

REVIEW ARTICLE

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Coccidioidomycosis and Histoplasmosis in Immunocompetent Persons

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N Engl J Med 2024;390:536-47.

DOI: 10.1056/NEJMra2306821

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OF THE ROUGHLY 150,000 RECOGNIZED FUNGAL SPECIES, AND PERHAPS the several million not yet identified, few cause disease in humans,¹ fewer do so in persons not overtly immunosuppressed, and only a handful are localized to specific geographic regions. Of these endemic mycoses, histoplasmosis and coccidioidomycosis are the ones most commonly encountered in the Americas.

The fungi causing these two endemic mycoses are dimorphic, in that they grow as mold in the environment and assume a different structure when causing infection in the host. Although both fungi are dimorphic, their resultant structures differ dramatically (Fig. 1) and they occupy very different niches in the environment. Histoplasma has been noted in many diverse areas worldwide, but in the Western Hemisphere, it is most commonly distributed in the central and mideastern United States and in Central America, where it thrives in soil with a high nitrogen content. In contrast, coccidioides is most prominent in arid regions, especially those of Arizona and California. Climate change is predicted to expand its domain across much of the western United States.²

These fungi differ with respect to their overall public health impact in immunocompetent persons, and understanding those differences enables rational management strategies to be developed. In this review, we focus on the distribution, acquisition, clinical manifestations, and underlying pathogenesis of the two diseases in immunocompetent persons; diagnostic methods and management are briefly discussed as well.

RECENT CHANGES IN NOMENCLATURE

For both coccidioidomycosis and histoplasmosis, there have been recent changes in nomenclature. Both were thought to be protozoan infections when first described^{3,4} and decades later were discovered to be mycoses. A century later, two genetically and geographically discrete clades of coccidioides have been defined: *Coccidioides immitis*, primarily endemic in California, and *C. posadasii*, endemic elsewhere throughout the Western Hemisphere.⁵ Differences in tolerance of heat and salts suggest that this divergence may have occurred in response to different environmental conditions.⁶ Similarly, *Histoplasma capsulatum* has now been separated into four species on the basis of genetic differences: *H. capsulatum* (the original Panamanian species), *H. mississippiense*, *H. ohiense*, and *H. suramericanum*.⁷ Ultimately, *H. duboisii*, which has different clinical manifestations and areas of endemicity, is likely to be classified as a separate species^{7,8} and is therefore not included in this review. For both coccidioides and histoplasma, no differences in clinical behavior have been identified among the various species, and clinical laboratories do not distinguish among them.

DISTRIBUTION

Coccidioidomycosis occurs exclusively in the Western Hemisphere. An understanding of its distribution in the United States has relied on maps derived from skin-test surveys performed in the 1940s and 1950s.⁹ Large population increases in Phoenix, Arizona, and in other portions of the Southwest have made coccidioidomycosis a growing public health problem in the United States. *Coccidioides* has been isolated from soil in Dinosaur National Monument in northeastern Utah, as well as in southeastern Washington,¹⁰ suggesting that there are likely to be additional cryptic regions of endemicity.

Histoplasma is distributed throughout the world, including areas of Africa, Southeast Asia, and Australia, but the areas with the highest concentration of cases of histoplasmosis remain the

midwestern United States and Central America.¹¹ Reports of cases from outside the areas in the United States where the infection is known to be endemic have raised concern about an expansion of the geographic range for histoplasma.^{12,13} This expansion has not been confirmed by isolation of the organism from the environment, but it is suggested by modeling of environmental and surveillance data and genomic analysis of isolates.^{14,15}

USUAL COURSE OF INITIAL ILLNESS

The initial infection is acquired by inhalation of airborne conidia (spores) from the environment. For most persons, this does not result in clinical illness. Symptomatic disease occurs in a very small proportion of persons infected with histoplasma, on the basis of data derived from skin testing large populations of healthy persons.¹⁶

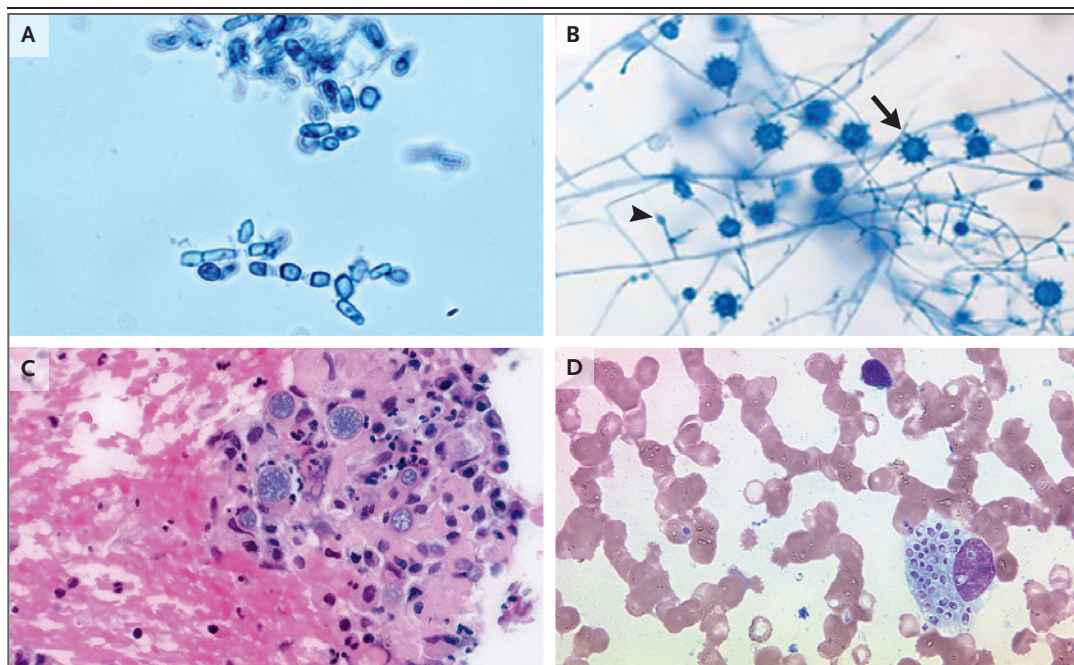


Figure 1. Appearance of Mycelial and Tissue Forms of Histoplasma and Coccidioides.

