BMJ Best Practice

Coccidioidomycosis

Straight to the point of care

Last updated: Feb 27, 2024

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Summary

Coccidioidomycosis is a fungal infection caused by the endemic fungus *Coccidioides* species.

Most symptomatic coccidioidal infections are mild to severe episodes of pneumonia.

Extrapulmonary infection in sites such as skin, soft tissue, or skeletal or central nervous system occurs infrequently.

Common symptoms include fever, headache, dry cough, shortness of breath, inspiratory chest pain, myalgia, and arthralgia, and may be accompanied by a rash.

Treatment ranges from close observation without medical treatment in mild cases, to medical therapy, primarily with azole antifungals, in more severe episodes.

Azole antifungal therapy is generally well tolerated, with few adverse events; alternative treatments are rarely required.

Definition

Coccidioidomycosis is a fungal infection caused by the endemic fungus *Coccidioides* species and is acquired through inhalation of airborne arthrospores within the endemic areas of the southwest US, northern Mexico, and limited areas of Central and South America. Both humans and animals may become infected. Coccidioidomycosis may be asymptomatic or can cause acute and chronic pulmonary syndromes and, rarely, extrapulmonary infection. No human-to-human transmission of infection occurs.

Epidemiology

The etiologic agents of coccidioidomycosis, *Coccidioides immitis* and *C posadasii*, inhabit ecologic niches found only in the western hemisphere (areas of low precipitation), primarily in the southwestern deserts of the US (California, Arizona, New Mexico, and western Texas) and northern deserts of Mexico.[3] [4] They are also endemic in limited areas of Utah, Nevada, and eastern Washington state, as well as Central and South America. Coccidioidomycosis is an infection identified primarily in people residing within these areas; cases outside the endemic areas may be identified in visitors returning to nonendemic areas. An estimated 150,000 cases of coccidioidomycosis occur in the US annually, although many of these are misdiagnosed and unreported.[5] In 2019, approximately 20,000 cases were reported to the Centers for Disease Control and Prevention (CDC), most of which were among people living in Arizona or California.[6] One retrospective analysis of data from 2007 to 2016 found that coccidioidomycosis was diagnosed in significant numbers outside the historical geographic distribution, with 69% of the US states above the clinically relevant threshold for coccidioidomycosis in at least one county.[7] The number of reported cases in the US varies year-to-year, but continues to increase yearly.[4] This variation is not fully understood, but suggested reasons include changes to: the number of people exposed to *Coccidioides* (owing to travel or relocation); environmental factors affecting fungal growth and circulation (such as temperature and rainfall); and the way cases are detected and reported.[6]

Coccidioidomycosis is acquired when airborne fungal arthroconidia (spores) are inhaled; therefore, occupational (e.g., construction, digging) or recreational (e.g., gardening) activities that increase the likelihood of dust inhalation also increase the likelihood of infection. Outbreaks have been associated with activities such as archaeological excavation, construction, and military training exercises.[8] They have also been reported in people who fight wildfires.[9] Climatic variables, such as precipitation, drought, temperature, wind speed, and dust, also affect the amount of airborne spores.[3]

Males are more likely to acquire infection; this may be due to increased likelihood of occupational or recreational dust exposure.[10] Race is a strong risk factor for developing severe and disseminated infection but not for acquisition of infection.[3] African-Americans and Filipinos have the highest risk for dissemination, approximately 10 to 175 times greater than other races.[3] [11] The evidence is poor on whether there exists an increased risk of dissemination for Asians, Hispanics, and American Indians. It is likely that race per se is not the predisposing risk but rather the associated genetic makeup that dictates the immune response. People with immunosuppression, such as organ transplant recipients, people with HIV, or pregnant people, are also at increased risk for developing disseminated disease.[3] [8][11] [12] [13] People ages ≥65 years, people with diabetes, people who smoke, and people with high inoculum exposure are at increased risk of developing severe pulmonary complications.[8]

Etiology

Coccidioidomycosis is caused by two nearly identical species, *Coccidioides immitis* and *C posadasii*.[14] Previously these two agents have been called the Californian and non-Californian species, respectively.[15] In the alkaline soils of the endemic area, the fungus grows as a saprophobic mold, the hyphae of which form arthroconidia (spores). Natural forces such as wind or earthquakes, or disruption of the soil by construction or various activities cause disruption of the hyphae and dispersion of the arthroconidia.[16] [17]

Most cases are spread via the respiratory route. The fungus is thermally dimorphic; therefore, once the airborne arthroconidia are inhaled, they settle in lung tissue where they undergo great morphologic change and develop into spherules. Spherules undergo repeated internal divisions until they are filled with hundreds

of endospores. When the spherule ruptures, endospores are released, and each is then capable of further spherule formation.[16]

Pathophysiology

Once inhaled, the arthrospore traverses the respiratory passages to the lung, where it begins to transform into a spherule. The spherule enlarges, septates, and forms endospores, which are subsequently released. The growth and rupture of the spherule incites an acute inflammatory response, which recruits neutrophils and eosinophils. Later, with further control of the infection, a chronic inflammatory response is elicited, with granuloma formation consisting of lymphocytes, histiocytes, and multinucleated giant cells surrounding unruptured spherules. Pulmonary macrophages, having ingested spherules in the acute infection, may move to hilar or regional lymph nodes. The incubation period is 7 to 21 days. About 40% of people develop symptomatic infection.

Extrathoracic spread occurs in approximately 0.5% of people; it is not fully understood how this happens, but it may be accomplished through a transient fungemia.[2] Meningitis is the most serious form of extrathoracic coccidioidomycosis. Dissemination to bones, joints, and skin also can occur.[8] Host cellular immune mechanisms serve to slow the progress of infection, but control of coccidioidomycosis is critically dependent on intact T-lymphocyte function.[2] People who lack intact T-lymphocyte function, such as those with advanced HIV infection, recipients of organ transplants, or those receiving immunosuppressants such as corticosteroids, are more susceptible to severe and disseminated infection.

The humoral immune system is active in producing antibodies to a variety of coccidioidal antigens, and some of these antibody responses form the basis of diagnostic serology. However, none of the humoral responses has a large role in the control of infection.[2]

Classification

Clinical classification

There is no formal classification schema; however, the presentations of coccidioidal illness generally fall into distinct groups as follows:[1] [2]

- Acute respiratory illness
- Chronic fibrocavitary pneumonia
- Pulmonary residua: nodules and cavities
- Extrapulmonary dissemination.

Case history

Case history #1

A 71-year-old male resident of Minnesota regularly spends several winter months in Arizona to play golf in the sun. Last March he experienced a gradual onset of fever and a headache, followed by a nonproductive cough, shortness of breath, inspiratory chest pain, myalgia, and profound fatigue. His local physician diagnosed bronchopneumonia on chest x-ray and prescribed azithromycin. The antibiotic provided no benefit, and ultimately the patient received two more courses of different empiric antibiotics.

He returned to Minnesota with continued cough and fatigue, even though the fever had abated somewhat. Two months following the initial onset of symptoms, a bronchoscopy was performed, and cultures grew *Coccidioides* species.

Other presentations

Months to years following a symptomatic or asymptomatic infection, the affected lung may show complete resolution or an area of calcified or uncalcified pulmonary nodule, similar radiographically to cancer. Microscopic examination of excised tissue identifies the organism. Occasionally the nodule liquefies to form a thin-walled cavity, which may close spontaneously or remain and become a nidus for suprainfection or spontaneous pneumothorax. Extrapulmonary dissemination can be identified in nearly all tissues, although skin and soft tissue, bones, and meninges are the most common sites of dissemination. Chronic fibrocavitary pneumonia is seen infrequently, with chronic cough and dyspnea, night sweats, weight loss, and lung fibrosis with thick-walled cavities.

Approach

The diagnosis of coccidioidomycosis often depends on maintaining a high degree of clinical suspicion, as symptoms and laboratory studies can be nonspecific. Initial investigation of all patients should include a chest x-ray, sputum culture, coccidioidal serology, complete blood count (CBC), and erythrocyte sedimentation rate (ESR). Further evaluation will depend on the site and severity of the disease.

