Coccidioidomycosis

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Coccidioidomycosis is a disease of the Western hemisphere caused by dimorphic soil-dwelling fungi of the genus *Coccidioides*. First recognized as a clinical entity in Argentina in 1882, the first case associated with the San Joaquin Valley in California was reported soon after [1]. Early cases presented with inflammatory lesions of the skin, bones, and joints that progressed to death despite attempts at treatment. By the turn of the century, the causative organism was identified as a mould despite its resemblance in tissue to a protozoan [2]. For the first 40 years after its initial description, coccidioidomycosis was thought to be a relatively rare but disfiguring and usually fatal disease. However, more benign cases of pulmonary disease associated with erythema nodosum or erythema multiforme were linked with coccidioidal infection during the 1930s [3]. This form of illness, called Valley Fever, led to speculation that not all cases of coccidioidomycosis were fatal and that there was a wide spectrum of clinical manifestations after infection [4].

These observations ushered in a watershed period in the understanding of coccidioidomycosis led by Charles E. Smith and his colleagues. Smith developed the coccidioidin skin test, defined the incidence and prevalence of infection within the San Joaquin Valley, and described the relationship of skin-test reactivity to clinical disease [5]. He also developed the coccidioidal serum antibody tests [6], variations of which are still in use today. However, there was no treatment for coccidioidomycosis until 1957, when Fiese reported the first use of amphotericin B to manage a case of disseminated disease [7]. Further strides in the therapy of coccidioidomycosis using amphotericin B were pioneered and described by Winn [8].

Since those times, much more has been elucidated about coccidioidomycosis, particularly with regard to immunology, treatment, identification of hosts at risk, and fungal antigen expression. However, it is astounding how much of the basic epidemiology, pathology, clinical expression, and mycology of coccidioidomycosis was established within the first 60 years of its recognition. This initial progress is eloquently reviewed in the monograph by Fiese [9] and subsequently updated by Drutz and Catanzaro [10, 11]. Recently, Hirschmann has succinctly detailed the history of coccidioidomycosis from its first description until 1945 [12].

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Organism

Life Cycle

Coccidioides is a soil-dwelling fungus in which humans are incidental and end-stage hosts. In the soil, the fungus exists as a mould with septate hyphae (Fig. 1). Intervening cells within the hyphal filaments degenerate. This arrangement allows for fragmentation of the hyphae with dislodgement of remaining intact cells, called arthroconidia. The barrel-shaped arthroconidia are approximately 2×5 μm, which makes airborne dispersal possible and increases the probability of reaching the small bronchi after inhalation into the lung of a susceptible host [13].

Once inside the host, the fungus undergoes a profound morphologic change in which the outer wall fractures, the inner wall thickens, and the entire structure rounds up. Increased temperature, a rise in CO_2 concentration [14], a decrease in pH, and an interaction with professional phagocytes [15] all facilitate this metamorphosis. The process can also be induced in vitro using a chemically defined medium [16]. The resulting structure, called a spherule and unique among pathogenic fungi, internally segments into multiple uninucleate compartments while growing to a size of up to 120 μm. These internal structures, called endospores, are 2–4 μm in diameter and are released into the surrounding tissue in packets if the spherule ruptures. After release, endospores can grow to become spherules themselves, repeating the cycle within the host [17]. Should the fungus subsequently encounter an environment outside the host, it returns to its mycelial morphology.