Panel A shows a wet preparation of arthroconidia from mycelial growth of coccidioides after 14 days, stained with lactophenol cotton blue. In Panel B, a lactophenol cotton blue preparation of the mycelial phase of *Histoplasma capsulatum* shows the larger tuberculate conidia (long arrowhead) that are characteristic of *H. capsulatum* and the smaller microconidia (short arrowhead) that are responsible for causing infection after inhalation into the alveoli. Panel C shows several spherules in a skin-biopsy specimen from a patient with disseminated coccidioidomycosis. Routine hematoxylin and eosin staining is usually adequate for visualizing spherules, although periodic acid–Schiff or Gomori or Grocott methenamine silver staining may improve sensitivity. Panel D shows Giemsa staining of a peripheral-blood smear from a patient with disseminated histoplasmosis. A monocyte is stuffed with small, oval-shaped yeasts, which are typical of *H. capsulatum*.

Studies of military populations, however, indicated that clinically apparent illness develops in one third of persons exposed to coccidioides.¹⁷

Ambient exposure that is not associated with outbreaks accounts for most cases of infection with both fungi and is likely to be the result of infection by very small numbers of conidia. The incidence of symptomatic infection is higher and pulmonary infection can be more severe with exposure to a high inoculum of either fungus, which often occurs in the context of an outbreak related to a specific point source.

Among the third of persons who become ill after exposure to coccidioides, the illness develops after a 1-to-3-week incubation period. The initial syndrome is not easily distinguishable from community-acquired pneumonia from any cause.¹⁸ Chest radiographs often show lobar air-space disease; peripneumonic effusions and mediastinal lymphadenopathy may be present. Systemic symptoms, which can predominate, include profound fatigue, possibly similar to that seen with long-term sequelae of coronavirus disease 2019 (“long Covid”); diffuse arthralgias; myalgias; erythema nodosum; and an acute generalized exanthem, which is often misdiagnosed as erythema multiforme.¹⁹

Infection with coccidioides is often debilitating, with respiratory and other symptoms persisting for weeks or months.²⁰ Many of these protracted symptoms are the consequence of a slowly resolving immunologic response to the infection rather than fungal proliferation, a fact that has profound implications for the possible value of antifungal therapy under these circumstances.²¹ Despite the impact that an episode of uncomplicated coccidioidal infection can have on a person’s quality of life, these symptoms resolve without residual damage to the lungs or other organs.

In the small number of patients who become ill from exposure to histoplasma, symptoms develop 2 to 3 weeks later. As with coccidioidomycosis, most infections are related to inhalation of a small number of conidia during everyday activities, and symptoms suggest community-acquired pneumonia (fever, mild chest discomfort, and dry cough). Arthralgias and erythema nodosum occur with histoplasmosis but less often than noted with coccidioidomycosis. In addition to patchy air-space disease, chest radiographs

frequently reveal hilar or mediastinal lymphadenopathy or both. The acute illness generally resolves in several weeks, but some patients, primarily those with more extensive pneumonia, have a prolonged course of asthenia after acute histoplasmosis.²²

Because the acute clinical illness caused by coccidioides or histoplasma is largely self-limited, the extent of misdiagnosis is hard to define precisely, and underreporting is likely to be extensive.²³ One reason for this is that reporting is incomplete. Histoplasmosis is a reportable disease in only 13 states.²⁴ Coccidioidomycosis is nationally reportable, but many states do not conduct surveillance for this infection.^{24,25} Also, many patients who have symptoms of community-acquired pneumonia, even in areas where the organisms are known to be highly endemic, are not tested for fungal infections.²⁶ Delayed or missed diagnoses result in inappropriate antibiotic therapy, repeated imaging, and occasionally, invasive procedures, which could all be avoided by including these diseases in the differential diagnosis of community-acquired pneumonia when appropriate.¹⁸

The initial infection resolves in almost all persons when specific T-cell-mediated immunity activates macrophages to inhibit or kill the fungus. With coccidioidal infection, immunity is lifelong, and reinfection does not occur, whereas histoplasma infection does not guarantee lifelong immunity, and reinfection can occur, especially with extensive exposure.²² Both fungi can remain dormant for years after resolution of the initial infection. This is generally of no clinical significance unless the host becomes immunocompromised, even years later, when T-cell-mediated immunity can no longer contain the organism and infection is reactivated.²⁷⁻³¹ Persons who have human immunodeficiency virus (HIV) infection; those who have been treated with tumor necrosis factor antagonists for rheumatologic, gastrointestinal, or other diseases; and solid-organ transplant recipients are at highest risk for reactivated infection.

PULMONARY NODULES

After uncomplicated coccidioidal infections, chest radiographs may show residual nodules, up to several centimeters in diameter, that appear to be

solitary. Computed tomographic (CT) scans often reveal smaller satellite nodules in the surrounding lung. The nodules can persist for many years, usually do not become calcified, and may be metabolically active, making it difficult to distinguish them from malignant nodules. Needle biopsy or a surgical procedure is often necessary to clarify the diagnosis.³²

After histoplasma infection, nodules are frequently seen, which are usually small, numerous, and calcified. In contrast to the findings with coccidioidomycosis, calcified hilar and mediastinal lymph nodes are also commonly observed. An uncommon complication of calcified lymphadenopathy that is seen after histoplasmosis has resolved is broncholithiasis, reflecting the intrusion of calcified material into a bronchus, with subsequent expectoration of gritty material or even small stones.²²

MEDIASTINAL COMPLICATIONS

Several mediastinal complications of histoplasmosis can develop during or after the primary infection. These complications, which are not reported in cases of coccidioidomycosis, include mediastinal lymphadenitis, mediastinal granuloma, and mediastinal fibrosis.^{22,33}

Mediastinal lymphadenitis involves individual nodes in children and teenagers, occurs soon after or during the initial infection, and can cause symptoms from compression of adjacent structures.³⁴ Mediastinal granuloma occurs at any age and is related to the coalescence of multiple mediastinal or hilar lymph nodes into a single encapsulated mass, often with central caseation. In many patients, this complication is discovered incidentally when they undergo thoracic radiography for another reason, but some patients have symptoms, including dysphagia, chest pain, cough, and dyspnea, from compression of mediastinal structures. A radiologic finding of calcification is a prominent sign that can help with the diagnosis.³⁵

Mediastinal fibrosis, which is rare, is found years after the initial, usually asymptomatic histoplasma infection and is unrelated to mediastinal granuloma and lymphadenitis. The symptoms (cough, dyspnea, and pleuritic chest pain) are related to the development of fibrosis that encases mediastinal and hilar structures, including

the superior vena cava, bronchi, and major pulmonary vessels.^{36,37} Why this fibrosis occurs has not been completely elucidated, but active inflammation, with a predominance of B cells in the fibrotic tissue, has been described.³⁶

CHRONIC PULMONARY DISEASE

The histopathological course of coccidioidal pneumonia is characterized by acute inflammation that includes neutrophils and eosinophils recruited by fungal propagation, leading to tissue necrosis and, in some cases, liquefaction and resulting cavitation.³⁸ In many patients, these cavitory lesions are solitary and peripherally located, as are coccidioidal nodules; possess thin walls; and are discovered only incidentally.