Clinical evaluation: acute coccidioidomycosis

In acute coccidioidomycosis, symptoms begin 7 to 21 days following an exposure. The onset may be abrupt or subacute, and symptoms include one or more of the following: fever, headache, nonproductive cough, shortness of breath, inspiratory chest pain, fatigue, dyspnea, myalgia or arthralgia, and rash.[24] These symptoms can be mild or severe.

Severe symptoms and signs (plus investigation results) include:

- Multiple symptoms lasting >2 months
- Weight loss of >10%
- Night sweats lasting >3 weeks
- Extensive pulmonary infiltrates (bilateral disease, persistent hilar adenopathy)
- Inability to work
- Age >55 years
- Serology titer >1:16.

Often symptoms resemble community-acquired pneumonia (CAP), and within endemic areas, acute pulmonary coccidioidomycosis accounts for nearly 30% of all CAP.[25] Features which may help to differentiate coccidioidomycosis from bacterial CAP include hilar or mediastinal adenopathy, upper lobe infiltrates, nodules, and peripheral blood eosinophilia.[23]

Symptoms may be self-limited or prolonged, lasting weeks to months.

Physical examination is notable for presence or absence of rash and signs of lung consolidation.

Clinical evaluation: diffuse coccidioidomycosis

These patients have bilateral reticulonodular or miliary infiltrates on imaging, a pattern that suggests fungemia. Often patients have either underlying immunosuppression or a high inoculum of inspired arthroconidia (spores).

Clinical evaluation: chronic fibrocavitary coccidioidomycosis

Some patients develop chronic infiltrates and cavities, often in more than one lobe. Nodules may develop following a pulmonary infiltrate, and cavities may form within these nodules. Nodules and cavities may be asymptomatic or associated with cough, hemoptysis, and pleuritic pain. Infrequently, a cavity may rupture, causing a pyopneumothorax.[24]

People with chronic fibrocavitary pneumonia may have weight loss and night sweats in addition to pulmonary symptoms.

Physical exam of the lung may identify rales, rhonchi, wheeze, or rub.

Clinical evaluation: disseminated coccidioidomycosis

The most common sites of extrapulmonary (disseminated) infection include lymph nodes, skin and soft tissue, bones and joints, and meninges. The location of the infection dictates the symptoms and physical findings; most patients will also experience fever, night sweats, and chills.[24] Less than 5% of people with coccidioidomycosis experience extrapulmonary spread of infection.[24]

Laboratory evaluation

Initial investigation of all patients should include a sputum culture, coccidioidal serology, CBC and ESR. Because no particular test has perfect sensitivity and specificity, multiple diagnostic tests should be considered.[26]

Sputum culture

A positive sputum culture gives a definitive diagnosis of coccidioidomycosis, because there is no colonized state; however, sputum can be difficult to obtain for culture, since patients' coughs are often nonproductive.[27]

Coccidioidal serology

Serologic testing is the most frequently used method for diagnosing coccidioidomycosis.[28] [29] [30] Both qualitative and quantitative antibody-detection methods are available:

1) Qualitative serology

- Enzyme immunoassay (EIA) is widely available and has the highest early (within 1 to 2 months of presentation) sensitivity of any method so is often used for initial screening.[5] [28] This method detects specific IgM and IgG antibodies against *Coccidioides* . Typically, IgM EIA testing is positive early in the course of illness, while IgG arises later. While detection of antibodies by EIA is more sensitive than other available tests for detecting early disease (immunodiffusion tube precipitin test (IDTP), complement fixation titers), it is less specific.[28] Furthermore, an isolated positive IgM needs confirmation with another serologic test (positive EIA IgG, immunodiffusion, or complement fixing) as false positives are possible.[23] [24][26] [31] Sensitivity of EIA is 87% in immunocompetent patients, but only 67% in immunosuppressed patients.[32]
- Immunodiffusion (ID) tests are less sensitive but more specific than EIA.[33] Due to their specificity, they are performed to confirm positive EIA and complement fixation results.[1] [23]
    - The IDTP assay tests for the presence of IgM antibodies directed against the tube precipitin (TP) antigen, a heat-stable carbohydrate antigen of the fungal cell wall. These antibodies form early in the infection, with around 90% of patients developing them in the first 3 weeks of symptomatic disease.[34]
    - The immunodiffusion complement fixation (IDCF) assay detects IgG antibodies directed against the chitinase antigen (an enzyme of the fungal cell wall), which are often detectable while the disease is active.[35] These antibodies arise later in illness (typically 8-10 weeks after symptom onset) and stay positive for longer than IgM antibodies.[36] If the IDCF is positive, quantification should be requested; a titer can be obtained by a quantitative ID test or by using a conventional CF assay.[35]

2) Quantitative serology

- The complement fixation (CF) assay detects complement-binding IgG antibodies and can be performed on body fluids other than serum. CF titers should be ordered in all cases of coccidioidomycosis and are important in assessing the burden of fungal infection and monitoring treatment responses.[28] IgG antibodies rise within the first 2 months of infection and fall over time, reflecting progress of convalescence. The titer is proportional to the severity of infection.[1] A titer >1:16 should alert one to the possibility of disseminated (extrapulmonary) infection.[1] Sensitivity in immunocompetent hosts is 75%.[32] CF levels of 1:2 to 1:4 may be due to a cross-reacting antibody; therefore, serologic results should be confirmed with another modality (generally immunodiffusion, but EIA would also be indicative).[1] [23] When following up a patient with coccidioidomycosis, the CF test is repeated every few months to assure declining titer.

High antibody titers in asymptomatic patients with advanced HIV may be predictive of subsequent symptomatic disease.[23] None of these serologic tests are considered definitive in the diagnosis of coccidioidomycosis.[23] It is recommended that all three serology methods are performed at initial evaluation, as performing multiple methods increases the sensitivity of the serologic assay.[32] Repeat serology every 1 to 2 weeks should be considered in symptomatic patients with negative results until a diagnosis is established.[23] Sensitivity of the tests is higher in immunocompetent hosts than in immunosuppressed hosts.[32]

Any positive test result for anticoccidioidal antibodies is usually associated with a recent or active (as opposed to past) coccidioidal infection. This is true for tests that detect either IgG and IgM antibodies, as in most patients these tests return to negative as the infection resolves. This interpretation differs from that of serologic tests for many other types of infection where IgG antibodies are often detectable for life.[5]

Coccidioidal antigen testing

Coccidioidal antigen testing has been found helpful for immunosuppressed patients with disseminated infection or as an adjunctive cerebrospinal fluid (CSF) test in suspected coccidioidal meningitis.[23] [26] It can be performed on body fluid samples including urine, serum, and CSF.[23]

Polymerase chain reaction (PCR) testing

A real-time PCR assay for detection of *Coccidioides* directly from lower respiratory specimens has been approved by the US Food and Drug Administration.[27] It can provide results from an extracted sample in approximately 1.5 hours (compared to traditional fungal culture which may take up to 3 weeks to return results). Compared to fungal culture, the assay has demonstrated sensitivity of 100%, and specificity of 93.8% to 100%.[37]

Cerebrospinal fluid (CSF) analysis

For any patient with symptoms or signs of meningitis, a lumbar puncture for CSF analysis is recommended.[4] CSF leukocytosis with positive serology identifies coccidioidal meningitis. Other CSF findings may include low glucose and elevated protein levels.

Blood tests

Nonspecific findings may include eosinophilia on CBC or an elevated erythrocyte sedimentation rate.[31]

Imaging

Initial investigation of all patients should include a chest x-ray. This may show a variety of findings, including single or multilobe consolidation, mass, nodules, or, less often, miliary infiltrates with or without cavities.[24] Hilar, paratracheal, and mediastinal adenopathy may be identified.[24] Extensive pulmonary infiltrates (bilateral disease, persistent hilar adenopathy) are indicative of severe disease.

Chest CT may be more sensitive to identify abnormalities, and is indicated when the chest x-ray does not provide adequate detail (e.g., to follow a nodule or cavity size that cannot be seen on chest x-ray, or when looking for characteristics that may distinguish between infection and tumor).

Bone scans may identify abnormalities in skeletal infections. MRI may define bone and soft tissue abnormalities in soft tissue infections.