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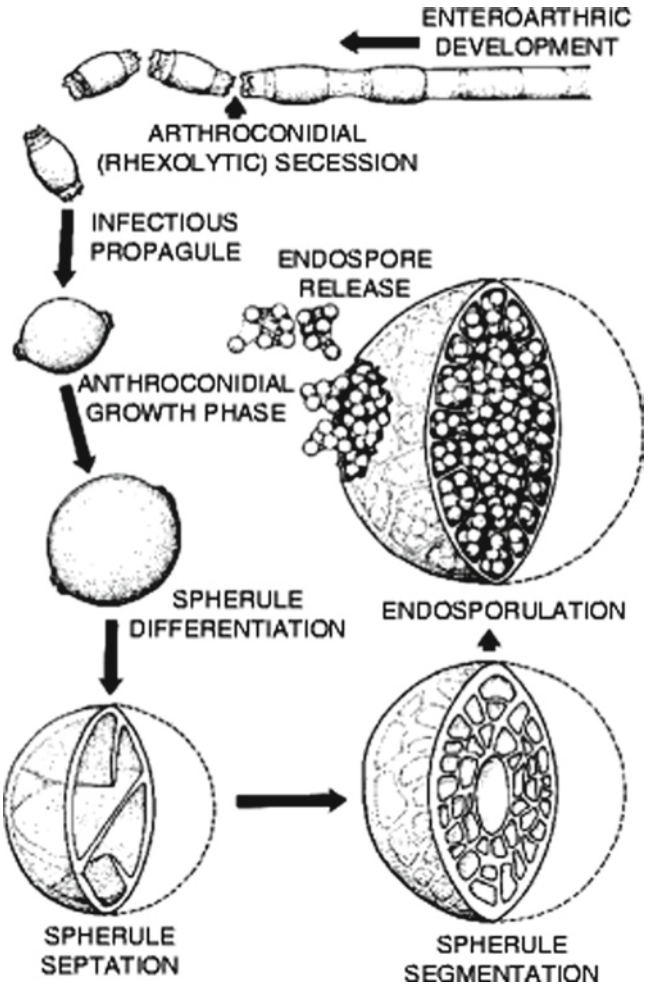

Fig. 1 Life cycle of *Coccidioides* (Based on Kirkland and Fierer [214])

Ecology

The observation that *Coccidioides* is a soil-dwelling organism was first made when it was isolated from the earth beneath a bunkhouse associated with an outbreak of coccidioidomycosis among farm workers [18]. Since then, several examples of organisms identified in the soil have been associated with human cases [19, 20]. Unfortunately, general soil sampling in the endemic area has not been very productive. Egeberg and Ely tested 500 soil samples obtained in and around animal burrows in the southern San Joaquin Valley and detected *Coccidioides* in only 35 [21]. More recently, Greene and colleagues isolated the organism only four times out of 720 samples from the San Joaquin Valley [22]. Overall, *Coccidioides* appears to prefer alkaline soils in relatively warm, dry climates [23], and it preferentially grows in soils of high salt content, including borates, at higher temperatures [24]. There are compelling data that it is not uniformly distributed in the soil but is concentrated in animal burrows [20, 21] or in other soils containing increased nitrogenous waste, such as Amerindian middens [25].

Fisher and coworkers have recently added to our knowledge by isolating *Coccidioides* from sites where human infection has repeatedly occurred. The index case was Swelter Shelter, an ancient Amerindian site located in Dinosaur National Monument in northeastern Utah, where an outbreak of coccidioidomycosis occurred in 2001 among workers building a retaining wall and sifting dirt. A similar outbreak of coccidioidomycosis may have occurred there in 1964–1965 [26]. At Swelter Shelter and at three other locations, Fisher and colleagues were able to isolate the fungus using mouse passage [27]. While no firm conclusions regarding soil type and vegetation could be made, the results demonstrate that *Coccidioides* resides for prolonged periods in certain environmental locations.

Taxonomy

The classification of *Coccidioides* remains uncertain but genetic analysis is clarifying this. Studies of 18 S ribosomal DNA confirms that *Coccidioides* is within the class Ascomycetes and is closely related to the pathogenic fungi *Histoplasma capsulatum* and *Blastomyces dermatiditis* [28]. Among all organisms, it is most closely related to the nonpathogenic soil-dwelling fungus *Uncinocarpus reesii.* [29] While no teleomorphic stage of *Coccidioides* has been observed, Burt and coworkers found molecular evidence for sexual recombination [30], and Mandel and colleagues have identified the genetic loci for mating [31]. Moreover, there is evidence of genetic variability between clinical isolates from California, Arizona, and Texas [32]. Isolates of *Coccidioides* from South America appear to have been derived from a single clade from Texas, arriving in the continent from 9,000 to 140,000 years ago, perhaps coincident with human migration into the area [33]. In addition, Fisher and colleagues have presented genetic evidence that *Coccidioides* consists of two distinct species, *C. immitis*, found only in California, and *C. posadasii*, found elsewhere [34]. Because to date there have been no clear microbiologic or clinical characteristics that distinguish these species, the genus term *Coccidioides* will be used throughout this chapter to refer to both species.