In some patients, cavities form thicker walls and, occasionally, air-fluid levels, indicating active inflammation. These patients frequently have symptoms, including chest pain, productive cough, mild hemoptysis, night sweats, and weight loss. Persons with poorly controlled diabetes are most likely to have this form of symptomatic, chronic, progressive cavitory coccidioidomycosis.^{39,40} A more progressive pattern is now very uncommon, perhaps because of oral antifungal therapies.⁴¹ An important but infrequent complication is cavity rupture into the pleural space, resulting in a pyopneumothorax, which requires prompt surgical repair.⁴²

In some patients with histoplasmosis, resolution of the initial pulmonary lesion is slow, and small cavities can form in nodules, which are similar to those seen in coccidioidomycosis. Patients may have fatigue and cough but few other symptoms, and they have a good response to antifungal therapy. In contrast, chronic cavitory pulmonary histoplasmosis occurs almost exclusively in persons who have chronic obstructive pulmonary disease (COPD).⁴³ Preexisting structural changes of COPD, especially emphysema, are likely to contribute to the pathogenesis. Symptoms include fever, fatigue, and weight loss, along with dyspnea, cough, and purulent, often bloody sputum. The radiographic picture is characterized by multiple thick-walled cavities, primarily in the upper lobes, and progressive interstitial changes in the lower lobes.³³ The natural history of this form of histoplasmosis is a progressive downhill course.⁴⁴

DISSEMINATED (EXTRATHORACIC) INFECTION

During the initial infection, hematogenous spread of histoplasma, primarily to organs of the reticuloendothelial system, occurs routinely before an effective cell-mediated immune response has developed.⁴⁵ In immunocompetent hosts, this event is silent and self-limited, as it is with tuberculosis. Multiple tiny splenic calcifications noted on radiographic studies may be the only residual evidence.

Whether asymptomatic coccidioidal dissemination is also common is not known, but it has been recognized as an incidental finding.⁴⁶

Disseminated coccidioidomycosis, characterized by destructive lesions in skeletal structures, the skin, and the meninges, develops more frequently than does disseminated histoplasmosis in apparently immunologically normal persons.⁴⁷ Risk factors for disseminated coccidioidomycosis include male sex, African or Filipino ancestry, and an age beyond puberty (Fig. 2).¹⁷

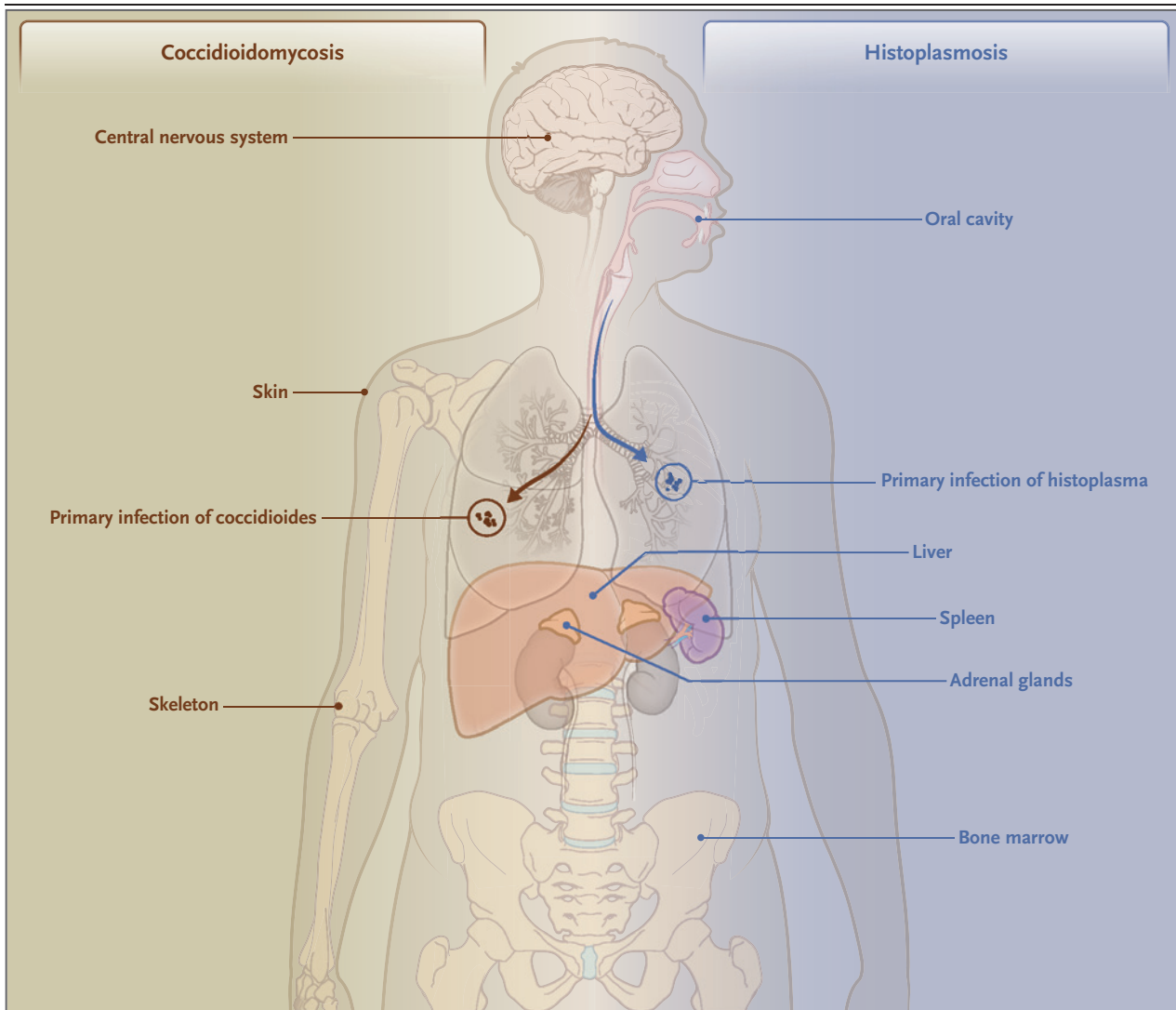


Figure 2. Differences in Common Locations of Disseminated Lesions between Coccidioidomycosis and Histoplasmosis in Immunocompetent Hosts.