Histopathology

This is a definitive test. A lung biopsy is indicated when the clinical presentation, together with radiographic and serologic results, is inconclusive, or when treatment or observation for a presumptive diagnosis (e.g., seropositive patients) is not resulting in expected improvement. Positive histopathology gives a definitive diagnosis of coccidioidomycosis, because there is no colonized state. Spherules are identified using microscopy.

Emerging tests

Lateral flow assay

A lateral flow assay (LFA) to detect the presence of total antibodies against *Coccidioides* species (IgM or IgG) in serum became commercially available in 2018, but is not yet in widespread use.[8] While the LFA can yield rapid point-of-care results, low sensitivity is a limiting factor in its use; in a prospective study, LFA showed only 31% sensitivity compared to EIA.[38]

DIAGNOSIS

History and exam

Key diagnostic factors

asymptomatic (common)

- Sixty percent of infections are asymptomatic.[39]

fever (common)

- A feature of acute or disseminated coccidioidomycosis.

cough (common)

- Generally dry and nonproductive cough.

rash (common)

- Around 10% to 50% of patients develop a rash, which is generally transient.[40]
- Erythema nodosum or erythema multiforme are commonly seen. Skin nodules and lesions are a sign of disseminated infection.

Other diagnostic factors

headache (common)

- Twenty percent of coccidioidal pneumonia is associated with significant headache.[40]

fatigue (common)

- A feature of acute coccidioidomycosis.

pleuritic chest pain (common)

- Usually inspiratory, pleuritic discomfort.

dyspnea (common)

- A feature of acute coccidioidomycosis.

myalgia or arthralgia (common)

- A feature of acute coccidioidomycosis.

weight loss (common)

- May be >10% of body weight in acute disease.[5] [41]
- Patients with chronic fibrocavitary pneumonia may have weight loss in addition to pulmonary symptoms.

night sweats (common)

- Associated with chronic fibrocavitary coccidioidomycosis or acute pulmonary infection.

chills (common)

- Associated with chronic fibrocavitary coccidioidomycosis or, more likely, acute pulmonary infection.

rales, rhonchi, wheeze, or rub (common)

- Associated with chronic fibrocavitary coccidioidomycosis.

bronchial breathing (common)

- Sign of lung consolidation.

hemoptysis (uncommon)

- Associated with nodules and cavities.

pyopneumothorax (uncommon)

- Can develop if a cavity bursts.

lymphadenopathy (uncommon)

- Extrathoracic lymphadenopathy suggests dissemination.

abnormal mental status or neurologic exam (uncommon)

- Suggests disseminated coccidioidomycosis.

Risk factors

Strong

immunosuppression, especially suppression of cell-mediated immunity

- Strong risk for developing severe and disseminated infection but not for acquisition of infection.
- Conditions included in this group are HIV (especially with CD4 count of ≤250 cells/microliter), organ transplantation, and hematological malignancies.[18] [19] [20] [21]

pregnancy

- Strong risk factor for dissemination, likely due to altered immune function associated with pregnancy.
- The risk of disseminated disease increases as pregnancy progresses: one literature review found that 96% of all coccidioidomycosis cases diagnosed in the third trimester were disseminated. The figures for the first and second trimester were 50% and 62%, respectively.[12]
- Among pregnant women with coccidioidomycosis, African-American women have a 13-fold higher risk of dissemination than white women.[11] [12]

Weak

occupation involving digging or construction

- Increases the likelihood of infection from inhalation of airborne fungal arthroconidia (spores).

recreational activities that increase likelihood of dust inhalation

- Increase the likelihood of infection from inhalation of airborne fungal arthroconidia.

extremes of age

- Young children or older adults may develop more severe infection.[3]

male sex

- Due to increased occupational or recreational dust exposure.

residing in or visiting endemic areas

- The southwestern deserts of the US (California, Arizona, New Mexico, and western Texas) and northern deserts of Mexico are considered to be endemic areas.[3] Infection is also endemic in limited areas of Utah, Nevada, Eastern Washington, and Central and South America.

African-American or Filipino ancestry

- Race is a strong risk factor for developing severe and disseminated infection but not for acquisition of infection.[3]
- African-Americans and Filipinos have the highest risk for dissemination, approximately 10 to 175 times more often than in other races.[3] [11]
- The evidence is poor on whether there exists an increased risk of dissemination for Asians, Hispanics, and American Indians. It is likely that race per se is not the predisposing risk but rather the associated genetic makeup that dictates the immune response.
- Among pregnant women with coccidioidomycosis, African-American women have a 13-fold higher risk of dissemination than white women.[11] [12]

blood group B

- A significant association has been identified between blood group B and disseminated coccidioidomycosis; this blood group is more common among people of African and Filipino ancestry.[3]
- This association is likely a marker of genetic influences that dictate the immune response (see HLA risk factor).

HLA groups

- HLA class II alleles have been identified as markers for risk of dissemination. However, while this information is useful in further study, it has limited use in clinical situations.[3]

diabetes mellitus

- Associated with cavitary lung disease and relapsed infection.[22]
- Patients with diabetes mellitus and poorly controlled glucose levels may have increased risk of dissemination.[22]

Investigations

1st test to order

Test	Result
sputum culture • Definitive test. A positive culture gives a definitive diagnosis of coccidioidomycosis, because there is no colonized state; however, sputum can be difficult to obtain for culture, since patients' coughs are often nonproductive.[27]	**growth of *Coccidioides* species**
enzyme immunoassay serology for coccidioidomycosis • Enzyme immunoassay (EIA) is widely available and has the highest early (within 1 to 2 months of presentation) sensitivity of any method so is often used for initial screening.[5] [28] This method detects specific IgM and IgG antibodies against *Coccidioides* . Typically, IgM EIA testing is positive early in the course of illness, while IgG arises later. While detection of antibodies by EIA is more sensitive than other available tests for detecting early disease (immunodiffusion tube precipitin test (IDTP), complement fixation titers), it is less specific.[28] Furthermore, an isolated positive IgM needs confirmation with another serologic test (positive EIA IgG, immunodiffusion, or complement fixing) as false positives are possible.[23] [24] [26] [31] Sensitivity of EIA is 87% in immunocompetent patients, but only 67% in immunosuppressed patients.[32] If other serologic modalities (immunodiffusion and complement fixing) are positive, no further study is needed. If other modalities are negative, repeat serology in 1 to 2 weeks to test for seroconversion in a patient with acute symptoms.[23]	**any of the following combinations would be a positive test: IgM positive and IgG positive, or IgM negative and IgG positive; when IgM is positive but IgG negative, there is a chance of a false-positive result**
immunodiffusion serology for coccidioidomycosis • Immunodiffusion (ID) tests are less sensitive but more specific than EIA.[33] Due to their specificity, they are performed to confirm positive EIA and complement fixation results.[1] [23] The IDTP assay tests for the presence of IgM antibodies directed against the tube precipitin (TP) antigen, a heat-stable carbohydrate antigen of the fungal cell wall. These antibodies form early in the infection, with around 90% of patients developing them in the first 3 weeks of symptomatic disease.[34] • The immunodiffusion complement fixation (IDCF) assay detects IgG antibodies directed against the chitinase antigen (an enzyme of the fungal cell wall), which are often detectable while the disease is active.[35] These antibodies arise later in illness (typically 8-10 weeks after symptom onset) and stay positive for longer than IgM antibodies.[36] If the IDCF is positive, quantification should be requested; a titer can be obtained by a quantitative ID test or by using a conventional CF assay.[35]	**positive for early IgM (IDTP) or late IgG (IDCF) antibodies**
complement fixation serology for coccidioidomycosis • The complement fixation (CF) assay detects complement-binding IgG antibodies. It is quantitative and can be performed on body fluids other than serum. CF titers should be ordered in all cases of coccidioidomycosis and are important in assessing the burden of fungal infection and monitoring treatment responses.[28] IgG antibodies rise within the first 2 months of infection and fall over time, reflecting progress of convalescence. The titer is proportional	**assay for late IgG antibodies; any positivity indicates present or recent infection; titers >1:16 should prompt evaluation for the possibility**

