum IgG titers are usually correlated with disease severity, and high or increasing titers may suggest dissemination. Titers generally decline with successful treatment. Serological tests for humans include ELISAs 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. A lateral flow assay has also been approved for humans, but estimates of its sensitivity vary and were low in some studies. Some limitations of serology are that early cases may be seronegative, and immunocompromised patients may have poor immune responses.

The coccidioidin or spherulin skin test was used extensively in epidemiological studies at one time, but it was withdrawn because some positive tests were caused by nonspecific reactions to thimerosol. A new formulation was recently approved for use in the US. This test is performed similarly to TB tests, and read 48 hours after inoculation. It indicates past as well as current infections. The skin test is not commonly used for diagnostic purposes, where it is sometimes negative in people who are immunocompromised or have chronic lung conditions. However, it may be helpful in primary cutaneous coccidioidomycosis, where serum IgG titers tend to be low but the skin test is usually positive early in the disease.

Treatment

Options for treatment range from observation to antifungal drugs, depending on the severity of the disease and risk factors for dissemination. Adjunct treatments may occasionally include surgical excision or debridement. The most commonly used drugs are azoles such as fluconazole, itraconazole, ketoconazole, voriconazole and posaconazole, or amphotericin B. These drugs are usually administered for several months or more. Prolonged or lifetime treatment may be necessary to prevent relapses in severely immunocompromised patients or those with CNS disease. Whether most healthy patients with primary pulmonary coccidioidomycosis should be treated is controversial, as most cases resolve on their own, antifungal drugs can have side effects, and some studies found no differences in outcome between treated and untreated patients.

Prevention

Coccidioidomycosis is difficult to prevent in endemic areas, though reducing exposure to airborne dust may be helpful. Dust control measures such as paving dirt roads, seeding lawns and using soil sealants have been employed in some areas. Wetting the soil may be useful for temporary dust control. Well-fitted dust masks might also provide some reduction in risk. Air filters have been installed in some institutions where the incidence of coccidioidomycosis was high, such as prisons in some endemic areas. Skin testing has also been used to identify prison inmates who have never had coccidioidomycosis and distribute them to prisons where they are less likely to be exposed. Preventive measures in immunocompromised people vary. Some people at risk for severe disease may be given prophylactic drug treatment, while yearly screening may be recommended for others.

Coccidioides spp. are not normally acquired from other people or from animals. Nevertheless, 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 arthroconidia can form.

Clinical specimens in endemic regions should be sent to a diagnostic laboratory; in-house fungal culture is inadvisable because arthroconidia from mature cultures are readily aerosolized and inhaled. Plates that are more than 3–5 days old are more likely to contain arthroconidia.

Morbidity and Mortality

Coccidioides spp. infections are common in people who live in endemic areas, with skin tests suggesting that 10-70% of the population in parts of the southwestern U.S. has been infected by this organism. Reactivity is also high in parts of Mexico and some locations in Central and South America. Rates are higher in people exposed to large amounts of dust. Coccidioidomycosis is a seasonal disease in some areas. Two yearly peaks are usually seen in Arizona and one in California, due to differences in the climate and pattern of rainfall. The annual incidence of coccidioidomycosis can fluctuate, but it seems to be increasing in parts of the U.S. Some possible reasons include the migration of previously unexposed, older people (retirees) to endemic areas, and increased numbers and survival of immunocompromised individuals. Rates also tend to be higher in certain occupational and recreational risk groups, such as farmers, construction workers, armadillo hunters and archaeologists. Major epidemics occur intermittently. Some have been associated with large earthquakes and windstorms. They can also be seen when heavy rains, which promote the growth of mycelia, are followed by drought and windy conditions. People who have recovered from coccidioidomycosis are resistant to reinfection.

The consequences of infection vary. In 50-70% of people, the infection is asymptomatic or so mild that it is not recognized. Historical data, collected before antifungal drugs became available, suggest that about 90-95% of untreated patients have self-limited infections that affect only the lungs and recover without clinical sequelae, while the remainder either have ongoing pulmonary disease or develop disseminated disease. Analyses of untreated historical cases found case fatality rates of 1% in infections limited to the lungs, 25% in disseminated disease without CNS involvement, and 88% or higher in CNS disease. Disseminated disease has been estimated to occur in 0.5- 1% of all infections in healthy people and less than 5% of symptomatic cases overall. Host genes, especially MHC class II genes, seem to influence this risk, and an African or Asian (especially Filipino) background increases the likelihood of severe illness.

Although people who are immunocompromised can have mild or asymptomatic infections, the potential for serious illness or disseminated disease is greater. Groups at elevated risk are those with impaired cell-mediated immunity and include HIV-infected individuals with decreased CD4 T cell counts; lymphoma and organ transplant patients; people who are receiving TNF inhibitors (e.g., infliximab, adalimumab, etanercept), long-term corticosteroids or other immunosuppressive agents; diabetics; and pregnant women, especially in the third trimester. Organ transplant patients who live in endemic areas have a 5% incidence of coccidioidomycosis during the first year after transplantation, and 2-3% over the next few years. Half of the cases in transplant patients are estimated to be symptomatic, and these cases are more likely to be fatal than in healthy people. A previous infection can also be reactivated if a person becomes immunosuppressed.

Internet Resources

Centers for Disease Control and Prevention (CDC). Information for Healthcare Professionals about Valley Fever (Coccidioidomycosis).

eMedicine. Coccidioidomycosis

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

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*Link defunct