Disseminated coccidioidomycosis typically involves the brain, skin, and skeleton. In disseminated histoplasmosis, lesions often occur in the oral cavity, liver, adrenals, spleen, and bone marrow.

Disseminated histoplasmosis in immunocompetent persons occurs most often in older men, but there are no racial differences.^{48,49} Skin and skeletal lesions, which are common in disseminated coccidioidal infection, are infrequent findings in disseminated histoplasmosis. Manifestations of this chronic progressive form of histoplasmosis include fevers, night sweats, weight loss, and fatigue.^{48,50,51} Patients may also have symptoms and signs of adrenal insufficiency and painful, nonhealing oral ulcers. Pancytopenia is common, as are elevated liver enzyme levels, reflecting the involvement of these tissues (Fig. 2). Uncommonly, disseminated infection with a rapidly progressive course occurs in otherwise healthy young children and infants.⁵²

Selective host immunologic defects are thought to account for disseminated infection in these apparently healthy persons. Specific mutations in genes controlling critical cellular immune responses, including receptors for interferon- γ and interleukin-12, have been found to explain the development of disseminated coccidioidomycosis or histoplasmosis in some persons but do not appear to account for most cases of disseminated infection.^{53,54} Recent studies have identified relatively common deleterious variants of innate immune pathway genes, which appear to be elements of complex genetic deficiencies that permit disseminated coccidioidal infection to progress.⁵⁵ These findings may perhaps explain the elevated risk of disseminated coccidioidal infection among persons of color, which is several times higher than the overall risk of 1% or less in the general population.

DIAGNOSTIC METHODS

Culture and histopathological assessment remain the definitive means of diagnosing histoplasmosis and coccidioidomycosis,⁵⁶ but other methods can provide earlier and sometimes more sensitive means for establishing a presumptive diagnosis (Table 1). For example, antigen detection allows for rapid diagnosis of probable histoplasmosis, and detection of specific anticoccidioidal antibodies is often used for the diagnosis of coccidioidomycosis.⁵⁷

Antibody testing for the diagnosis of coccidioidomycosis is performed either with immuno-

diffusion or, more frequently, with an enzyme immunoassay (EIA) for IgM and IgG antibodies. Specimens must be sent to a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory, so there is a delay of days to weeks before the results are available. Although immunodiffusion tests are considered to be more specific than EIA tests, positive results of either assay are considered very likely to be diagnostic in a patient who has a compatible clinical illness.⁵⁸ False negative serologic test results are common, especially in the first few weeks after the onset of symptoms. Thus, for patients who have rapidly progressive disease, culture and histopathological assessment of involved tissue are especially important. A test for coccidioidal antigen is available but is relatively insensitive; however, it is useful in testing cerebrospinal fluid from patients with suspected coccidioidal meningitis.⁵⁹ A recent review provides detailed information about diagnostic testing for coccidioidomycosis.⁶⁰

In contrast to antibody testing for the diagnosis of coccidioidomycosis, antigen testing in urine and serum has become a major tool for rapid diagnosis of histoplasmosis in persons who have disseminated infection, those with severe pulmonary infection, and some persons with acute pulmonary histoplasmosis.⁶¹ In immunocompetent persons with these forms of histoplasmosis, the standard antibody assays of complement fixation and immunodiffusion are also positive, but the results take longer to become available. A more sensitive EIA test has less specificity,⁶² but when EIA is combined with antigen testing, the diagnosis of acute pulmonary histoplasmosis is enhanced.⁶³ When there is a low burden of organisms, which occurs in localized mediastinal syndromes, antigen is rarely found, and antibody may or may not be detected. As with coccidioidomycosis, testing for antigen in cerebrospinal fluid from patients thought to have central nervous system infection is very helpful.⁶⁴

MANAGEMENT

Before the introduction of the imidazole class of antifungals, ketoconazole, and later, the triazoles, including fluconazole and itraconazole, amphotericin B was the only treatment for most serious

forms of coccidioidomycosis and histoplasmosis. Treatment involved a long hospitalization, drug toxicity, and frequent relapses. Triazole therapy revolutionized the treatment of both diseases. Although the approach is similar in many regards, there are important differences in the treatment of these two endemic mycoses in immunocompetent hosts (Table 2).

The approach to managing newly diagnosed coccidioidal infection depends on whether fungal growth is continuing to occur, in which case antifungal drug therapy is warranted. Many of the symptoms in patients with initial coccidioidal infection are not from fungal growth but rather are the consequence of immunologic responses to the infection that are nondestructive, do not benefit from antifungal drug treatment, and eventually resolve, regardless of management.^{21,65} Asymptomatic residual nodules from a previous coccidioidal infection do not require treatment.⁶⁶ Pulmonary cavities present more complicated management decisions. Patients who have symptoms benefit from oral triazole treatment. Patients with disseminated infection are typically treated with oral triazoles, occasionally in combination with surgery. Triazole treatment is often required for years, since active tissue destruction may recur when treatment is discontinued. Because the consequences of relapse for patients with coccidioidal meningitis are so serious, such patients should be treated for life.⁵⁹

For most patients who require treatment of coccidioidomycosis, the triazole of choice is fluconazole (Fig. 3). Itraconazole is also effective, especially with infections of osteoarticular structures, but is associated with more adverse effects and has more variable absorption. For patients with severe disease, therapy with a lipid formulation of amphotericin B should be provided initially, with a step down to a triazole once clinical improvement is apparent.⁶⁶

Severe pulmonary or disseminated histoplasmosis should be treated initially with a lipid formulation of amphotericin B.⁶⁷ Histoplasma is exquisitely sensitive to this agent, and clinical improvement generally occurs within 1 to 2 weeks after the initiation of therapy. A recent phase 2 study explored the use of a single dose (10 mg per kilogram of body weight) of liposomal amphotericin B in persons with HIV infection, with promising results.⁶⁸ For step-down therapy and for initial therapy of less severe disease, oral

itraconazole is the agent of choice, with proper attention to achieving serum concentrations that are adequate for the resolution of infection and are not toxic. In contrast to the treatment of coccidioidomycosis, fluconazole is not as efficacious as itraconazole and is not recommended.