Test	Result
to the severity of infection.[1] A titer >1:16 should alert one to the possibility of disseminated (extrapulmonary) infection.[1] Sensitivity in immunocompetent hosts is 75%.[32] CF levels of 1:2 to 1:4 may be due to a cross-reacting antibody; therefore, serologic results should be confirmed with another modality (generally immunodiffusion, but EIA would also be indicative).[1] [23] When following up a patient with coccidioidomycosis, the CF test is repeated every few months to assure declining titer.	**of disseminated coccidioidomycosis**
CBC • Nonspecific test.	**eosinophilia**
chest x-ray • May show a variety of findings, including single or multilobe consolidation, mass, nodules, or, less often, miliary infiltrates with or without cavities.[24] • Hilar, paratracheal, and mediastinal adenopathy may be identified.[24] • Extensive pulmonary infiltrates (bilateral disease, persistent hilar adenopathy) are indicative of severe disease.	**lobar pneumonia (single site or multifocal); single or multifocal nodular infiltrate; single or multiple cavities; calcified or uncalcified nodule; hilar or mediastinal adenopathy**

Other tests to consider

Test	Result
antigen testing • Coccidioidal antigen testing has been found helpful for immunosuppressed patients with disseminated infection or as an adjunctive cerebrospinal fluid (CSF) test in suspected coccidioidal meningitis.[23] [26] Can be performed on body fluid samples including urine, serum, and CSF.[23]	**positive for coccidioidal antigen**
polymerase chain reaction (PCR) • A real-time PCR assay for detection of *Coccidioides* directly from lower respiratory specimens has been approved by the US Food and Drug Administration.[27] It can provide results from an extracted sample in approximately 1.5 hours (compared to traditional fungal culture which may take up to 3 weeks to return results). Compared to fungal culture, the assay has demonstrated sensitivity of 100%, and specificity of 93.8% to 100%.[37]	**positive for coccidioidal DNA**
lung biopsy • Definitive test. A lung biopsy is indicated when the clinical presentation, together with radiographic and serologic results, is inconclusive, or when treatment or observation for a presumptive diagnosis (e.g., seropositive patients) is not resulting in expected improvement. Positive histopathology gives a definitive diagnosis of coccidioidomycosis, because there is no colonized state.	**identification of spherules on microscopy**
lumbar puncture • For any patient with symptoms or signs of meningitis, a lumbar puncture for CSF analysis is recommended.[4] Identifies coccidioidal meningitis with positive serology.[23]	**low glucose levels, elevated protein levels, leukocytosis; positive coccidioidal serology with complement fixation (CF)**
erythrocyte sedimentation rate • Nonspecific test.	**elevated**
CT chest • May be more sensitive to identify abnormalities, and is indicated when the chest x-ray does not provide adequate detail (e.g., to follow a nodule or cavity size that cannot be seen on chest x-ray, or when looking for characteristics that may distinguish between infection and tumor).[42]	**acute pulmonary coccidioidomycosis: consolidation, streaky densities, nodular or patchy opacities, hilar and/or mediastinal adenopathy, pleural effusion.** **chronic pulmonary coccidioidomycosis: nodules, cavities, persistent pneumonia, chronic progressive pneumonia, adenopathy, pleural effusion.** **regressive end-stage disease: fibrosis, bronchiectasis, calcifications**

Test	Result
bone scan • May identify abnormalities in skeletal infections.[43]	**single or multifocal lesions, most common on axial skeleton, but can be seen in any bone of the body; lesions may be described as punched-out lytic, permeative/ destructive, or involving a joint and/or disk space; generally, lesions have well-demarcated borders, but sometimes have an ill-defined border and diffuse appearance to the bony destruction**
MRI • May define bone and soft tissue abnormalities in soft tissue infections.	**bone findings can include erosions, abscesses, masses; soft-tissue findings may include nonspecific soft-tissue inflammation, swelling, abscess, mass, lymphadenopathy, fat stranding**

Emerging tests

Test	Result
lateral flow assay (LFA) • A LFA to detect the presence of total antibodies against *Coccidioides* species (IgM or IgG) in serum became commercially available in 2018, but is not yet in widespread use.[8] While the LFA can yield rapid point-of-care results, low sensitivity is a limiting factor in its use; in a prospective study, LFA showed only 31% sensitivity compared to enzyme immunoassay.[38]	**positive for IgM or IgG**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Tuberculosis	• Symptoms and signs of tuberculosis and coccidioidomycosis may be similar. For patients with suspected tuberculosis, residence in or travel to an endemic area for coccidioidomycosis is not needed for diagnosis. • Tuberculosis has an indolent onset and symptoms are unremitting until proper treatment is begun.	• Mycobacterial culture of sputum or other sites of clinical involvement will yield positive results for *Mycobacterium tuberculosis* . • Chest x-ray may show chronic infiltrate, fibrosis, cavities, and retraction, often upper lobe.
Nontuberculous pulmonary mycobacterial infections	• Residence in or travel to an endemic area for coccidioidomycosis is not needed for diagnosis. • Onset of symptoms may be acute, but often indolent.	• Mycobacterial culture of sputum or other sites of clinical involvement will yield positive results.
Community-acquired pneumonia	• Signs of lobar or atypical pneumonia including crackles and dyspnea. • Generally, shorter duration of symptoms compared with tuberculosis or coccidioidomycosis. • If diagnosis is in doubt, presumptive treatment for bacterial pneumonia is recommended (without using fluoroquinolones, or other antibiotics with significant antituberculous activity), and assessment for response.	• Sputum examination with presence of bacteria other than normal flora.
Histoplasmosis	• Residence in or travel to an area endemic for histoplasmosis (Mississippi and Ohio river valleys). • Around 50% to 90% of patients have self-limited or asymptomatic pulmonary infection not requiring treatment.[44] Symptoms include dry cough, chest pain, sweating, fever, and weight loss.	• Fungal culture will grow *Histoplasma capsulatum* . • Biopsy shows characteristic organism with fungal stains. • Histoplasma urine and serum antigen positivity. • Histoplasma antibody assays may be positive.[44]
Blastomycosis	• Residence in or travel to an area endemic for	• Culture of sputum or bronchoalveolar lavage fluid.

Condition	Differentiating signs / symptoms	Differentiating tests
	blastomycosis (southeastern and south-central states, especially bordering on the Mississippi or Ohio rivers).[45] • Symptoms include cough, fever, night sweats, weight loss, chest pain, and dyspnea.	• Histopathology of biopsied specimens.[45]
Cryptococcosis	• History of immune deficiency. Headache, pyrexia, cranial neuropathies, and alteration of consciousness indicate central nervous system involvement. • Cutaneous involvement presents with molluscum contagiosum-like and acneiform lesions.	• Cryptococcal polysaccharide antigen is positive in serum, cerebrospinal fluid, and pleural fluid. • Cultures positive with growth of *Cryptococcus* species.
Actinomycosis	• Typically presents as a chronic, slowly progressive, indurated mass. History of previous injury to mucosal surface or aspiration enhances the risk of pulmonary disease. • Cough may be productive of blood-streaked sputum.	• Culture of pus or affected tissue positive for actinomycetes. • Histology of affected tissue demonstrates acute or chronic inflammation and granulation tissue; sulfur granules may also be seen.
Sporotrichosis	• Clinical presentation of pulmonary sporotrichosis is similar to that of pulmonary tuberculosis with fever, chills, night sweats, weight loss, malaise, cough, shortness of breath, and, occasionally, hemoptysis.	• Repeated cultures from sputum, bronchoalveolar lavage, or bronchial biopsy may be positive. • Bronchial biopsy may demonstrate cigar- or oval-shaped *Sporothrix* yeast forms.
Aspergillosis	• History of immune deficiency. Mostly asymptomatic but commonly presents as self-limiting mild hemoptysis. Other symptoms include cough and pleuritic chest pain. • Fever is rare. • May have concomitant skin involvement and/or invasive sinus disease.	• High-resolution chest CT scan demonstrates nodules with or without halo sign or air-crescent sign.
Small cell lung cancer	• Strong risk factors include cigarette smoking and exposure to second-hand	• Chest x-ray: central mass, hilar lymphadenopathy, pleural effusion.

