Coccidioidomycosis and other endemic mycoses in Mexico

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The endemic mycoses traditionally include coccidioidomycosis, histoplasmosis, blastomycosis and paracoccidioidomycosis. Although sporotrichosis and chromomycosis are technically not included among the endemic mycoses, they are frequently diagnosed in Mexico. Most systemic endemic mycoses are a consequence of inhaling the fungi, while subcutaneous mycoses are acquired through the inoculation of vegetable matter or soil containing the organism.
Coccidioidomycosis is caused by *Coccidioides* spp., a dimorphic pathogenic fungus. Approximately 60% of exposures result in asymptomatic infection; in the rest there are protean manifestations that range from a benign syndrome also known as "Valley Fever" to progressive pulmonary or extrapulmonary disease.
Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is endemic to the Americas. Pulmonary histoplasmosis manifestations are protean, ranging from a brief period of malaise to a severe, prolonged illness.
The spectrum of illness in disseminated histoplasmosis ranges from a chronic, intermittent course to an acute and rapidly fatal infection.
Paracoccidioidomycosis is a chronic, granulomatous systemic disease caused by *Paracoccidioides brasiliensis* that characteristically produces a primary pulmonary infection, often asymptomatic, and then disseminates to form ulcerative granulomata of the oral, nasal and occasionally the gastrointestinal mucosa.
Sporotrichosis, caused by *Sporothrix schenckii*, has diverse clinical manifestations; the most frequent is the lymphocutaneous form. Generally, infection results from inoculation of the fungus through thorns, splinters, scratches and small traumas.
Chromomycosis (Chromoblastomycosis) is a slowly progressive cutaneous and subcutaneous mycosis attributed to various saprophyte *Hypomycetes* fungi. The primary lesion is also thought to develop as a result of percutaneous traumatic inoculation.

Coccidioidomicosis y otras micosis endémicas en México

El término de micosis endémicas tradicionalmente incluye a la coccidioidomicosis, la histoplasmosis, la blastomicosis y la paracoccidioidomicosis. A pesar de que la esporotricosis y la cromoblastomicosis no se incluyen en este grupo, son diagnosticadas frecuentemente en México.
La coccidioidomicosis es causada por el hongo dimórfico *Coccidioides* spp. Aproximadamente 60% de las infecciones evolucionan en forma asintomática; en el resto existen manifestaciones muy diversas que van desde un cuadro benigno conocido como "Fiebre del Valle" hasta formas progresivas pulmonares o diseminadas.
La histoplasmosis, causada por el hongo dimórfico *Histoplasma capsulatum*, es endémica en las regiones templadas del mundo, incluyendo el continente americano. La histoplasmosis pulmonar presenta también manifestaciones muy variadas, que van desde un síndrome breve y autolimitado, hasta un cuadro severo y prolongado. Las formas diseminadas pueden presentar una evolución tórpida e intermitente, o rápidamente fatal.
La paracoccidioidomycosis es una enfermedad sistémica crónica cuyo agente etiológico es el *Paracoccidioides brasiliensis*. Típicamente produce infección pulmonar asintomática, y posteriormente se disemina con la formación de granulomas ulcerados en la mucosa oral, nasal y ocasionalmente gastrointestinal.
La esporotricosis, causada por *Sporothrix schenckii*, tiene diversas manifestaciones clínicas, de las cuales la más frecuente es la forma linfocutánea. La infección casi siempre resulta de la inoculación percutánea del hongo como consecuencia de traumas menores.
La cromomicosis es una micosis cutánea y subcutánea, progresiva, atribuida a diversos hongos *Hypomycetes*. La infección también casi siempre resulta de la inoculación percutánea del hongo como consecuencia de traumas menores.

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The endemic mycoses traditionally include coccidioidomycosis, histoplasmosis, blastomycosis and paracoccidioidomycosis. All of them are caused by fungi that share important characteristics. These organisms are true pathogens in that they are capable of causing infection in otherwise healthy persons. The severity of infection is determined both by the extent of the exposure to the organism and by the immune status of the patient.

Most systemic endemic mycoses are a consequence of inhaling the fungus, while subcutaneous mycoses are acquired through the inoculation of vegetable matter or soil containing the organism [1].

Although sporotrichosis and chromomycosis are technically not included among the endemic mycoses, they are frequently diagnosed in Mexico and therefore will be included in this review.

Blastomycosis, a systemic mycosis caused by the dimorphic fungus *Blastomyces dermatitidis* is not endemic to Mexico, where only two non-autochthonous cases have been reported [7,18]. It will not be discussed further.

Early recognition of these diseases can be challenging because the endemic mycoses can mimic many common infections. The mobility of the population nowadays coupled with the ability of these diseases to remain dormant in the host's body for prolonged periods of time explain why patients with endemic mycoses frequently present outside the classic endemic areas.

Endemic mycoses remain a major public health problem in Mexico. They are most often acquired through contact with nature and rarely with infected humans or animals. Most cases in Mexico originate in rural areas, particularly in low socioeconomic groups.

Coccidioidomycosis

Coccidioidomycosis was the first of the major mycoses to become recognized [37]. It is caused by *Coccidioides* spp., a dimorphic pathogenic fungus.

Ecology. The endemic region for *Coccidioides* spp. lies exclusively in the Western Hemisphere [52], between 40 degree latitudes north and south. This life zone corresponds with the hot deserts of the southwestern United States and northwestern Mexico. The climate in this region is arid with a yearly rainfall ranging from 10 to 50 centimeters, with extremely hot summers, winters with few freezes and alkaline, sandy soil [40,82] (Figure 1).