Treatment is not recommended for residual pulmonary nodules or mediastinal fibrosis. A several-month course of itraconazole is often used for patients who have mediastinal lymphadenitis or mediastinal granuloma, with the thought that active infection is possibly present in these conditions. However, there are no data verifying that treatment of these conditions is effective. In contrast, patients with chronic cavitary pulmonary histoplasmosis require itraconazole treatment for at least a year.⁶⁷

PREVENTIVE VACCINES

Coccidioidomycosis is a serious public health problem for those living in or visiting regions where the infection is endemic, which are projected to expand.² Because natural infection affords lifelong protection for most people, prevention of this infection by vaccination has seemed a feasible goal for more than 70 years. A gene-deletion mutant ($\Delta cps1$) of *C. posadasii* that has recently been developed is highly attenuated.⁶⁹ Mice and dogs vaccinated with $\Delta cps1$ were afforded a high degree of protection. This mutant is under development as a vaccine for the prevention of coccidioidomycosis in dogs,⁷⁰ and it is possible that a similar vaccine could be used in humans. With recent advances in nucleic acid vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, this platform might also be adapted for a coccidioidal vaccine in the future.⁷¹ Although not currently in development, vaccine strategies might also be successful for preventing histoplasmosis.

CONCLUSIONS

Coccidioidomycosis and histoplasmosis differ in important characteristics, even though both infections are dimorphic endemic fungal diseases. These differences include divergent ecologic niches, initial signs and symptoms of infection and the course of illness, the potential for and frequency of various complications, and

Table 1. Laboratory Tests for the Diagnosis of Coccidioidomycosis and Histoplasmosis.*

Diagnostic Test	Coccidioidomycosis	Histoplasmosis
Culture: confirms diagnosis	Grows at room temperature on Sabouraud's agar; growth usually appears within 5 days as a non-pigmented mold, and all subsequent work must be conducted in a BSL-3 containment hood; arthroconidia alternating with autolyzed cells develop over a period of weeks as the culture matures, but this is not diagnostic; the commercial diagnostic probe is no longer available; identification is currently performed by reference laboratories with the use of mass spectroscopy or PCR assay	Grows as a white-to-tan mold at room temperature on Sabouraud's agar; may take up to 6 weeks for growth; tuberculate conidia are distinctive but are not proof of histoplasma; proof must be obtained in a reference laboratory, where work is performed under a BSL-3 containment hood; identification can be made with the MALDI-TOF technique, a PCR assay, or targeted DNA sequencing; alternatively, the mold can be converted to the yeast phase, but this process is slow and difficult; the yield of blood cultures in disseminated infection is increased with the lysis-centrifugation system
Histopathological assessment: confirms diagnosis	Distinctive features: large spherules (40–90 μm) with doubly refractile walls containing internal endospores; strong staining with hematoxylin and eosin, as well as GMS and PAS; if tissue fixation is delayed or if sample is from within pulmonary cavities, mycelial growth can be evident	Distinctive features: oval yeast (2–4 μm) with single budding found inside phagocytic cells but also in extracellular spaces; strong staining with GMS or PAS; aspirates and touch preparations (e.g., bone marrow) stain with Giemsa; intracellular yeasts seen in a buffy coat of peripheral blood can provide a rapid diagnosis; poor staining with hematoxylin and eosin, and no staining with Gram's stain
Antigen assays	EIA: performed by a reference laboratory; urine is more likely to be positive than serum; highest sensitivity is for extensive disease; less useful for milder disease; positive CSF is diagnostic for coccidioidal meningitis	EIA: several commercial EIA tests are available, with varying performance characteristics; sensitivity is as high as 95% in persons with HIV infection and disseminated histoplasmosis, with lower sensitivity in those with pulmonary infection; not useful for local disease with a low organism burden; cross-reaction with EIA tests for blastomyces, coccidioides, and several other fungi; helpful to test both serum and urine; CSF and BAL fluid should be tested when indicated clinically; rapid test with quick turnaround time; positive test indicates probable histoplasmosis; repeated testing is used to gauge response to treatment Lateral flow assay: developed for use as a point-of-care test by two companies; neither test is approved for general use; appears to be as sensitive as EIA, but only small numbers of test results reported to date
Antibody assays: for both fungal diseases, often negative early in acute infection; poor sensitivity in immunocompromised persons who do not have a robust antibody response to infection	EIA: commercial kits used by reference laboratories for initial screening test; although false positive results occur, in a patient with a compatible clinical illness, either IgM or IgG reactivity likely to be diagnostic, even if not confirmed by other tests Immunodiffusion test: generally less sensitive than EIA test but considered to be more specific Complement fixation test: quantitative antibody test traditionally used to monitor disease activity Lateral flow assay: dipstick assay approved for use in CLIA laboratories; highly specific, but sensitivity varies according to patient population tested	EIA: more sensitive than complement fixation and immunodiffusion tests, but false positive results occur; some laboratories use EIA as a screening test Immunodiffusion test: qualitative test that is slightly less sensitive but more specific than complement fixation test; M band more common, appears earlier than H band, and can persist for several years; H band found less often, always with M band, usually in chronic disease and severe acute disease; long turnaround time at reference laboratories Complement fixation test: both mycelial phase and yeast phase antigens used in this quantitative assay; perhaps yeast phase more sensitive than mycelial phase, but depends on reagents used in specific labs; more sensitive but slightly less specific than immunodiffusion test; titer of 1:32 is strongly suggestive of histoplasmosis, but increase in titer by a factor of 4 over time is diagnostic; long turnaround time at reference laboratories
Nucleic acid tests	No standardized PCR assay commercially available; several laboratories have developed in-house assays	No standardized PCR assay commercially available; several laboratories have developed in-house assays

* BAL denotes bronchoalveolar lavage, BSL-3 biosafety level 3, CLIA Clinical Laboratory Improvement Amendments, CSF cerebrospinal fluid, EIA enzyme immunoassay, GMS Gomori or Grocott methenamine silver, HIV human immunodeficiency virus, MALDI-TOF matrix-assisted laser desorption ionization–time of flight mass spectrometry, PAS periodic acid–Schiff, and PCR polymerase chain reaction.