Epidemiology

The endemic regions of coccidioidomycosis lie between the latitudes of 40°N and 40°S in the Western Hemisphere. Within this general region, there is great variability in risk of infection. The endemic regions of coccidioidomycosis in North America have been associated with the Lower Sonoran Life Zone, a geoclimatic region characterized by

hot summers, mild winters, rare freezes, and alkaline soil [10]. In Central and South America, there are several geographic pockets where individuals have acquired coccidioidal infection [13], including north-central Argentina, where the disease was first recognized. There are also reports of cases acquired in northeast Brazil [20, 35]. In general, these Central and South American areas are arid or semi-arid.

Smith and colleagues made the initial association of dust exposure and risk of coccidioidomycosis in a study of military personnel in the San Joaquin Valley [36]. They also found a strong inverse association in the frequency of cases and precipitation. That is, the number of cases waxed during the dry central California summers and waned during the relatively wet winters. Galgiani has noted a similar association in Arizona, except that there are two periods of increased frequency of cases. The first occurs in the spring, after the winter rains, and the second occurs during the autumn, after the summer monsoon [37].

Comrie has developed a predictive model of coccidioidal incidence in the endemic area using reports of symptomatic cases of coccidioidomycosis in Pima County, Arizona, in combination with monthly climate data for southeastern Arizona [38]. A striking relationship was that increased precipitation 1.5–2 years before the season of exposure was associated with an increased risk of coccidioidomycosis. Although this model is imperfect because of its reliance on reports of symptomatic cases rather than soil isolates of *Coccidioides*, it has gained validation after a similar model was applied to Maricopa County, Arizona, using data from 1998 to 2001 [39].

Epidemics of coccidioidomycosis may occur when geoclimatic patterns are exaggerated. For example, in December 1977, high-velocity winds over the lower San Joaquin Valley induced not only a local dust storm but also threw dust high into the atmosphere that blanketed regions to the north and west outside of the endemic zone, including the San Francisco Bay and Sacramento metropolitan regions. Within weeks of the storm, the number of cases of coccidioidomycosis in California was five times normal, with many cases being reported from outside the endemic region [40, 41]. Similarly, in January 1994, an earthquake-generated cloud of dust, emanating from the Santa Susana Mountains, dispersed over Ventura County, California, an area of low coccidioidal endemicity. Within 2 weeks, increasing numbers of cases of coccidioidomycosis occurred in Simi Valley, a city located at the base of the mountains and in the plume of the dust cloud [42]. In the early 1990s, a nearly tenfold increase in the number of cases of coccidioidomycosis was seen in the lower San Joaquin Valley. In this case, drought, followed by heavy rains and then another drought, was climatologically associated with the marked increase in cases [43]. Currently, both Arizona and the San Joaquin Valley of California have been experiencing increasing numbers of cases of symptomatic coccidioidomycosis [39, 44]. The reasons for this are not clear but probably are related to an influx of susceptible individuals into these areas and climatic changes.

There have also been many focal outbreaks of coccidioidomycosis associated with local conditions [19, 45–51]. These outbreaks share common traits. First, there was intense exposure to soil in a confined area, often in association with an archeological dig or other soil disturbance. In addition, those exposed were either young or not from the endemic region and so could be presumed to be nonimmune. These outbreaks are notable for their high attack rate and association with diffuse rash and extensive pulmonary infiltrates. When calculable, the incubation period between exposure and development of active disease was between 2 and 4 weeks. Because of this, the diagnosis was often established only after the individuals had returned to their homes outside the coccidioidal endemic area.

The prevalence and incidence of coccidioidomycosis in a region has been estimated using skin test studies measuring delayed-type dermal hypersensitivity. A study of the prevalence of coccidioidin skin test reactivity among naval recruits and others by Edwards and Palmer in 1957 did much to define the coccidioidal endemic area in the United States (Fig. 2) [52]. In this study, highest prevalence was found in the southern San Joaquin Valley, in south-central Arizona, and along the western portion of the lower Rio Grande Valley in Texas. Regions of lesser endemicity included most of southwestern Arizona, southern Nevada and southwestern Utah, southern New Mexico and far western Texas.