Cases of coccidioidomycosis may also arise outside endemic areas, related to a recent visit to an endemic area or infection through exposure to fomites from such an area [33].

Etiology and Epidemiology. There are two nearly identical species of *Coccidioides*: *Coccidioides immitis*, which is found in California, and *Coccidioides posadasii*, formerly known as non-California *C. immitis*, which is found primarily in Texas, Arizona, and the areas of endemicity in Mexico, Central and South America [103]. These two species of fungi are genetically different, but at this time they cannot be distinguished phenotypically, nor is the disease or immune response to the organism's distinguishable [21].

Coccidioides spp. grow as a mold in the soil and develop hyphae in their saprobic form, producing arthroconidia. As the soil dries or nutrients become limiting, the fungus reproduces asexually by disarticulating the hyphae into small, environmentally-resistant arthroconidia. These are easily aerosolized when the soil is disturbed by wind or human activities. Consequently, it is the inhalation of the dust-borne arthroconidia that leads to infection in both humans and domestic or wild mammals. Upon inhalation, the fungus converts to a unique life cycle of alternating spherules and progeny endospores, which comprises the parasitic phase of this dimorphic fungus [52,98]. Coccidioidomycosis is not contagious; reports of human-to-human spread are extremely rare.

The main risk factors for acquiring the infection or developing active disease are dust exposure (since *Coccidioides* infects humans by the respiratory route, exposure to dust is one critical factor), sex (males are more often infected, which is likely related to occupational dust exposures) [21,23,40,61,82], race (although there is no known race predilection for the acquisition of the infection, disseminated disease occurs 10-175 times more often among Filipinos and African Americans) [29], pregnancy (could be related to high levels of hormones that stimulate the growth of the fungus) [32], age, and immunosuppression (including that associated with solid organ transplantation [65] and hemodyalisis [1]).

Acquired resistance to coccidioidomycosis strongly correlates with the development of delayed-type hypersensitivity skin test response to coccidioidal antigens and the production of T-helper-1 (Th1)-associated cytokines to coccidioidal antigens, such as interferon-gamma (IFN-γ) and interleukin-2 (IL-2). Humoral immunity plays no known role in overcoming infection [52].

Coccidioidomycosis is a recognized opportunistic infection among persons infected with human immunodeficiency virus (HIV). Early in the HIV epidemic, most cases presented as overwhelming diffuse pulmonary disease with a high mortality rate. The incidence of severe symptomatic coccidioidomycosis has declined dramatically since the advent of potent antiretroviral therapy [4,6].

In recent years the incidence of the disease has increased in California and Arizona, which may be partially due to the massive migration of Americans to the

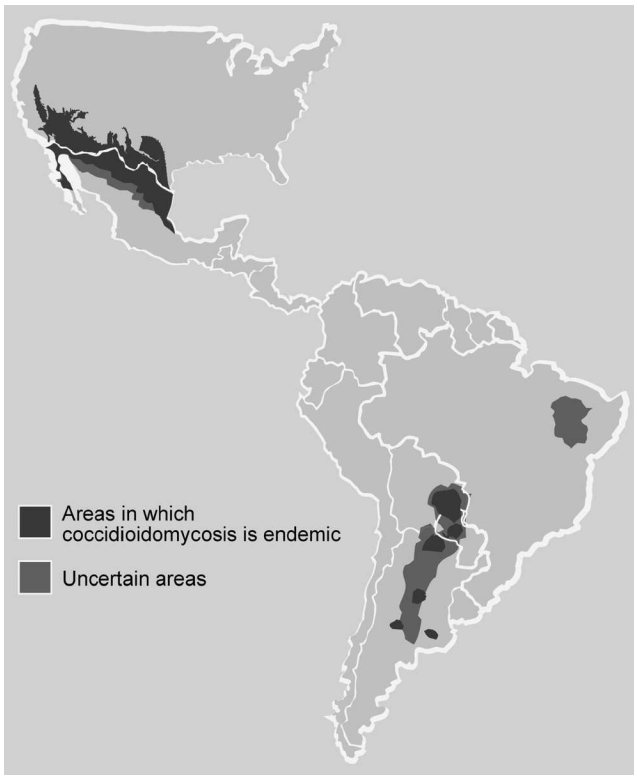

Figure 1: Geographic distribution of Coccidioidomycosis (From Hector RF, Laniado-Laborin R [52]).

Sunbelt states and, in particular, to Arizona, one of the fastest-growing states in the United States [41].

Statistics on the prevalence and incidence of coccidioidomycosis in Latin America either are fragmentary or simply not available. In Mexico most clinical case reports originate in the northern region of the country. Since it is not a reportable disease, its true incidence is unknown [20].

Skin test surveys carried out in Mexico indicate that coccidioidomycosis is as prevalent there as in the endemic areas of the United States [2]. The studies by González-Ochoa (*Encuesta Nacional 1961-1965*) with coccidioidin skin testing defined the epidemiologic distribution of *Coccidioides* spp. infection in Mexico [48]. More recently, skin testing regional surveys for prevalence of infection have shown rates of 10% (Tijuana, Baja California, 1991 [63]), 40% (Torreón, Coahuila, 1999 [81]) and 93% (12 communities in the state of Coahuila, 2005 [75]).

As mentioned, coccidioidomycosis is caused by two nearly identical species, *C. immitis* and *C. posadasii*. To determine the prevalent species in Mexico, Bialek et al [11], through conventional nested PCR and real-time PCR assay, tested 120 clinical strains isolated in Monterrey, Mexico. All the strains corresponded to the Silveira strain (now known to be *C. posadasii*).