Table 2. Approaches to the Management of Coccidioidomycosis and Histoplasmosis in Immunocompetent Persons.*

Clinical Manifestation		Coccidioidomycosis		Histoplasmosis	
		Management	Comments	Management	Comments
Initial pulmonary infection					
Mild symptoms		No antifungal treatment or fluconazole, 400 mg/day for 3–6 mo†	No controlled trials or consensus on the need for antifungal treatment	No antifungal treatment or itraconazole, 200 mg twice a day for 6–12 wk‡	Self-limited infection; if symptoms persist for >4 wk, treatment may be beneficial
Moderate-to-severe symptoms or clinically significant coexisting cardiopulmonary disorders		Fluconazole, 400 mg/day, or lipid amphotericin B, 3 mg/kg/day, initially, then fluconazole for ≥6 mo	Treatment may be needed for as long as 1 yr, depending on severity of infection	Itraconazole, 200 mg twice a day, or liposomal amphotericin B, 3 mg/kg/day, initially, then itraconazole for 3–12 mo	Severe pneumonia may require hospitalization and ventilatory support; duration of treatment depends on severity of infection
Pulmonary nodules					
Asymptomatic residual nodules		No antifungal treatment	Important to rule out cancer	No antifungal treatment	Important to rule out cancer
Fever, malaise, cough, dyspnea		Not commonly encountered		Itraconazole, 200 mg twice a day for 6–12 wk	
Pulmonary complications					
Asymptomatic cavity		No antifungal treatment	Often thin-walled	No antifungal treatment	Not commonly seen with histoplasmosis
Cavitary infection with fever, fatigue, sputum production, hemoptysis, dyspnea		Fluconazole, 400 mg/day for 1 yr or longer; posaconazole,§ 300 mg/day, can be given in refractory cases	Symptoms may recur when treatment is stopped; surgical resection in selected patients	Itraconazole, 200 mg twice a day for 1–2 yr, or posaconazole, 300 mg/day for 1–2 yr	Usually occurs in persons with advanced COPD; progressive course if not treated
Ruptured cavity, pyopneumothorax		Prompt surgical correction		Not commonly encountered	
Mediastinal lymphadenitis		Not commonly encountered		No antifungal treatment or itraconazole, 5–10 mg/kg/day in 2 doses for 6–12 wk	Seen mostly in children; glucocorticoids sometimes given for several weeks to decrease inflammation
Mediastinal granuloma		Not commonly encountered		No antifungal treatment or itraconazole, 200 mg twice a day for 6–12 wk	Not clear whether antifungal agents are useful, but they are often tried; surgery may be needed to relieve compression of mediastinal structures
Mediastinal fibrosis		Not commonly encountered		No antifungal treatment	Intravascular stenting helpful to decrease vascular compromise

Disseminated infection

Mild systemic symptoms, one or more local lesions, or both	Soft-tissue lesions: fluconazole, 400 mg/day for ≥1 yr; skeletal lesions: fluconazole, 800 mg/day or a higher dose, or itraconazole, 200 mg twice a day for ≥2 yr	Surgical débridement to treat abscesses, or stabilize skeleton	Itraconazole, 200 mg twice a day for 6–12 mo	Localized lesions uncommon; usually multisystem involvement. If itraconazole has unacceptable side effects, posaconazole, 300 mg/day for 6–12 mo
Moderate-to-severe systemic symptoms and multisystem involvement	Lipid amphotericin B, 3 mg/kg/day for 2–6 wk, then fluconazole, 400 mg/day or a higher dose for >1 yr	Surgical débridement to treat abscesses, or stabilize skeleton	Liposomal amphotericin B, 3 mg/kg/day until improvement occurs, then itraconazole, 200 mg twice a day for 1 yr	If itraconazole has unacceptable side effects, posaconazole, 300 mg/day for 1 yr for step-down therapy
Meningitis (CNS infection)	Lifelong fluconazole, 400 mg/day or higher dose, or other azoles	Intrathecal amphotericin B is uncommonly used for refractory infections; hydrocephalus usually requires a ventriculoperitoneal shunt	Liposomal amphotericin B, 5 mg/kg/day for 6 wk, then itraconazole, 200 mg twice a day, or voriconazole, 200–400 mg twice a day for ≥1 yr¶	Duration of treatment not known; many patients treated for longer than 1 yr, some for life

* For all triazoles, drug–drug interactions are numerous and should be carefully assessed before treatment is started. Information on drug–drug interactions is available at www.drugs.com/drug_interactions.html. CAP denotes community-acquired pneumonia, and COPD chronic obstructive pulmonary disease.

† Fluconazole is well absorbed; therapeutic drug monitoring is typically not performed.

‡ Itraconazole absorption is variable. A loading dose of 200 mg three times a day for 3 days should be given, followed by 200 mg twice a day. Itraconazole suspension can be given without food and in patients taking gastric acid–inhibiting agents, but its taste may be disagreeable for some patients. Itraconazole capsule formulation requires both food and gastric acid for maximal absorption, cannot be given with gastric acid–inhibiting agents, and is less likely to be associated with unacceptable adverse effects than the suspension. Therapeutic drug levels should be measured after approximately 2 weeks of therapy, when a steady state is reached, to ensure adequate absorption and avoid toxic effects. The preference is for serum concentrations that are higher than 2 µg per milliliter and lower than 4 µg per milliliter (combined itraconazole and hydroxyitraconazole concentrations, measured with high-performance liquid chromatography).

§ Posaconazole delayed-release tablets, at a loading dose of 300 mg twice a day for the first day, followed by 300 mg per day, are given with food. Therapeutic drug monitoring should be performed, with a goal of a serum concentration that is higher than 1.75 µg per milliliter and lower than 3.75 µg per milliliter.

¶ A loading dose of either oral or intravenous voriconazole, 6 mg per kilogram of body weight twice a day, is given for the first day, followed by 4 mg per kilogram twice a day. The oral dose should be taken on an empty stomach. Therapeutic drug monitoring should be performed, with a goal of serum concentrations that are higher than 2 µg per milliliter and lower than 5.5 µg per milliliter.

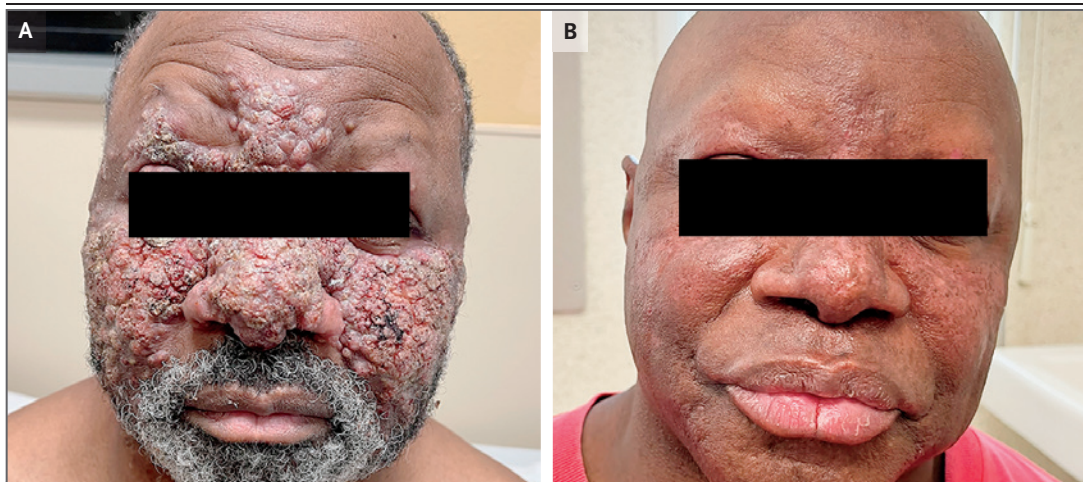


Figure 3. Cutaneous Coccidioidomycosis before and after Treatment.