Condition	Differentiating signs / symptoms	Differentiating tests
	tobacco smoke, radon gas, and asbestos; more common in patients ages 65 to 70 years and in men; presents most commonly with cough, dyspnea, hemoptysis, chest pain, weight loss; other presenting features related to metastases to brain, bone, and lymph nodes.	• CT chest, liver, and adrenal glands: massive lymphadenopathy and direct mediastinal invasion are common features of small cell lung cancer; determines extent of disease. • Sputum cytology: malignant cells in sputum. • Bronchoscopy: endobronchial lesions. • Biopsy: malignant cells, high nuclear to cytoplasmic ratio, nuclear fragmentation often present. • Thoracentesis: malignant cells within the pleural fluid. • Thoracoscopy: pleural involvement. • Further tests depend on the presence of metastasis.
Non-small cell lung cancer	• Most signs and symptoms are similar to small cell lung cancer. Typical features include cough, hemoptysis, chest pain, dyspnea, and hoarseness (if recurrent laryngeal nerve paralysis). Patients frequently appear sick and short of breath, with signs of recent weight loss. • Finger clubbing and hypertrophic osteoarthropathy may be present and are more common in non-small cell lung cancer.	• Chest x-ray variable; may detect a solitary pulmonary nodule, mass, pleural effusion, lung collapse, or mediastinal or hilar fullness. • CT chest shows size, location, and extent of primary tumor; evaluates for hilar and/or mediastinal lymphadenopathy and distant metastases. • Sputum cytology shows characteristic malignant cells. Specificity >95%, sensitivity variable between 20% and 70%. More likely to be positive with central lesions compared with peripheral lesions. • Flexible bronchoscopy plus biopsy provides pathologic confirmation of diagnosis. Endobronchial masses can be biopsied with forceps. Endobronchial brushings, washings, and alveolar lavage increase the diagnostic yield. Transbronchial needle aspiration biopsy of accessible parenchymal lesions and mediastinal lymph nodes is now possible. Detection of small

Condition	Differentiating signs / symptoms	Differentiating tests
		peripheral lesions (<2 cm) is improved by use of endobronchial ultrasound.
Pneumocystis jirovecii pneumonia	• Can occur within or outside the *Coccidioides* -endemic area in persons with severe cellular immunodeficiency. May be similar in presentation to miliary coccidioidomycosis with dyspnea, cough, fever, and diffuse infiltrates.	• Induced sputum and (more often) flexible bronchoscopy with bronchoalveolar lavage, with cytology and special stains or polymerase chain reaction for *Pneumocystis* . Serum lactate dehydrogenase may be elevated.
Eosinophilic pneumonia (eosinophilic granulomatosis with polyangiitis)	• Can occur within or outside the *Coccidioides* -endemic area. May be similar with eosinophilia and focal nodular infiltrates, cough, and chest pain.	• Flexible bronchoscopy and biopsy with histopathology; serum antineutrophil cytoplasmic antibodies (ANCA) may be positive. Peripheral eosinophilia >10% of total WBC count. Asthma, sinus disease, and neuropathy may be present, as well as kidney disease.
Coronavirus disease 2019 (COVID-19)	• Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset. • See our COVID-19 topic for further information.	• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA. • Distinguishing covid and coccidioidomycosis is often possible radiographically.

Approach

The main goal of treatment is to relieve clinical symptoms and signs, reduce anticoccidioidal antibodies, and return organ function to normal.[5] Preventing relapse is also a goal, but not always achievable with current treatment.[5] Treatment depends on the presentation and host category. Many coccidioidal infections are self-limited, mild, or asymptomatic, and do not require treatment.[5] [47] However, some pulmonary, and nearly all extrapulmonary, infections will require treatment.[5] [47] Nonresolving, progressive, or severe symptoms also warrant treatment.[5] [47]

If patients are asymptomatic or have mild infection, but are at risk for disseminated infection (such as African-Americans, Filipinos, people who are immunocompromised, pregnant women, or patients with diabetes mellitus), they should either be monitored very closely or treated with antifungal therapy.[5] The patient is usually involved in the decision-making process. If the patient has symptomatic infection and is at risk for disseminated infection, treatment should be considered.[5]

Acute coccidioidal pneumonia: mild symptoms

For patients with no risk factors for dissemination, no treatment is required.[5] [47] Often, by the time the diagnosis is made, symptoms have improved or resolved. Close clinical, serologic, and radiographic follow-up is indicated and treatment in the form of an azole antifungal (e.g., fluconazole, itraconazole) should be considered if symptoms are worsening with time.[5]

Patients with risk factors for dissemination (e.g., African-Americans, Filipinos, people who are immunocompromised, pregnant women, or patients with diabetes mellitus) are either monitored very closely or may be treated prophylactically with fluconazole or itraconazole.[5] [47]

Acute coccidioidal pneumonia: severe and/or diffuse symptoms

Indicators of severe infection include:[5]

- Symptoms lasting >2 months
- Weight loss of >10%
- Night sweats lasting >3 weeks
- Extensive pulmonary infiltrates (bilateral disease, persistent hilar adenopathy)
- Inability to work
- Age >55 years
- Serology titer >1:16.

The goal of therapy is to gain control of the infection as quickly as possible and ideally prevent the establishment of an extrapulmonary focus of infection.[5] The risks of not treating include progressive pulmonary and extrapulmonary infection that may result in severe morbidity or death.

Patients are treated with either fluconazole or itraconazole daily for 3 to 6 months.[5] [47] If a patient's symptoms are not improving with an azole antifungal, therapy can be switched to amphotericin-B.[5] Azole antifungal therapy is recommended for ongoing treatment; therefore, if amphotericin-B was used initially, treatment can be switched to fluconazole or itraconazole after several weeks or when the patient is stable.

Pulmonary nodule

A radiographically stable nodule (not enlarging with time) due to coccidioidomycosis (as determined by noninvasive or invasive means such as fine-needle biopsy or nodule resection) in an otherwise healthy (nonimmunosuppressed) person who is asymptomatic requires no treatment.[5] [47]

A patient with a coccidioidal pulmonary nodule that begins to enlarge should be evaluated by serology and sputum culture to assess whether the infection is active. If infection is active, treatment with fluconazole or itraconazole is recommended.[5]

A common differential for a pulmonary nodule is a malignant lesion, and therefore the nodule is often removed by a local wedge or, if necessary, lobar resection. If a nodule is determined to be due to coccidioidomycosis, a subsequent clinical assessment should be performed. Patients with risk factors for dissemination (such as immunosuppression) should have a directed evaluation for evidence of such dissemination, by review of symptoms, physical examination, and serology. If there is no evidence of another focus of coccidioidomycosis, no treatment is indicated.

Coccidioidal pulmonary cavity

Symptomatic cavities may be accompanied by local pain or discomfort, hemoptysis, secondary bacterial or fungal infection, or cavity rupture. Fluconazole or itraconazole may alleviate symptoms but are unlikely to result in cavity closure and symptoms may recur with treatment cessation.[5] Surgical resection may be considered to alleviate symptoms.[41]

For an asymptomatic cavity, no treatment is indicated, but periodic follow-up should be performed to assure stability, over an indefinite period of time.[5] [47] Some cavities will close over time with no need for treatment.

For asymptomatic cavities that persist longer than 2 years, are adjacent to the pleura, or are enlarging, resection can be considered to avoid complications associated with the cavity.[41]

Chronic progressive fibrocavitary coccidioidomycosis

Initial treatment consists of fluconazole or itraconazole to alleviate symptoms, and to prevent further infection and fibrosis, and loss of lung function. Treatment is continued for 12 months or until a response is seen.[5] [47]

If there is no response to initial treatment, options include increasing the dose, switching to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [47] [48] [49] [50] [51] [52] [53]

Skin and soft tissue coccidioidomycosis

Treatment is aimed at alleviating symptoms, controlling infection, and limiting the destruction of tissues and damage to organ function.[5] Treatment of skin and soft tissue infections is commonly associated with response rates ranging from 25% to 91%, with relapse rates as high as 50%.[54]

Initial treatment should include fluconazole or itraconazole.[5] [47] Surgical excision or debridement is often needed as an adjunctive measure, especially if lesions are large, destructive, or impinging on critical structures.[5] [54] Treatment is continued until a response is seen clinically and serologically, which can take months to years. After treatment is discontinued, close follow-up is needed to monitor for relapse.[5]

If there is no response to initial treatment, options include increasing the dose, switching to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [47] [48] [49] [50] [51] [52] [53] Surgical excision or debridement may also be indicated if lesions do not respond to medication alone, or if they recur after completion of antifungal therapy.