Clinical Features. Approximately 60% of exposures to the fungus result in asymptomatic infection or have symptoms mild enough that medical attention is not sought [40,94]. In the rest of infected individuals who have symptomatic disease, there are protean manifestations that range from a primary (usually benign) pulmonary infection, also known as "Valley Fever" to a progressive pulmonary or extrapulmonary disease [52].

Primary pulmonary disease is a usually sub-acute and self-limited syndrome, characterized by fatigue, cough, chest pain, dyspnea and, occasionally, hemoptysis. Systemic symptoms include fever, arthralgia and diverse skin reactions (maculopapular rash, erythema multiforme, erythema nodosum).

Fortunately most patients with primary disease recover spontaneously and retain lifelong immunity to exogenous infection [52].

People with compromised immune systems are particularly susceptible to chronic forms of pulmonary disease, characterized by complications such as pleural empyema and bronchopleural fistulas [96].

Chest radiographs might show pneumonia plus hilar adenopathy, cavities, pleural effusion, pneumothorax or pulmonary nodules [40].

Diffuse involvement of the lungs is secondary to fungemia and a manifestation of widespread infection. It is usually a complication in immunocompromised patients such as those with lymphoma, organ transplants or acquired immunodeficiency syndrome (AIDS) [6,40]. Coccidioidomycosis is a recognized opportunistic infection among persons infected with HIV.

Extrapulmonary coccidioidomycosis is almost always the result of hematogenous spread from an initial pulmonary focus. Symptomatic extrapulmonary disease develops in about 1 of 200 people infected with *Coccidioides* [96]. The most frequently affected sites are the skin, joints, bones and meninges [40].

Meningeal infection is the most serious form of the disease; it occurs in about 0,5% of extrapulmonary cases and requires treatment for life [43,57].

Tuberculosis and coccidioidomycosis share epidemiological, clinical, radiographic and even histopathological features. Because tuberculosis also is endemic in Mexico, coccidioidomycosis and tuberculosis frequently coexist making the correct diagnosis of both entities extremely difficult. In areas where both diseases are endemic the pertinent studies for diagnosing both conditions should be performed in every patient with compatible clinical features. The diagnosis of one does not exclude the possible existence of the other [19,52].

Diagnosis. The definite method for establishing the diagnosis of coccidioidomycosis is the isolation of the fungus from a clinical specimen. *Coccidioides* spp. readily grow on most media used in clinical laboratories. They grows rapidly, and can be detected within five days after the media has been inoculated. Colonial structure of the mycelial phase is not diagnostic; identification is done through a commercial DNA probe [40]. It must be remembered that *Coccidioides* spp. cultures pose a risk to laboratory personnel because the mycelial form is highly infectious. Cultures should processed only within a biological containment cabinet by experienced personnel.

The identification of spherules in infected tissues or cytologic preparations is also considered as diagnostic, although neither technique has the sensitivity of culture isolation [40].

A skin test using *Coccidioides* spp. antigens, coccidioidin or spherulin can detect delayed hypersensitivity. Its major use is in the epidemiologic evaluation of populations exposed to the fungus. A positive test indicates that infection has occurred but does not indicate when. A negative test does not exclude active infection; indeed, the test is often negative in patients with disseminated disease [5].

One of the best tests currently available for the diagnosis of fungal infections is the serological test for Coccidioidomycosis [30]. An IgM precipitating antibody appears early in the course of the disease, so its presence is an indication of acute disease. After a couple of months after the initial infection, a complement fixation (CF) IgG antibody gradually appears and peaks in approximately 70% of the patients; it will persist if the patient develops disseminated disease. Coccidioidal serology is also valuable in that it inversely follows response to therapy, and thus can be used prognostically. CF titers should decrease under effective treatment, and the reverse is also true. A rise in CF antibody titers should prompt intensification or a change in therapy. CF titers are also useful in distinguishing patients that have localized versus those with disseminated disease. Titers of 1:16-1:32 or more are associated with disseminated disease. These elevated titers can appear before there is any clinical evidence of dissemination [97].

Treatment. Management of coccidioidomycosis first involves recognizing that a coccidial infection exists and then defining the extent of infection and identifying host factors that predispose to disease severity. After these assessments, patients with localized acute pulmonary infections and no risk factors for complications, according to the current treatment guidelines of the Infectious Disease Society of America [43], require only periodic reassessment to demonstrate resolution of their self-limited disease. In recent years however, an increasing number of physicians are prescribing azole antifungals for primary disease, both because these drugs have a good safety record, and because there is a perception that treatment may prevent progression to more serious forms of the disease. This latter presumption however, is not supported by controlled trial data [52].

Patients with extensive spread of infection or who are at high risk of complications because of immunosuppression or other preexisting factors require treatment that may include antifungal drug therapy, surgical debridement, or a combination of both [43].

There are two classes of antifungal therapy routinely used for treatment of coccidioidomycosis. The first

class is the polyenes, with amphotericin B desoxycholate and the newer lipid formulations used for the more serious forms of disease. The second class is the azoles, with fluconazole, itraconazole, and the newer analogues voriconazole and posaconazole as available options [52]. In Mexico treatment usually consists of one of the azoles (fluconazole or itraconazole) and/or amphotericin B desoxycholate; lipid formulations are too costly to be accessible [52].

Itraconazole and fluconazole have replaced amphotericin B as the initial therapy of choice for most chronic pulmonary or disseminated infections. Amphotericin B is now reserved for patients with severely acute forms complicated with respiratory failure, those with rapidly progressive coccidioidal infections, or women during pregnancy. Nephrotoxicity, the most serious adverse effect, is manifested by azotemia and hypokalemia, requiring potassium supplementation. Normocytic anemia can also occur but, like azotemia, usually resolves after discontinuation of the medication [43].