In the past, rates of skin test positivity were quite high in endemic regions. Among the few recent studies, that rate appears to be declining. In an analysis of skin test responses in high school students in the southern San Joaquin Valley, Larwood found that the incidence of new skin test reactions had decreased from greater than 10% each year in 1937–1939 to 2% in 1995 [53]. A study performed in 1985 in Tucson, Arizona, found a prevalence of positive skin test response of

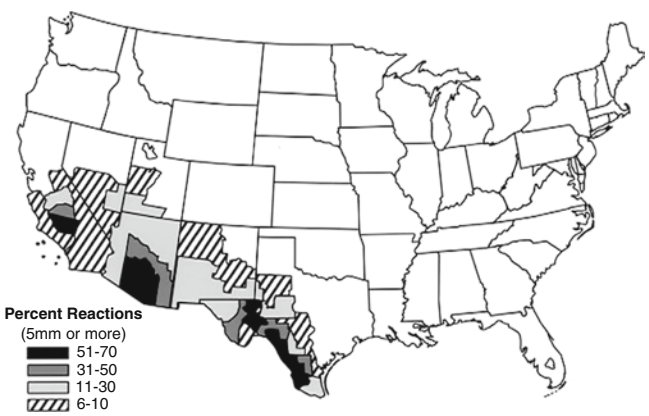

Fig. 2 Endemic regions for coccidioidomycosis in the United States based on response to dermal hypersensitivity testing. Increased intensity of shading indicates increased rates of positivity (Based on Edwards and Palmer [52])

approximately 30% [54], with an estimated yearly conversion rate of 3% each year. A recent study of Torreón, a city in northeastern Mexico in the state of Coahuila, found a prevalence of 40% [55]. These data indicate that even in the coccidioidal endemic regions, most individuals have not acquired coccidioidomycosis and remain susceptible to infection.

Given the ability of arthroconidia to become airborne, it is not surprising that most cases of coccidioidomycosis are due to inhalation, with the lung as the primary site of infection. A variety of occupations have been associated with an increased risk of acquiring coccidioidomycosis, and most of these are associated with working with soil or dust in endemic regions. These include agricultural workers, excavators, military personnel [56], and archeologists [45, 46].

In addition, there are numerous reports of laboratory-acquired coccidioidomycosis [9, 56–58]. *Coccidioides* grows readily as a mould on a variety of artificial laboratory media, and aerial mycelia begin to develop after 4 days. These can easily become dislodged and airborne. The concentrations of airborne arthroconidia from artificial media are undoubtedly far higher than might be encountered naturally and are presumed to result in a high-inoculum exposure. Recently, Stevens and colleagues have outlined an approach when accidental exposures to *Coccidioides* occur in the laboratory [59]. Initial advice includes having the clinician alert laboratory personnel whenever coccidioidomycosis is suspected and not opening any culture plate containing an unknown mould outside of a biologic safety cabinet. When a significant exposure has been deemed to have occurred, evacuation of the area with subsequent disinfection is recommended. All exposed personnel should have coccidioidal serologic tests performed at the time of exposure and after 6 weeks. Although not all experts would agree, Stevens et al. also recommend 6 weeks of prophylactic antifungal therapy [59]. In addition to airborne exposure, care should be taken to avoid percutaneous injury with cultures of *Coccidioides*, since laboratory instances of primary cutaneous coccidioidomycosis have also occurred [58]. In recognition of the potential of the mycelial phase for infectivity, *Coccidioides* is the only fungus listed by the United States government as a possible bioterrorist agent [60].

There is no evidence for person-to-person spread of coccidioidomycosis. However, interhuman transmission has been reported to occur via a contaminated fomite. In this case, pulmonary coccidioidomycosis occurred in six healthcare workers who changed the dressings and cast covering an area of draining osteomyelitis of a patient with disseminated coccidioidomycosis. Subsequent investigation revealed *Coccidioides* growing on the dressings and cast, which were dry at the time of removal. It was presumed that mycelial growth occurred on these objects and was the source of infection [61]. Fomite transmission of coccidioidomycosis has been reported under a variety of other circumstances. The handling of raw cotton grown in the endemic area has been noted in several instances [9, 62, 63]. Cleaning of dusty artifacts from an archeology site obtained from the coccidioidal endemic region has also resulted in infection [9]. Even a “dusty and dirty” suitcase from the endemic region has been the presumed source of infection in a child living outside the endemic region [64].