Skeletal coccidioidomycosis

Skeletal coccidioidomycosis is a chronic and progressive infection.[55] Treatment is given to limit the destruction of involved bones and adjacent structures (muscle, joint, supporting structures) and to limit loss of function.

A comparison of fluconazole and itraconazole in the treatment of skeletal coccidioidomycosis demonstrated slight superiority of itraconazole.[56] Initial treatment should therefore include itraconazole, if the patient is able to tolerate it.[47] Fluconazole is an alternative.

Surgical excision or debridement is often needed as an adjunctive measure.[5] [55] Treatment is continued until a response is seen clinically and serologically, which can take months to years. After treatment is discontinued, close follow-up is needed to monitor for relapse.

If there is no response to initial treatment, options include increasing the medication dose, switching to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [47] [48] [49] [50] [51] [52] [53]

Coccidioidal meningitis

Treatment is required to alleviate symptoms, control infection, limit destruction of tissue and neurologic function, and prevent hydrocephalus.[5]

Fluconazole is the preferred treatment but itraconazole has also shown efficacy.[5] [47] [57] If treatment is failing with either of these, then voriconazole is recommended. Azole treatment is continued indefinitely.[5] [47] Intrathecal amphotericin-B (ITAMB) should then be considered if the patient does not show response to azole therapy.[5] [57]

ITAMB may be complicated by neurotoxicity of amphotericin-B deoxycholate and complications of the application of treatment (such as cisternal bleeding or bacterial infection of an Ommaya reservoir).[57]

Pregnancy

Pregnant women with mild or resolving illness may be observed closely without treatment. Serial evaluations are needed to reassess the decision to treat or not treat.

Treatment is given to alleviate severe symptoms, control infection, and prevent extrapulmonary dissemination. Poor outcome is correlated with diagnosis later in pregnancy.[12]

Pregnant women are at increased risk of disseminated infection. However, unlike treatment of all other patient groups, azoles are not considered first-line because fetal abnormalities have been described.[12] Instead, if it is decided that the potential benefits of treating coccidioidomycosis in a pregnant woman outweigh the risks, amphotericin B is given first-line.[5] Following delivery of the child, treatment may be changed to fluconazole or another azole, in conjunction with effective methods of birth control.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
mild coccidioidal pneumonia (nonpregnant)		
■ without risk factors for dissemination; symptoms improving	1st	observation
■ without risk factors for dissemination; symptoms worsening	1st	azole antifungal
■ with risk factors for dissemination (African-American, Filipino, immunocompromised, or diabetes mellitus)	1st	observation ± azole antifungal
severe or diffuse coccidioidal pneumonia (nonpregnant)		
	1st	azole antifungal or amphotericin-B
pulmonary nodule (nonpregnant)		
■ radiographically stable in healthy patient	1st	observation
■ enlarging with active infection	1st	azole antifungal
asymptomatic pulmonary cavity (nonpregnant)		
	1st	observation
	adjunct	surgical resection
symptomatic pulmonary cavity (nonpregnant)		
	1st	azole antifungal
	adjunct	surgical resection
chronic progressive fibrocavitary coccidioidomycosis (nonpregnant)		
	1st	azole antifungal or amphotericin-B
skin and soft tissue coccidioidomycosis (nonpregnant)		

MANAGEMENT

Acute		(summary)
	1st	azole antifungal or amphotericin-B
	adjunct	surgical excision or debridement
skeletal coccidioidomycosis (nonpregnant)		
	1st	azole antifungal or amphotericin-B
	adjunct	surgical excision or debridement
coccidioidal meningitis (nonpregnant)		
	1st	azole antifungal or intrathecal amphotericin-B
pregnant		
	1st	observation or amphotericin-B

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

mild coccidioidal pneumonia (nonpregnant)

without risk factors for dissemination; symptoms improving — **1st** — **observation**

» For patients without risk factors for dissemination no treatment is required. Often, by the time the diagnosis is made, symptoms have improved or resolved.[5] [47]

» Close clinical, serologic, and radiographic follow-up is indicated and treatment in the form of an azole antifungal (e.g., fluconazole, itraconazole) should be considered if symptoms are increasing with time.[5]

without risk factors for dissemination; symptoms worsening — **1st** — **azole antifungal**

Primary options

» fluconazole: 400 mg orally/intravenously once daily for 3-6 months

OR

» itraconazole: 200 mg orally twice daily for 3-6 months

» Following close clinical, serologic, and radiographic follow-up, treatment in the form of an azole antifungal (e.g., fluconazole or itraconazole) should be considered if symptoms are increasing with time.[5]

with risk factors for dissemination (African-American, Filipino, immunocompromised, or diabetes mellitus) — **1st** — **observation ± azole antifungal**

Primary options

» fluconazole: 400 mg orally/intravenously once daily for 3-6 months

OR

» itraconazole: 200 mg orally twice daily for 3-6 months

» Patients with risk factors for dissemination (African-Americans, Filipinos, immunocompromised patients, or patients with diabetes mellitus) should be closely monitored with clinical, serologic, and radiographic follow-

Acute

up, or may be treated prophylactically with fluconazole or itraconazole.[5]

severe or diffuse coccidioidal pneumonia (nonpregnant)

1st **azole antifungal or amphotericin-B**

Primary options

» fluconazole: 400 mg orally/intravenously once daily for 3-6 months

OR

» itraconazole: 200 mg orally twice daily for 3-6 months

Secondary options

» amphotericin B lipid complex: 2-5 mg/kg intravenously once daily for 1-6 months

OR

» amphotericin B liposomal: 2-5 mg/kg intravenously once daily for 1-6 months

OR

» amphotericin B deoxycholate: 0.5 to 1.5 mg/kg/day intravenously given once daily or on alternate days for 1-6 months

» Indicators of severe infection include: symptoms lasting >2 months; weight loss >10%; night sweats lasting >3 weeks; extensive pulmonary infiltrates (bilateral disease, persistent hilar adenopathy); inability to work, age >55 years; and serology titer >1:16.[5]

» The goal of therapy is to gain control of the infection as quickly as possible and ideally prevent the establishment of an extrapulmonary focus of infection.[5] The risks of not treating include progressive pulmonary and extrapulmonary infection that may result in severe morbidity or death.

» Patients are treated with either fluconazole or itraconazole daily for 3 to 6 months.[5] If a patient's symptoms are not improving with an azole antifungal, therapy can be switched to amphotericin-B.[5]

» Azole antifungal therapy is recommended for ongoing treatment and, therefore, if amphotericin-B was used initially, treatment can

Acute

be switched to fluconazole or itraconazole after several weeks or when the patient is stable.

pulmonary nodule (nonpregnant)

radiographically stable in healthy patient — **1st** — **observation**

» A radiographically stable nodule (not enlarging with time) due to coccidioidomycosis (as determined by noninvasive or invasive means such as fine-needle biopsy or nodule resection) in an otherwise healthy (nonimmunosuppressed) person who is asymptomatic requires no treatment.[5] [47]

» If the abnormality can be seen and measured on chest x-ray, then no further imaging is necessary. If more precision is needed, or the abnormality cannot be seen on chest x-ray, CT is recommended.

» Follow-up can be every 3 to 4 months for the first year, then every 6 months for the second year. If the lesion is radiographically stable, it will not require long-term follow-up.

enlarging with active infection — **1st** — **azole antifungal**

Primary options

» fluconazole: 400-800 mg orally/ intravenously once daily, continued until a clinical or serologic response is seen

OR

» itraconazole: 200 mg orally twice daily, continued until a clinical or serologic response is seen

» A patient with a coccidioidal pulmonary nodule that begins to enlarge should be evaluated by serology and sputum culture to assess whether the infection is active. If infection is active, treatment with fluconazole or itraconazole is recommended.[5]

asymptomatic pulmonary cavity (nonpregnant)

1st — **observation**

» For an asymptomatic coccidioidal cavity no treatment is indicated, but periodic follow-up should be performed to assure stability, over an indefinite period of time.[5] Some cavities will close over time with no need for treatment.

MANAGEMENT

Acute

» If the abnormality can be seen and measured on chest x-ray, then no further imaging is necessary. If more precision is needed, or the abnormality cannot be seen on chest x-ray, CT is recommended.