Typically, prescribed therapies for acute primary forms include an oral azole antifungal agent at dosages of 200-400 mg per day; duration of treatment range from 3 to 6 months [43]. Treatment of the more serious or aggressive forms of the disease is typically of long duration and often results in less than complete resolution of disease; relapse is common [42].

Disease is only suppressed in patients with meningitis who achieve remission while receiving azole therapy and discontinuing therapy is considered unsafe. The alternative is lifelong treatment with azoles; this appears to be acceptable, because toxicity is uncommon with triazole therapy, even when used for long periods of time [34].

Surgery is sometimes indicated to remove focalized infections, such as pulmonary cavities, or to debride soft tissue or osseous forms of the disease [54]. Recovery from disease confers lifelong immunity to reinfection, and is a rationale for the development and implementation of a vaccine for the prevention of symptomatic or serious forms of the disease. A university-based consortium, the Valley Fever Vaccine Project (www.valleyfever.com), has identified and cloned immunogenic proteins that have proven effective in the prevention of deaths and fungal burdens in mouse models of coccidioidomycosis. This suggests that a vaccine for use in humans could be created [52].

Histoplasmosis

Ecology and epidemiology. Histoplasmosis, caused by the dimorphic fungus *Histoplasma capsulatum*, is endemic to the temperate zones of the world, including the Americas, Asia, and Africa [87]. It is highly endemic to the Ohio and Mississippi river valleys of the United States. An estimated 40 million people in the United States have been infected with *H. capsulatum*, with 500,000 new cases occurring each year [62].

Outbreaks of acute histoplasmosis have often been reported. These outbreaks have usually been associated with disturbances of accumulations of bird or bat droppings. The exposures to droppings have typically occurred while visiting caves or following cleaning and construction activities at infested sites in endemic areas [17,105]. In areas endemic for histoplasmosis typical exposures to accumulated bird or bat droppings may not be necessary for infection. People may be exposed to environmental sources of the disease regardless of their activities while in these areas [77].

Although is highly likely that histoplasmosis has been endemic to Mexico since very remote eras, the first confirmed case in the country was reported in 1957 in a university student that had visited a cave contaminated with bat droppings [46]. Because the endemic mycoses are not included in the list of diseases that require an obligatory report to the health authorities in Mexico, the exact number of cases of histoplasmosis is unknown. During the period 1953-1997 a total of 102 outbreaks including 1,444 cases, were reported to the Instituto Nacional de Diagnóstico y Referencia Epidemiológica (INDRE) [25] and from 1988 through 1994 the Direccion General of Epidemiología reported 1,065 cases from several outbreaks (annual rate 0.1-0.29 per 100,000); most of the cases were diagnosed in the central and southeast region of the country (Veracruz, Oaxaca, Campeche, Colima and Tabasco). Histoplasmin skin test surveys in different regions of the country have revealed a prevalence of infection that ranges from 5 to 50% [49,88,92,100,101].

Pathogenesis. The mycelial form of *H. capsulatum* is found in the soil, especially in areas contaminated with bird or bat droppings, which provide added nutrients for growth. Infections are typically caused by wind-borne spores emanating from point sources such as bird roosts, old houses or barns, or just like in coccidioidomycosis, activities involving disruption of the soil such as farming and excavation. *H. capsulatum* infection is not transmissible through person-to-person contact [62].

When spores produced by the mycelial form of *H. capsulatum* become airborne, they are inhaled and deposited in alveoli. At normal body temperature the spores germinate into yeast and are ingested by pulmonary macrophages. The yeasts become parasitic, multiply within these cells, and travel to hilar and mediastinal lymph nodes, where they gain access to the blood circulation that disseminate them to various organs. About 10 to 14 days after exposure, cellular immunity develops, and macrophages become fungicidal and control the infection. Necrosis develops at the sites of infection leading to caseation, fibrous encapsulation, calcium deposition and, within a few years of the primary infection, calcified granulomas [62]. After initial infection, the organism can persist in the host for years and reactivate when immunity wanes [39,110]. It is possible that *H. capsulatum* survives for long periods of time in more than one type of host cell [86].

Cellular immunity attained through previous exposure decreases the incidence and severity of symptomatic infections. Therefore, infants and children are affected more frequently than adults. Any defects in cellular immunity result in a progressive disseminated form of infection that can be lethal [62].

Clinical Presentation. Clinical diagnosis of histoplasmosis is based upon clinical, radiological and epidemiological aspects. Infection with *H. capsulatum* in immunocompetent individuals is typically asymptomatic or clinically insignificant. Symptomatic illness is usually caused by an intense exposure, and the severity of disease is related to the number of spores inhaled [62,101].

Acute pulmonary histoplasmosis manifestations are protean, ranging from a brief period of malaise to a severe, prolonged illness. Symptoms include fever, nonproductive cough, pleuritic chest pain, weight loss, malaise and myalgias. Symptoms usually resolve spontaneously [62,101].

The physical examination is frequently unremarkable; in symptomatic cases hepatosplenomegaly, adenopathy, erythema nodosum, and erythema multiforme can be encountered. Arthritis may occur as an inflammatory reaction to the primary infection, and distribution is often symmetric and polyarticular [62,101].

Acute pulmonary infections are not typically associated with abnormalities on chest radiography. The most frequent finding consists in airspace opacities, mostly in the lower lung areas; hilar and mediastinal adenopathy is sometimes present. More severe infections frequently show small diffuse pulmonary nodules; cavitation is rare [62].