A 65-year-old man with extensive cutaneous coccidioidomycosis (Panel A) was treated with oral fluconazole at a dose of 400 mg per day. The lesions resolved after several months of oral treatment (Panel B).

the general approach to diagnosis and treatment. It is hoped that a fuller appreciation of these differences will help clinicians understand the important health issues posed by these two endemic mycoses.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Bridget M. Barker, at Northern Arizona University, and Drs. Arati Pandya and Ron Galbraith, at Carl T. Hayden Veterans Administration Medical Center, for providing histopathological and clinical images.

REFERENCES

- Hawksworth DL, Lücking R. Fungal diversity revisited: 2.2 to 3.8 million species. *Microbiol Spectr* 2017;5(4).
- Gorris ME, Treseder KK, Zender CS, Randerson JT. Expansion of coccidioidomycosis endemic regions in the United States in response to climate change. *Geohealth* 2019;3:308-27.
- Baum GL, Schwarz J. The history of histoplasmosis, 1906 to 1956. *N Engl J Med* 1957;256:253-8.
- Hirschmann JV. The early history of coccidioidomycosis: 1892-1945. *Clin Infect Dis* 2007;44:1202-7.
- Fisher MC, Koenig GL, White TJ, Taylor JW. Molecular and phenotypic description of *Coccidioides posadasii* sp. nov., previously recognized as the non-California population of *Coccidioides immitis*. *Mycologia* 2002;94:73-84.
- Mead HL, Hamm PS, Shaffer IN, et al. Differential thermotolerance adaptation between species of *Coccidioides*. *J Fungi (Basel)* 2020;6:14.
- Sepúlveda VE, Márquez R, Turissini DA, Goldman WE, Matute DR. Genome sequences reveal cryptic speciation in the human pathogen *Histoplasma capsulatum*. *mBio* 2017;8(6):e01339-17.
- Develoux M, Amona FM, Hennequin C. Histoplasmosis caused by *Histoplasma capsulatum* var. *duboisii*: a comprehensive review of cases from 1993 to 2019. *Clin Infect Dis* 2021;73(3):e543-e549.
- Edwards PQ, Palmer CE. Prevalence of sensitivity to coccidioidin, with special reference to specific and nonspecific reactions to coccidioidin and to histoplasmin. *Dis Chest* 1957;31:35-60.
- McCotter OZ, Benedict K, Engelthaler DM, et al. Update on the epidemiology of coccidioidomycosis in the United States. *Med Mycol* 2019;57:Suppl 1:S30-S40.
- Scully MC, Baddley JW. Epidemiology of histoplasmosis. *Curr Fungal Infect Rep* 2018;12:51-8.
- Benedict K, Thompson GR III, Deresinski S, Chiller T. Mycotic infections acquired outside areas of known endemicity, United States. *Emerg Infect Dis* 2015;21:1935-41.
- Benedict K, Toda M, Jackson BR. Revising conventional wisdom about histoplasmosis in the United States. *Open Forum Infect Dis* 2021;8(7):ofab306.
- Hepler SA, Kaufeld KA, Benedict K, et al. Integrating public health surveillance and environmental data to model presence of histoplasma in the United States. *Epidemiology* 2022;33:654-9.
- Dingle TC, Croxen MA, Fathima S, et al. Histoplasmosis acquired in Alberta, Canada: an epidemiological and genomic study. *Lancet Microbe* 2021;2(5):e191-e197.
- Edwards LB, Acquaviva FA, Livesay VT, Cross FW, Palmer CE. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *Am Rev Respir Dis* 1969;99:Suppl:1-132.
- Smith CE, Beard RR. Varieties of coccidioid infection in relation to the epidemiology and control of the diseases. *Am J Public Health Nations Health* 1946;36:1394-402.
- Thompson GR III, Chiller TM. Endemic mycoses: underdiagnosed and underreported. *Ann Intern Med* 2022;175:1759-60.
- DiCaudo DJ, Yiannias JA, Laman SD, Warschaw KE. The exanthem of acute pulmonary coccidioidomycosis: clinical and histopathologic features of 3 cases and review of the literature. *Arch Dermatol* 2006;142:744-6.
- Tsang CA, Anderson SM, Imholte SB, et al. Enhanced surveillance of coccidioidomycosis, Arizona, USA, 2007-2008. *Emerg Infect Dis* 2010;16:1738-44.
- Galgiani JN, Blair JE, Ampel NM, Thompson GR. Treatment for early, uncomplicated coccidioidomycosis: what is success? *Clin Infect Dis* 2020;70:2008-12.
- Goodwin RA, Loyd JE, Des Prez RM. Histoplasmosis in normal hosts. *Medicine (Baltimore)* 1981;60:231-66.
- National Academies of Sciences, Engineering, and Medicine. Impact and control