Pathogenesis

Necrotizing granulomata surrounding coccidioidal spherules are the classic pathologic manifestations of coccidioidomycosis and suggested to early investigators a similarity to the reaction seen in tuberculosis [9]. However, it was also recognized that an acute pyogenic response with polymorphonuclear leukocytes could occur, particularly in association with rapidly progressive lesions of disseminated disease. Some observers have suggested that this latter reaction is due to endospores and not to spherules. In many instances, the two reactions are in close proximity [65]. The concept proposed is that with unrestrained fungal growth, endospores are released from the spherule, and there is an intense but nonprotective polymorphonuclear response. Soluble extracts of both mycelia and spherules are chemotactic for polymorphonuclear leukocytes and may play a role in initiating inflammation [15]. This process may then evolve into a more protective granulomatous response surrounding the spherule in those individuals who are able to control their disease [9]. While in vitro data suggest that polymorphonuclear leukocytes can inhibit fungal growth [66], their role in controlling coccidioidal growth in vivo is unclear.

There have been numerous reports of tissue and peripheral blood eosinophilia in coccidioidomycosis. Peripheral blood eosinophilia during primary illness and eosinophils in cerebrospinal fluid in coccidioidal meningitis are common enough in coccidioidomycosis to suggest the respective diagnoses [67]. Pulmonary eosinophilia due to coccidioidomycosis may resemble idiopathic eosinophilic pneumonia histologically except for the finding of spherules in tissue [68]. Extreme peripheral blood eosinophilia (>20%) has been associated with disseminated disease [69, 70]. The pathologic finding of eosinophilic abscesses in coccidioidal-infected tissues has been associated with rupturing spherules with release of endospores.

The finding of the spherule in tissue is the sine qua non of coccidioidomycosis. The spherules seen are often of all sizes and sometimes can be shown to be rupturing and dislodging endospores. In addition, there have been reports of mycelia within pre-existing coccidioidal cavities [71, 72], a report of mycelia being found in a coccidioidal empyema [73], and another of mycelia identified in the CSF in a severe case of coccidioidal meningitis [74]. It is presumed that in these

cases, local conditions allowed the fungus to revert to its saprophytic phase. There is no evidence that such patients are infectious.

Coccidioidomycosis may involve nearly any organ of the body. The most common symptomatic sites include the lungs, skin and subcutaneous soft tissue, bones and joints, and meninges. However, a variety of other organs may also be involved, often silently. These include the liver and spleen [9], peritoneum [75, 76], and female genital tract [77, 78]. While coccidioidomycosis of the male genital tract can present as symptomatic epididymitis, it also has been incidentally diagnosed during surgery or biopsy of the prostate [79, 80]. There have been numerous reports of pericarditis due to *Coccidioides* [81]. Unlike histoplasmosis and tuberculosis, direct involvement of the gastrointestinal mucosa is extremely rare [82], but there may be extension to the gastrointestinal tract from an adjacent site [83]. In addition, there are reports of direct infection of the tracheobronchial tree [84]. Eye involvement with coccidioidomycosis has been reported sparingly, mostly as asymptomatic chorioretinal scars [85] or as a scleritis or conjunctivitis associated with primary infection and erythema nodosum. Active iridocyclitis and chorioretinitis have been reported, usually as part of overtly disseminated disease [86].

While the most frequent pathologic response to central nervous system infection by *Coccidioides* is a basilar granulomatous meningitis, a variety of other processes are seen, including intracranial abscesses [87], parenchymal granulomata, and vasculitis [88]. Williams and colleagues have described the clinical presentation of vasculitis associated with CNS coccidioidomycosis in a small cohort [89]. Onset may occur early or late in the course of disease, and there are no clear predisposing factors. Patients usually present with a stroke-like syndrome, such as hemiparesis or aphasia, and the mortality rate is high.

A strong cellular immune response is critical to the control of coccidioidal infection. It is well-documented that patients with defects in such defenses, such as those with HIV infection [90], organ transplant recipients [91], and those on long-term corticosteroid therapy [92], are at increased risk for developing severe symptomatic coccidioidomycosis. In addition, there is an association between the strength and type of the coccidioidal-specific immune response and the severity of clinical infection. Persons with self-limited pulmonary illness usually express a strong cellular immune response, manifested as a positive coccidioidin skin test reaction, and transiently produce low-titer anticoccidioidal antibodies in their serum. On the other hand, those with disseminated coccidioidomycosis tend to lack a cellular immune response and have high and prolonged serum antibody titers [11].