Chronic pulmonary histoplasmosis is characterized by malaise, fatigue, low grade fever, mucoid sputum, chest pain, and weight loss; chest radiographs usually reveal reticulonodular and fibrotic lesions associated with cavitations [87].

The spectrum of illness in disseminated histoplasmosis ranges from a chronic, intermittent course in immunocompetent persons to an acute and rapidly fatal infection that usually occurs in infants [45,78] and severely immunosuppressed persons. Fever is the most common symptom; cephalalgia, anorexia, weight loss, and malaise are also frequent complaints. Physical examination may reveal hepatosplenomegaly and lymphadenopathy [28,78]. Laboratory evaluation frequently reveals pancytopenia caused by bone marrow involvement and abnormal results on hepatic function tests. Chest radiographs usually display small, diffuse, nodular opacities. Diffuse, interstitial infiltrates are common; on the contrary, airspace disease and adenopathy are rare [28,78].

Histoplasmosis is a common opportunistic infection in patients infected with HIV who reside in disease-endemic areas, especially in those with CD4 lymphocyte count below 150 to 200 per mm^3 [31,83]. Disseminated histoplasmosis has been an AIDS–defining illness since 1987 [22]. It is reported to occur in approximately 5% of patients with AIDS who live in disease-endemic areas.

Patients with lymphoreticular neoplasms and patients who are receiving corticosteroids, cytotoxic therapy, and immunosuppressive agents are also predisposed to disseminated histoplasmosis. Acute life-threatening histoplasmosis may complicate immunotherapy with tumor necrosis factor α (TNFα) antagonists, particularly infliximab. Histoplasmosis should be considered early in the evaluation of patients who reside in endemic areas in whom infectious complications develop during treatment with infliximab or etanercept [64]. About 20 percent of disseminated cases occur in otherwise healthy persons who have received a heavy inoculum [78].

Other clinical manifestations of histoplasmosis include granulomatous mediastinitis (with the presence of large caseous lymph nodes in the mediastinum), central nervous system histoplasmosis and a cutaneous form with no obvious evidence of disseminated disease. Cutaneous lesions are either, primary from direct inoculation or secondary from hematogenous dissemination [87].

Diagnosis. Histoplasmosis can be diagnosed by culture, fungal stains, serologic tests for antibodies, and antigen detection. The specific role of each test varies according to the clinical form, since variations in sensitivity have been associated to different clinical presentations. Skin testing is rarely useful because of high background positivity in endemic areas and false-negative results associated with chronic pulmonary and disseminated disease [62].

The gold standard method for diagnosis of histoplasmosis is the isolation of *H. capsulatum* in culture. *H. capsulatum* requires up to four weeks to grow in vitro.

Cultures of *Histoplasma capsulatum* represent a severe biohazard to laboratory personnel and must be handled with extreme caution in an appropriate pathogen handling cabinet [87].

Fungal staining of tissue is rapid but has a significantly lower sensitivity than culture or antigen detection. Bone marrow produces the highest yield, staining positive in as many as 75 percent of cases of disseminated disease (and up to 90% of AIDS patients) [97].

Serologic tests that detect antibodies to *H. capsulatum* are rapid and relatively sensitive but have some important limitations. False-negative results can occur in immunocompromised patients and during the first two months of the post-exposure period while antibodies are still developing. Precipitins to the M antigen rise early in disease and persist, but are increased by *Histoplasma* skin testing, and only 75% sensitive. Precipitins to H antigen rise late, do not persist, and have only 20% sensitivity. Neither is specific; both have false positives due to other diseases, including other fungal diseases. Complement fixing antibodies (CF) to the M antigen rise late, and titers are low; it is a less sensitive test compared with CF testing for Y antigen in primary infection, though in chronic disease it may be the only positive test. In general, CF testing is more useful for pulmonary forms of the disease, although variable in disseminated disease. There is no titer cut-off that it is useful for diagnosis, and other fungal diseases can produce false-positive results. In AIDS patients the immunodiffusion technique is only 50% sensitive and CF only 70% sensitive [97].

Antigen detection is a rapid means of diagnosis in patients with disseminated disease. Sensitivity is greater with urine (92 percent) than other fluids (serum, plasma, cerebrospinal fluid and bronchoalveolar lavage fluid); however, optimal diagnostic yield is the result of testing both urine and serum. Because antigen levels decrease with effective treatment and increase with relapse, this method is a useful tool in monitoring therapy [87]. The recommended approach is to carry out antigen testing in patients in whom histoplasmosis is suspected. Then the type of test selected will depend on the type of clinical presentation. In pulmonary disease bronchoalveolar lavage would be the sample of choice; in central nervous system disease, cerebrospinal fluid should be obtained for testing [97].

There is a recent report about the usefulness of a quantitative real-time polymerase chain reaction-based (RT-PCR) technique for clinical diagnosis of histoplasmosis. The RT-PCR assay was tested in 22 clinical samples from 14 patients with proven histoplasmosis. In addition, 30 samples from patients without histoplasmosis and from healthy volunteers were analyzed as controls. Sensitivity of the assay was 78.6%. It was positive in 100% of respiratory secretions and bone marrow samples, but only 70% of serum samples ($p < 0.01$). Also, RT-PCR results were positive in serum from three HIV patients for which antibody detection by immunodiffusion was negative. Specificity was 100%, since PCR results were negative for all the control samples [15].

Treatment. Treatment of histoplasmosis depends on the severity of the clinical syndrome. Mild cases may require only symptomatic measures, but antifungal therapy is indicated in all cases of chronic or disseminated disease and in severe or prolonged acute pulmonary infection. Treatment should be continued until all clinical findings have resolved and *H. capsulatum* antigen levels have returned to normal.