» Follow-up can be every 3 to 4 months for the first year, then every 6 months for the second year. Periodic follow-up thereafter can be 6 to 12 months. The interval is judged on whether the patient is doing well, and if the cavity is stable or smaller over time.

» Patients may require follow-up sooner in the event of any new or recurrent respiratory symptoms.

adjunct **surgical resection**

Treatment recommended for SOME patients in selected patient group

» For asymptomatic cavities that persist >2 years, are adjacent to the pleura, or are enlarging, resection can be considered to avoid complications associated with the cavity, such as secondary bacterial or fungal infection, or cavity rupture.[41]

symptomatic pulmonary cavity (nonpregnant)

1st **azole antifungal**

Primary options

» fluconazole: 400 mg orally/intravenously once daily for 3-6 months or longer

OR

» itraconazole: 200 mg orally twice daily for 3-6 months or longer

» Symptomatic cavities may be accompanied by local pain or discomfort, hemoptysis, secondary bacterial or fungal infection, or cavity rupture.

» Fluconazole or itraconazole may alleviate symptoms but are unlikely to result in cavity closure and symptoms may recur with treatment cessation.[5]

adjunct **surgical resection**

Treatment recommended for SOME patients in selected patient group

» Symptomatic cavities may be accompanied by local pain or discomfort, hemoptysis, secondary bacterial or fungal infection, or cavity rupture.

Acute

» Surgical resection may be considered to alleviate symptoms.[41]

chronic progressive fibrocavitary coccidioidomycosis (nonpregnant)

1st **azole antifungal or amphotericin-B**

Primary options

» fluconazole: 400-800 mg orally/intravenously once daily for at least 1 year or until a clinical or serologic response is seen

OR

» itraconazole: 200-400 mg orally twice daily for at least 1 year or until a clinical or serologic response is seen

Secondary options

» voriconazole: 6 mg/kg intravenously every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours

OR

» posaconazole: 400 mg orally (suspension) twice daily; 300 mg orally (delayed-release tablet) twice daily for 1 day, followed by 300 mg once daily thereafter

OR

» amphotericin B lipid complex: 2-5 mg/kg intravenously once daily

OR

» amphotericin B liposomal: 2-5 mg/kg intravenously once daily

OR

» amphotericin B deoxycholate: 0.5 to 1.5 mg/kg/day intravenously given once daily or on alternate days

» Initial treatment consists of fluconazole or itraconazole to alleviate symptoms, and to prevent further infection and fibrosis, and loss of lung function. Treatment is continued for 12 months or until a response is seen.[5]

» If there is no response to initial treatment, options include increasing the dose, switching

Acute

to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [48] [49] [50] [51] [52] [53]

skin and soft tissue coccidioidomycosis (nonpregnant)

1st **azole antifungal or amphotericin-B**

Primary options

» fluconazole: 400 mg orally/intravenously once daily initially, continued until a clinical or serologic response is seen, increase to 800 mg/day according to response

OR

» itraconazole: 200 mg orally twice daily initially, continued until a clinical or serologic response is seen, increase to 400 mg twice daily according to response

Secondary options

» voriconazole: 6 mg/kg intravenously every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours

OR

» posaconazole: 400 mg orally (suspension) twice daily; 300 mg orally (delayed-release tablet) twice daily for 1 day, followed by 300 mg once daily thereafter

OR

» amphotericin B lipid complex: 2-5 mg/kg intravenously once daily

OR

» amphotericin B liposomal: 2-5 mg/kg intravenously once daily

OR

» amphotericin B deoxycholate: 0.5 to 1.5 mg/kg/day intravenously given once daily or on alternate days

» Treatment is aimed at alleviating symptoms, controlling infection, and limiting the destruction of tissues and damage to organ function.[5]

Acute

Treatment of skin and soft tissue infections is commonly associated with response rates ranging from 25% to 91%, with relapse rates as high as 50%.[54]

» Initial treatment should include fluconazole or itraconazole.[5] Treatment is continued until a response is seen clinically and serologically, which can take months to years. After treatment is discontinued, close follow-up is needed to monitor for relapse.[5]

» If there is no response to initial treatment, options include increasing the dose, switching to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [48] [49] [50] [51] [52] [53]

adjunct **surgical excision or debridement**

Treatment recommended for SOME patients in selected patient group

» Surgical excision or debridement is often needed as an adjunctive measure, especially if lesions are large, destructive, or impinging on critical structures.[5] [54] Surgical excision or debridement may also be indicated if lesions do not respond to medication alone, or if they recur after completion of antifungal therapy.

skeletal coccidioidomycosis (nonpregnant)

1st **azole antifungal or amphotericin-B**

Primary options

» itraconazole: 200 mg orally twice daily initially, continued until a clinical or serologic response is seen, increase to 400 mg twice daily according to response

OR

» fluconazole: 400 mg orally/intravenously once daily initially, continued until a clinical or serologic response is seen, increase to 800 mg/day according to response

Secondary options

» voriconazole: 6 mg/kg intravenously every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours

OR

Acute

» posaconazole: 400 mg orally (suspension) twice daily; 300 mg orally (delayed-release tablet) twice daily for 1 day, followed by 300 mg once daily thereafter

OR

» amphotericin B lipid complex: 2-5 mg/kg intravenously once daily

OR

» amphotericin B liposomal: 2-5 mg/kg intravenously once daily

OR

» amphotericin B deoxycholate: 0.5 to 1.5 mg/kg/day intravenously given once daily or on alternate days

» Skeletal coccidioidomycosis is a chronic and progressive infection.[55] Treatment is given to limit the destruction of involved bones and adjacent structures (muscle, joint, supporting structures) and to limit loss of function.

» A comparison of fluconazole and itraconazole in the treatment of skeletal coccidioidomycosis demonstrated slight superiority of itraconazole.[56] Initial treatment should therefore include itraconazole, if the patient is able to tolerate it. Fluconazole is an alternative.

» If no response to initial treatment, options include increasing the medication dose, switching to an alternative azole such as voriconazole or posaconazole (both of which have been reported to have efficacy in selected patients failing traditional treatment), or switching to amphotericin-B.[5] [48] [49] [50] [51] [52] [53]

adjunct **surgical excision or debridement**

Treatment recommended for SOME patients in selected patient group

» Surgical excision or debridement is often needed as an adjunctive measure.[5] [55] Treatment is continued until a response is seen clinically and serologically, which can take months to years.

» After treatment is discontinued, close follow-up is needed to monitor for relapse.[5] [55]

Acute

coccidioidal meningitis (nonpregnant)

1st **azole antifungal or intrathecal amphotericin-B**

Primary options

» fluconazole: 400-800 mg orally/intravenously once daily, continued until a clinical response is seen

OR

» itraconazole: 200 mg orally twice daily

Secondary options

» voriconazole: 4 mg/kg orally/intravenously every 12 hours

Tertiary options

» amphotericin B deoxycholate: consult specialist for guidance on intrathecal dosing

» Treatment is required to alleviate symptoms, control infection, limit destruction of tissue and neurological function, and prevent hydrocephalus.[5]

» Fluconazole is the preferred treatment but itraconazole has also shown efficacy.[5] [57] If treatment is failing with either of these, then voriconazole is recommended. Azole treatment is continued indefinitely.[5]

» Intrathecal amphotericin-B (ITAMB) should be considered if the patient does not show response to azole therapy.[5] [57] ITAMB may be complicated by neurotoxicity of amphotericin-B deoxycholate and complications of the application of treatment (such as cisternal bleeding or bacterial infection of an Ommaya reservoir).[57]

pregnant

1st **observation or amphotericin-B**

Primary options

» amphotericin B lipid complex: 2-5 mg/kg intravenously once daily

OR

» amphotericin B liposomal: 2-5 mg/kg intravenously once daily

Acute

OR

» amphotericin B deoxycholate: 0.5 to 1.5 mg/kg/day intravenously given once daily or on alternate days

» Pregnant women with mild or resolving illness may be observed closely without treatment. Serial evaluations are needed to reassess the decision to treat or not treat.