- of valley fever: proceedings of a workshop in brief. Washington, DC: National Academies Press, 2023 (<https://doi.org/10.17226/26928>).
24. Benedict K, McCracken S, Signs K, et al. Enhanced surveillance for histoplasmosis — 9 States, 2018-2019. *Open Forum Infect Dis* 2020;7(9):ofaa343.
 25. Benedict K, Ireland M, Weinberg MP, et al. Enhanced surveillance for coccidioidomycosis, 14 US States, 2016. *Emerg Infect Dis* 2018;24:1444-52.
 26. Pu J, Miranda V, Minior D, et al. Improving early recognition of coccidioidomycosis in urgent care clinics: analysis of an implemented education program. *Open Forum Infect Dis* 2023;10(1):ofac654.
 27. Blair JE, Ampel NM, Hoover SE. Coccidioidomycosis in selected immunosuppressed hosts. *Med Mycol* 2019 57:Suppl: S56-S63.
 28. Adamian CMC, de Lima Mota MA, Martins AAF, et al. Progressive disseminated histoplasmosis in HIV-positive patients. *Int J STD AIDS* 2022;33:544-53.
 29. Vergidis P, Avery RK, Wheat LJ, et al. Histoplasmosis complicating tumor necrosis factor- α blocker therapy: a retrospective analysis of 98 cases. *Clin Infect Dis* 2015;61:409-17.
 30. Ciochetto Z, Georgen M, Hadro A, et al. Reactivation of *Coccidioides immitis* in a prosthetic knee after initiation of chemotherapy. *Case Rep Hematol* 2021;2021:3964465.
 31. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev* 2007;20:115-32.
 32. Sachdeva M, Ronaghi R, Mills PK, Peterson MW. Complications and yield of computed tomography-guided transthoracic core needle biopsy of lung nodules at a high-volume academic center in an endemic coccidioidomycosis area. *Lung* 2016; 194:379-85.
 33. Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA. Current concepts in the epidemiology, diagnosis, and management of histoplasmosis syndromes. *Semin Respir Crit Care Med* 2020;41:13-30.
 34. Staszak JK, Zmijewski P, Arnold S, Bagga B, Williams RE. Mediastinal lymphadenopathy in children with histoplasmosis. *J Surg Res* 2019;244:558-65.
 35. Landay MJ, Rollins NK. Mediastinal histoplasmosis granuloma: evaluation with CT. *Radiology* 1989;172:657-9.
 36. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore)* 2011;90:412-23.
 37. Davis AM, Pierson RN, Loyd JE. Mediastinal fibrosis. *Semin Respir Infect* 2001; 16:119-30.
 38. Echols RM, Palmer DL, Long GW. Tissue eosinophilia in human coccidioidomycosis. *Rev Infect Dis* 1982;4:656-64.
 39. Santelli AC, Blair JE, Roust LR. Coccidioidomycosis in patients with diabetes mellitus. *Am J Med* 2006;119:964-9.
 40. Shemuel J, Bays DJ, Thompson GR III, et al. Natural history of pulmonary coccidioidomycosis: further examination of the VA-Armed Forces Database. *Med Mycol* 2022;60(10):myac054.
 41. Sarosi GA, Parker JD, Doto IL, Tosh FE. Chronic pulmonary coccidioidomycosis. *N Engl J Med* 1970;283:325-9.
 42. Ashfaq A, Vikram HR, Blair JE, Jaroszewski DE. Video-assisted thoracoscopic surgery for patients with pulmonary coccidioidomycosis. *J Thorac Cardiovasc Surg* 2014;148:1217-23.
 43. Goodwin RA Jr, Owens FT, Snell JD, et al. Chronic pulmonary histoplasmosis. *Medicine (Baltimore)* 1976;55:413-52.
 44. Baker J, Kosmidis C, Rozaliyani A, Wahyuningsih R, Denning DW. Chronic pulmonary histoplasmosis — a scoping literature review. *Open Forum Infect Dis* 2020;7(5):ofaa119.
 45. Goodwin RA Jr, Des Prez RM. Pathogenesis and clinical spectrum of histoplasmosis. *South Med J* 1973;66:13-25.
 46. Humphrey PA. Fungal prostatitis caused by coccidioides. *J Urol* 2014;191:215-6.
 47. Bays DJ, Thompson GR, Reef S, et al. Natural history of disseminated coccidioidomycosis: examination of the Veterans Affairs-Armed Forces Database. *Clin Infect Dis* 2021;73(11):e3814-e3819.
 48. Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. *Medicine (Baltimore)* 2007;86:162-9.
 49. Wheat LJ, Slama TG, Norton JA, et al. Risk factors for disseminated or fatal histoplasmosis: analysis of a large urban outbreak. *Ann Intern Med* 1982;96:159-63.
 50. Goodwin RA Jr, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. *Medicine (Baltimore)* 1980;59:1-33.
 51. Wheat J. Histoplasmosis: experience during outbreaks in Indianapolis and review of the literature. *Medicine (Baltimore)* 1997;76:339-54.
 52. MacInnes R, Warris A. Paediatric histoplasmosis 2000-2019: a review of 83 cases. *J Fungi (Basel)* 2021;7:448.
 53. Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. *Emerg Infect Dis* 2017;23:308-11.
 54. Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. *Clin Infect Dis* 2005;41(4):e38-e41.
 55. Hsu AP, Korzeniowska A, Aguilar CC, et al. Immunogenetics associated with severe coccidioidomycosis. *JCI Insight* 2022;7:15.
 56. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020;71:1367-76.
 57. Pappagianis D, Zimmer BL. Serology of coccidioidomycosis. *Clin Microbiol Rev* 1990;3:247-68.
 58. Lindsley MD, Ahn Y, McCotter O, et al. Evaluation of the specificity of two enzyme immunoassays for coccidioidomycosis by using sera from a region of endemicity and a region of nonendemicity. *Clin Vaccine Immunol* 2015;22:1090-5.
 59. Thompson GR, Ampel NM, Blair JE, et al. Controversies in the management of central nervous system coccidioidomycosis. *Clin Infect Dis* 2022;75:555-9.
 60. McHardy IH, Barker B, Thompson GR III. Review of clinical and laboratory diagnostics for coccidioidomycosis. *J Clin Microbiol* 2023;61(5):e0158122.
 61. Linder KA, Kauffman CA. Current and new perspectives in the diagnosis of blastomycosis and histoplasmosis. *J Fungi (Basel)* 2020;7:12.
 62. Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. *J Clin Microbiol* 2017;55:1612-20.
 63. Richer SM, Smedema ML, Durkin MM, et al. Improved diagnosis of acute pulmonary histoplasmosis by combining antigen and antibody detection. *Clin Infect Dis* 2016;62:896-902.
 64. de Oliveira VF, Kruschewsky WLL, Sekiguchi WK, et al. Clinical, radiological and laboratory characteristics of central nervous system histoplasmosis: a systematic review of a severe disease. *Mycoses* 2023;66:659-70.
 65. Gupta S, Ashcherkin N, Blair JE. Do all patients with primary pulmonary coccidioidomycosis need antifungal therapy? *Cleve Clin J Med* 2022;89:451-5.
 66. 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;63(6):e112-e146.
 67. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2007; 45:807-25.
 68. Pasqualotto AC, Lana DD, Godoy CSM, et al. Single high dose of liposomal amphotericin B in human immunodeficiency virus/AIDS-related disseminated histoplasmosis: a randomized trial. *Clin Infect Dis* 2023;77:1126-32.
 69. Galgiani JN, Shubitz LF, Orbach MJ, et al. Vaccines to prevent coccidioidomycosis: a gene-deletion mutant of coccidioides posadasii as a viable candidate for human trials. *J Fungi (Basel)* 2022;8:838.
 70. Shubitz LF, Robb EJ, Powell DA, et al. Acps1 vaccine protects dogs against experimentally induced coccidioidomycosis. *Vaccine* 2021;39:6894-901.
 71. Rando HM, Lordan R, Kolla L, et al. The coming of age of nucleic acid vaccines during COVID-19. *mSystems* 2023;8(2): e0092822.

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