Amphotericin B is the therapeutic agent of choice for induction therapy of moderate to severe disseminated histoplasmosis [83,107]. However, treatment of severe disease with amphotericin B has not produced optimal results. Liposomal amphotericin B seems to be a less toxic alternative to amphotericin B and is associated with improved survival [56].

Treatment can usually be changed to an oral azole drug within a couple of weeks. Itraconazole is an effective

treatment in mild or moderate cases of disseminated histoplasmosis, as well as in acute and chronic pulmonary disease. Although itraconazole is not as rapid-acting as amphotericin, it has the advantage of being well tolerated even in long-term use. Most side effects, including headache, dizziness, and gastrointestinal symptoms, are transient. Biliary excretion eliminates the need for adjusting dosages in patients with renal disease; the risk of hepatitis is rare [106,107]. Fluconazole is less effective than amphotericin B or itraconazole in the treatment of histoplasmosis and is associated with more relapses [108].

The optimal treatment for CNS histoplasmosis in unknown; liposomal amphotericin B achieves higher concentrations in brain tissue than does the standard deoxycholate formulation and was a more effective treatment in patients with AIDS [56]. Also, reduced nephrotoxicity allows more-aggressive dosing. The role of the triazoles in the treatment of *H. capsulatum* meningitis is unclear. Fluconazole achieves high concentrations in the CSF and has been used successfully for treatment of Histoplasma meningitis [60,90,109], but there also have been failures. Itraconazole does not penetrate the CSF, but was effective in an experimental model of *Histoplasma* meningitis [51]. There are also reports of success and failure using itraconazole for treatment of *Histoplasma* meningitis [106]. Fluconazole antagonizes amphotericin B in the mouse model, whereas no adverse interaction occurs with itraconazole [51].

Paracoccidioidomycosis

Paracoccidioidomycosis (South American Blastomycosis) [16] is a chronic, granulomatous systemic disease that characteristically produces a primary pulmonary infection, often unapparent, and then disseminates to form ulcerative granulomata of the oral, nasal and occasionally the gastrointestinal mucosa. Besides overt disease, subclinical infections have been documented in healthy residents of areas where the disease is endemic [14].

The only etiologic agent is a thermally dimorphic fungus, *Paracoccidioides brasiliensis*, which grows as a yeast form in cultures at 37 °C and in host tissues; at lower temperatures, the fungus grows as a mold. The most characteristic feature of the yeast form is the pilot's wheel appearance, i.e., multiple budding mother cells surrounded by various peripheral daughter cells, on which cultural and histological diagnoses are based [14].

Ecology and epidemiology. Its geographical distribution is confined to the region between the tropics (i.e., restricted to Latin America from Mexico [23 °N] to Argentina [34 °S]); however, the disease does not occur in every country within these limits. Brazil accounts for 80% of reported cases (more than 5,000 reported cases); Colombia and Venezuela are next. In Mexico, 70% of the cases have been reported in the state of Veracruz, in the region of the Gulf of Mexico [7,76].

The ecological niche of Paracoccidioides brasiliensis is still unknown. It is generally accepted that the habitat of *P. brasiliensis* is exogenous to humans. It is thought that humans acquire the infection by inhalation of the spores during agricultural pursuits. The fungus has been rarely isolated from the soil; there are reports of isolation from penguin excreta in Antarctica, and recently, armadillos (*Dasypus novemcinctus*) were shown to harbor the fungus in their internal organs [24].

Paracoccidioidomycosis is observed only exceptionally in children (3%) and young adults (10%). It is diagnosed more frequently in males (in Mexico male to female ratio is 28:1) between the ages of 30 and 50 years, most of them (70%) are farmers [7]. Interestingly, paracoccidioidin skin tests in healthy individuals from the same areas do not reveal sex differences; this indicates that both sexes acquire subclinical infections but that progression toward disease is much more frequent in males [24]. One aspect of the host-parasite relationship that has proven revealing is the effect of mammalian hormones on the mycelium-to-yeast transformation. In vitro experiments revealed that beta-estradiol specifically inhibits the transformation of the mycelium into the yeast form inhibiting the adaptation of the fungus to host tissues; this would explain the resistance of females to paracoccidioidomycosis. [89].

Pathogenesis. Infection with *P. brasiliensis* usually begins following inhalation of conidia. These conidia transform into yeast, which cause both pulmonary and disseminated disease [39]. When experimental animals are infected with conidia by the respiratory route, these small (approximately 4 mm) propagules reach the distal portions of the lungs, where they transform into yeast cells and grow in the lung parenchyma, producing a progressive disease that disseminates to extrapulmonary organs. It is likely that humans also acquire the infection in this fashion. In a competent host, fungal growth is halted and the interaction ends with no apparent damage to the host (subclinical infection). In such a setting, the primary foci disappear and the fungus is usually destroyed, but host cells retain a "memory" of the infection. If the host-parasite balance is upset by immunosuppression or other causes, then the infection progresses and gives rise to full-blown disease [84].

Clinical features. Clinical manifestations vary from subclinical infections that are detected only by skin-test positivity to chronic multifocal infection where more than one organ is involved.

Two forms of the disease are distinguished: the acute (subacute) juvenile form and the chronic adult form.

The juvenile form represents only 3 to 5% of all cases. This form is characterized by a rapid course (weeks to months) and by marked involvement of the reticuloendothelial system (spleen, liver, lymph nodes, and bone marrow). Cell-mediated immune function is severely depressed in these patients, most of whom are children or young adults. This is the severest form and the one with the worst prognosis. The chest radiograph frequently shows hypertrophied hilar lymph nodes and pulmonary infiltrates [14,50].