» Treatment is given to alleviate severe symptoms, control infection, and prevent extrapulmonary dissemination. Poor outcome is correlated with diagnosis later in pregnancy.[12]

» Pregnant women are at increased risk of disseminated infection. However, unlike treatment of all other patient groups, azoles are not considered first-line because fetal abnormalities have been described.[12] Instead, if it is decided that the potential benefits of treating the infection outweigh the risks in a pregnant woman, amphotericin B is given first-line.[5]

» Following delivery of the child, treatment may be changed to fluconazole or another azole, in conjunction with effective methods of birth control.

Emerging

CYP51 inhibitors

VT-1598, a tetrazole-based fungal CYP51-specific inhibitor, is in early-phase clinical development for the treatment of coccidioidomycosis.[58] Oral administration improved survival and decreased fungal burden in mouse models.[58]

Primary prevention

Primary prevention measures are limited for immunocompetent individuals. Travelers should limit exposure to outdoor dust in endemic areas; during dust storms, they should stay inside and close windows. Air filtration measures can be used indoors.[8]

Patients with HIV who live in or visit endemic areas are particularly encouraged to heed the above advice, as well as to avoid long periods of exposure to disturbed native soil (e.g., at building excavation sites).[23] Serologic testing for coccidioidomycosis is advised in patients with HIV who have previously traveled to or lived in endemic areas.[23] Annual to biannual testing should be considered for those currently living in endemic areas.[23] Primary prophylaxis with fluconazole is indicated for HIV-positive patients with a positive serologic test for coccidioidomycosis; CD4 counts <250 cells/mm^3; and an absence of signs, symptoms, or laboratory abnormalities compatible with coccidioidal disease.[23] Primary prophylaxis can be discontinued when the patient's CD4 count is ≥250 cells/mm^3 and when viral suppression is documented.[23] For patients with CD4 counts already ≥250/mm^3 and with viral suppression on antiretrovirals, primary prophylaxis with antifungal therapy is not indicated and only close clinical follow-up is recommended.[23]

Monitoring

Monitoring

Regardless of whether patients are actively treated, ongoing follow-up should be arranged to assess for improvement or stabilization in clinical symptoms, and monitor radiographic abnormalities and complement fixation serologic titer.

Initially, a patient may require follow-up every 2 to 4 weeks, but as they improve, the interval can be increased to every 3 to 4 months. Following an initial response, changes in serologic and radiographic findings may improve only slowly with time and changes might not be appreciated in less than 3 months.

Depending on the severity of initial findings, radiographic and serologic abnormalities, and resolution of abnormalities, follow-up for 1 to 2 years is recommended.

For patients with severe infection, immunosuppression, or other risk factors for dissemination, lifelong follow-up may be required. In patients discontinuing treatment, follow-up to detect relapsed infection is important.

This disease is nationally notifiable and is reportable in the following states: Arizona, Arkansas, California, Delaware, Louisiana, Maryland, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Ohio, Oregon, Rhode Island, South Dakota, Utah, Washington, and Wyoming.

[CDC: Valley fever (Coccidioidomycosis)] (http://www.cdc.gov/fungal/diseases/coccidioidomycosis/index.html)

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
amphotericin-B cumulative toxicity	**short term**	**high**
Symptoms can be absent, but if present, may include malaise or fatigue. Laboratory abnormalities include low potassium and/or magnesium and elevation of creatinine. Serum levels of creatinine, potassium, and magnesium should be assessed frequently (daily to weekly) while on treatment. Amphotericin can be held temporarily and electrolytes should be quickly replaced.		
amphotericin-B-related infusion toxicity	**short term**	**medium**
Symptoms include fever, chills, and phlebitis. Can treat or pretreat with acetaminophen, antihistamines, or hydrocortisone. Rigors may respond also to meperidine.		
coccidioidal meningitis: with progressive neurologic symptoms from hydrocephalus	**long term**	**low**
Decompression using a shunt is needed to treat the increased intracranial pressure.[5] Azole antifungal treatment does not necessarily require change of regimen.		
coccidioidal meningitis: with central nervous system vasculitis, resulting in cerebral ischemia, infarction, and hemorrhage	**long term**	**low**
No clear guideline for treatment.[5] Use of short-term, high-dose corticosteroids can be considered to treat the vasculitis.[5]		
ruptured pulmonary cavity	**variable**	**low**
A cavity that ruptures into the pleural space causes a pyopneumothorax. Surgical resection with decortication and antifungal therapy is the recommended management strategy.[5] Fluconazole and itraconazole are preferred antifungal treatments, but amphotericin-B can be used if the patient cannot tolerate azoles or requires two or more surgical procedures for control.[5] Duration of treatment is 3 to 6 months or longer, depending on risk factors for dissemination, presence of immunosuppression, and the serologic response to interventions.		

Prognosis

Pulmonary coccidioidomycosis

Prognosis is very good for most patients with pulmonary coccidioidomycosis. Many patients have a period of significant fatigue following resolution of acute pulmonary symptoms, but most recover completely and without sequelae.[17]

Extrapulmonary coccidioidomycosis

The outlook for extrapulmonary coccidioidomycosis depends on the location and extent of infection, as well as the underlying immunity of the patient. Relapse is common.[5] [54] [55] [57]

Patients with HIV

Lack of viral suppression and CD4 counts <250 cells/mm^3 are associated with increased disease severity in patients with HIV.[23]

Diagnostic guidelines

International

CDC Yellow Book: health information for international travel - coccidioidomycosis/valley fever (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [8]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Clinical testing guidance for coccidioidomycosis, histoplasmosis, and blastomycosis in patients with community-acquired pneumonia (https://www.cdc.gov/fungal) [30]

Published by: Centers for Disease Control and Prevention; Mycoses Study Group; Coccidioidomycosis Study Group **Last published:** 2023

Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new) [23]

Published by: Centers for Disease Control and Prevention **Last published:** 2021

Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice (https://www.thoracic.org/statements/index.php) [26]

Published by: American Thoracic Society **Last published:** 2019

Guidance for managing select communicable diseases: coccidioidomycosis (valley fever) (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/IDBGuidanceforManagingSelectCommunicableDiseases.aspx) [46]

Published by: California Department of Public Health **Last published:** 2018

Global guideline for the diagnosis and management of the endemic mycoses (https://pubmed.ncbi.nlm.nih.gov/34364529) [4]

Published by: European Confederation of Medical Mycology; International Society for Human and Animal Mycology **Last published:** 2021

Treatment guidelines

International

CDC Yellow Book: health information for international travel - coccidioidomycosis/valley fever (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [8]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new) [23]

Published by: Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America **Last published:** 2021

Guidance for managing select communicable diseases: coccidioidomycosis (valley fever) (https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/IDBGuidanceforManagingSelectCommunicableDiseases.aspx) [46]

Published by: California Department of Public Health **Last published:** 2018

Clinical practice guideline for the treatment of coccidioidomycosis (https://www.idsociety.org/practice-guideline/alphabetical-guidelines) [5]

Published by: Infectious Diseases Society of America **Last published:** 2016

Treatment of fungal infections in adult pulmonary and critical care patients (http://www.thoracic.org/statements/tuberculosis-pneumonia.php) [47]

Published by: American Thoracic Society **Last published:** 2011

Global guideline for the diagnosis and management of the endemic mycoses (https://pubmed.ncbi.nlm.nih.gov/34364529) [4]

Published by: European Confederation of Medical Mycology; International Society for Human and Animal Mycology **Last published:** 2021

Online resources

1. CDC: Valley fever (Coccidioidomycosis) (http://www.cdc.gov/fungal/diseases/coccidioidomycosis/index.html) *(external link)*

Key articles

- Thompson GR 3rd, Le T, Chindamporn A, et al. Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. Lancet Infect Dis. 2021 Dec;21(12):e364-74. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34364529?tool=bestpractice.bmj.com)

- Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. Full text (https://academic.oup.com/cid/article/63/6/e112/2389093) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27470238?tool=bestpractice.bmj.com)

- Centers for Disease Control and Prevention. CDC Yellow Book 2024: health information for international travel. Section 5: travel-associated infections and diseases - coccidioidomycosis/valley fever. May 2023 [internet publication]. Full text (https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/coccidioidomycosis-valley-fever)

- National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: Coccidioidomycosis. 2021 [internet publication]. Full text (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/coccidioidomycosis?view=full)

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

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Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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