The chronic adult form occurs in more than 90% of patients, most of whom are adult males. The disease progresses slowly and may take months or even years to become fully established. In approximately 25% of cases, the lungs (rarely other organs) are the only system clinically afflicted [14].

Most cases of pulmonary paracoccidioidomycosis cases have an indolent onset and patients present with chronic nonspecific symptoms such as cough, fever, night sweats, malaise and weight loss. Pulmonary lesions revealed by x-rays are preferentially located in the central and lower portion of the lungs, with the apices remaining free of disease. Sometimes there is a resemblance to tuberculosis, with which the mycosis can coexist [50,79].

In the chronic multifocal form, the symptoms are variable and referred to more than one organ or system. Most frequently, lesions occur in the oral and nasal mucosa, skin, lymph nodes, and adrenal glands. The mouth and nose are the most usual mucosal sites of infection [16]. Painful ulcerated lesions develop on the gums, tongue, lips or palate and can progress over weeks or months. Perforation of the palate or nasal septum may occur. Lymphadenitis is common in younger patients. Cervical and subman-

dibular chains are the most commonly involved and the affected lymph nodes may progress to form abscesses with draining sinuses; haematogenous spread of *P. brasiliensis* can result in widespread disseminated disease [14]. Central nervous system (CNS) involvement of paracoccidioidomycosis (neuroparacoccidioidomycosis) should always be considered in the differential diagnosis of meningoencephalitis and in expansive processes of the CNS, especially in endemic areas or among individuals who have visited these regions [76]. In AIDS patients, paracoccidioidomycosis appears as a severe and disseminated disease with a wide spectrum of clinical findings. The CD4 counts are usually less than 200 cells/µl [30].

Diagnosis. The definite method for establishing the diagnosis of paracoccidioidomycosis is the isolation in culture of the causative agent from a clinical specimen, or its unequivocal physical identification in clinical specimens. The most rapid way to establish the diagnosis is by direct examination, which allows detection of the fungal elements. *P. brasiliensis* appears as globose yeast cells with multiple buds. As a rule, a direct microscopy demonstrating the presence of large (20-60 µm), round, narrow base yeast cells with multiple budding (also described as "steering wheels" or "Mickey mouse") from any specimen should be considered significant. Clinical specimens should be inoculated onto primary isolation media (i.e. Sabouraud's dextrose agar); a positive culture is considered to be diagnostic [14,79]. For cases in which *P. brasiliensis* is not observed through direct examination, several serological tests have been used to detect antibodies against the fungus in order to establish the diagnosis [3]. More recently, immunodiffusion (ID) has been the test of choice for the initial diagnosis of paracoccidioidomycosis. The ID test has high specificity and sensitivity may vary from 65 to 100% depending on the kind of antigen used. Counter-immunoelectrophoresis (CIE) is another test used to provide early diagnosis; like in ID test, the antigens used varied from laboratory to laboratory. There is an ELISA test for anti-*P. brasiliensis* antibodies. The one using a *P. brasiliensis* yeast filtrate as an antigen has a reported 100% sensitivity and 88% specificity, considering a cut off of 1:40 [84].

Treatment. Cotrimoxazole (960 or 1,240 mg IV or PO every 12 hrs), amphotericin B deoxycholate (total dose up to 30 mg/kg), ketoconazole (200 to 400 mg PO every day), and itraconazole (100 or 200 mg PO once a day) are the recommended antifungal drugs for treatment of Paracoccidioidomycosis [85]. Usually, itraconazole is preferred over amfotericin B, which is reserved for the acute juvenile form and disseminated cases in adults [79]. Both meningitis and the parenchymatous form of neuroparacoccidioidomycosis are treated with trimethoprim-sulphamethoxazole as the first therapeutic option. Sulfas are considered the drugs of choice, with amphotericin B being used only in cases with resistance or intolerance to sulfonamides. There are some reports of central nervous system paracoccidioidomycosis that have been successfully treated with itraconazole [102]. Fluconazole could be an alternative for treatment because it has excellent penetration into the CNS. The reader interested in Paracoccidioidomycosis is referred to an excellent review by Brummer et al [14].

Sporotrichosis

Sporotrichosis is a dimorphic fungus that was described for the first time by Benjamin Schenck in 1898. After isolation of the etiological agent, mycologist Erwin Smith concluded that the agent was a microorganism of the genus *Sporotrichum*. In 1900, the etiological agent was classified as *Sporothrix schenckii* [67]. This fungus is dimorphic with a mycelial phase and a yeast phase. The mycelial saprophytic phase is characterized by branched hyphae, thin conidiophores, and conidia formed in a terminal radial fashion [44].

Ecology and epidemiology. Sporothrix schenckii is widely distributed in nature and can be found in soil associated with plant organic matter, water and decomposing organic matter, among others. In Mexico it has been found in the central region of the country (México City, and the states of México, Pueba, Guanajuato, Jalisco, Hidalgo, Veracruz, Michoacan, Oaxaca, San Luis Potosi) [68].

It has been mainly reported in tropical and temperate zones [10]. In South America the disease occurs more frequently in the humid autumn or in summer [66], whereas in Mexico the highest incidence is observed in cold and dry seasons [47].

Sporotrichosis can affect all ages [104]; sex distribution varies from region to region [10] and this might be related to the type of fungal exposure. Generally, infection results from inoculation of the fungus through thorns, splinters, scratches and small traumas during activities such as floriculture, horticulture, gardening, fishing, hunting, farming and cattle raising, mining, and wood exploration. It can be acquired through bites or scratches from infected animals (cats, armadillos) [58]. There are reports of epidemics of sporotrichosis due to zoonotic transmission especially from domestic cats [9,10]. Laboratory professionals can be infected accidentally while manipulating *S. schenckii* cultures [26].

Clinical features. Sporotrichosis has diverse clinical manifestations. The most frequent clinical form (about 80%) is the lymphocutaneous form. It starts with a nodular or ulcerated lesion at the site of fungal inoculation and follows a regional lymphatic trajectory characterized by nodular lesions that ulcerate, fistulae and heal, representing true gummae [67]. The disseminated cutaneous forms have mainly been observed among immunosuppressed patients, especially HIV-positive individuals. Among the extracutaneous forms, osteoarticular and pulmonary involvement are the most common, but there are reports of cases of severe hematogenous dissemination with involvement of multiple organs. Although sporotrichosis is not an AIDS-defining infection, reports of sporotrichosis in individuals infected with HIV are increasing [67,91].

Diagnosis. Direct observation of the fungus in clinical specimens rarely is positive, but visualization of asteroid bodies is of diagnostic value and might be of importance to initiate treatment before the reporting of cultures. In the lymphocutaneous form of disease, the fungus can easily be isolated from pus aspirated from the skin lesions [44].

Intradermal skin tests using sporotrichin as antigen are useful in epidemiological studies; however the intradermal test is not routinely used for the diagnosis due to poor sensitivity and specificity [99].

An ELISA test is available for serology, with reported 90% sensitivity and 86% overall efficacy when tested against sera obtained from patients with the lymphocutaneous, fixed cutaneous, disseminated cutaneous or multiple and extracutaneous forms of sporotrichosis [99].

Treatment. Different drug regimens are used for the treatment of sporotrichosis, including potassium iodide, fluconazole [93], itraconazole [8], terbinafine, and amphotericin B. The choice is based on the individual's clinical condition, the extent of the cutaneous lesions, assessment of drug interactions and adverse events, and systemic involvement [67].

Itraconazole is recommended in immunosuppressed patients with more extensive clinical forms and systemic involvement. Reports on the successful treatment with fluconazole are found in the literature, but this is not a first choice drug. Amphotericin B is indicated for the treatment of moderate to severe clinical forms in immunosuppressed individuals and those who did not respond to the drugs described above. Amphotericin B is the drug of choice during pregnancy [59]. The duration of treatment until clinical cure is 6 to 8 weeks, on average, in immunocompetent patients [67].

The recommended treatment for sporotrichosis in AIDS patients includes amphotericin B as the drug of choice for initial use, and itraconazole as maintenance therapy [59,91].

The prognosis of sporotrichosis is generally good even in immunosuppressed patients, although its outcome may in a few cases be incapacitating or even fatal.

Chromomycosis (Chromoblastomycosis)

Chromomycosis (Chromoblastomycosis) is a slowly progressive cutaneous and subcutaneous mycosis. It is diagnosed by the presence in the tissue of phaeoid (from the Greek *phaeios,* "dusky") muriform cells and by isolation and identification of the pathogenic fungus. The muriform cells represent an intermediate vegetative fungal form arrested between yeast and hyphal development. The dusky colour of these muriform cells results from a melanin pigment. Chromomycosis is attributed to various saprophytic hypomycetous fungi of the Dematiaceae ("black fungi") family; *Fonsecaea pedrosoi* is the most commonly isolated agent in Mexico (95%). Other etiological agents are *Exophiala jeanselmei*, *Fonsecaea compacta*, *Cladophialophora carrionii* and *Phialophora verrucosa*. [55] These agents are found worldwide in soil and in decaying plant materials, including wood [53,80].

Epidemiology. In Mexico Chromomycosis is the third most frequent cutaneous mycosis (after mycetoma and sporotrichosis). The endemic zone is located in the northeastern and central regions of the country (Tamaulipas, Veracruz, San Luis Potosi, Hidalgo and Puebla) [53,55]. The primary lesion is thought to develop as a result of percutaneous traumatic inoculation. The injury may be so minor as to go unnoticed and may have occurred years before the slow-growing lesion is noticed. From the site of inoculation, the lesion usually restricts itself to cutaneous and subcutaneous tissue, especially in parts of the body not protected by clothing [55]. The disease affects predominantly men [74].

Clinical features. Typical lesions grow slowly over many years and tend to be found on the lower limbs. It can involve other areas, including the face, neck, shoulder, chest, wrist and buttocks. The morphology of the lesion may be tumor, nodular, verrucous, plaque-like, psoriasiform, or scar. If not diagnosed and treated early, chromomycosis has a chronic course [53,55,80]. Chronic chromomycosis has potential association with epidermoid carcinoma [38]. Central nervous system invasion is possible and may be fatal [55].

Diagnosis. Scraping from a verrucous lesion in potassium hydroxide preparation reveals mycelia arising from sclerotic bodies. Culture in Sabouraud glucose agar media or Micosel agar allows isolation and identification of causal organisms within 7 and 10 days. Histologic features of a skin biopsy show a dermal granulomatous infiltrate with a predominance of epithelioid cells surrounding fumagoid bodies [55,80].

Treatment. Chromoblastomycosis is frustratingly difficult to treat. Treatment in localized lesions can be surgically removed (cryosurgery) [12]. Widespread lesions can be treated with itraconazole which is the treatment of choice, partly because itraconazole accumulates in the skin and subcutaneous tissues owing to its lipophilic nature [13]. Treatment should be maintained for as long as required. Amphotericin B has been used in severe forms [55].

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