Human in vitro immunologic studies have confirmed the importance of the cellular immune response in coccidioidomycosis. Peripheral blood mononuclear cells from subjects with disseminated coccidioidomycosis produce less interferon-gamma (IFN-γ) in response to coccidioidal antigen than do cells from healthy, immune donors, but the suppressive cytokines interleukin-4 (IL-4) and interleukin-10 (IL-10) are not demonstrated [93, 94]. However, secretion of IFN-γ by cells from immune donors can be increased in vitro by the addition of the stimulatory interleukin-12 and by addition of antibody directed against IL-10 in cells from anergic donors [95]. Pulmonary granulomata from patients with coccidioidomycosis contain both IFN-γ and IL-10 and are associated with peripheral clusters of lymphocytes containing B cells and well as CD4 and CD8 T cells [96].

Clinically, the expression of delayed-type hypersensitivity (DTH) after skin testing with a coccidioidal antigen has been associated with an intact cellular immune response. The lack of such expression, called anergy, has been clearly associated with more severe, disseminated disease [11, 97]. This has led to the speculation that agents that could reverse coccidioidal anergy might serve as potential treatments for disseminated coccidioidomycosis. A recent report on the use of dendritic cells in human coccidioidomycosis holds promise [98].

Vaccination of mice with whole, formalin-killed spherules protects them from subsequent lethal challenge with *Coccidioides* [99]. Unfortunately, the dose used proved to have a high incidence of local toxicity in humans [100]. A double-blind, placebo-controlled study inoculating a lower dose of formalin-killed spherules in nonimmune people living in the coccidioidal endemic area showed a trend toward disease reduction in the vaccine group, but the differences were not statistically significant [101]. Since this trial, several laboratories have shown that immunization with fungal subunits may be protective in mice and could serve as human vaccine candidates in future studies. These include the 27 K antigen preparation [102], recombinant Ag2/PRA [103, 104], and recombinant urease [105]. Recently, Xue and colleagues have successfully immunized mice using a live mutant of *Coccidioides* in which two chitinase genes were disrupted [106].

Clinical Manifestations

Primary Pulmonary Infection

Sixty percent of persons are completely asymptomatic at the time of initial pulmonary coccidioidal infection [5]. Their only indication of infection is a positive reaction to a coccidioidal skin test. The rest of those infected manifest a variety of symptoms, most commonly cough, usually dry but occasionally blood-tinged, fever, night sweats, pleuritic chest pain, and headache [107]. Fatigue may be prominent and

profound [108]. In some cases, there is an evanescent, diffuse, pruritic rash over the trunk and extremities early in the course of illness that may be confused with contact dermatitis or measles [109, 110]. In up to one-quarter of cases, patients develop either erythema nodosum or erythema multiforme, usually a few days to weeks after the initial pulmonary symptoms. Erythema nodosum generally occurs as bright red, painful nodules on the lower extremities, while erythema multiforme tends to occur on the upper trunk and arms, often in a necklace distribution (Fig. 3). In about one-third of these cases, arthralgia may be present, most commonly of the ankles and knees and called desert rheumatism [9]. Primary pulmonary coccidioidomycosis with erythema nodosum or erythema multiforme has a predilection for white females and is rarely seen in African-American patients [97]. Smith correlated the onset of erythema nodosum with the development of coccidioidal skin test reactivity [4]. The development of either of these rashes during primary coccidioidomycosis is considered an indicator of a decreased risk for subsequent dissemination or chronic active infection [9, 111].

There is great variability in the radiographic findings of primary pulmonary coccidioidomycosis [112]. Most frequently, a unilateral parenchymal infiltrate is present. The appearance may range from a subsegmental patchy alveolar process to a dense lobar infiltrate with atelectasis (Fig. 4). Ipsilateral or bilateral hilar adenopathy or mediastinal adenopathy is often present [113]. A small pleural effusion ipsilateral to the pulmonary infiltrate occurs in about one-fifth of cases. Occasionally, large pleural effusions occur [114].

It is not uncommon for primary coccidioidal pneumonia to be confused with a community-acquired bacterial pneumonia. A recent study found that up to 29% of persons living in the coccidioidal endemic region diagnosed with a bacterial pneumonia had evidence of recent coccidioidal infection [115]. While at times difficult to distinguish, clues favoring a diagnosis of pulmonary coccidioidomycosis include persistent fatigue and headache, failure to improve with antibiotic therapy, hilar or mediastinal adenopathy on chest radiograph, and peripheral blood eosinophilia.

Pulmonary Sequelae of Primary Coccidioidal Pneumonia

In the vast majority of individuals with symptomatic primary coccidioidomycosis, the symptoms resolve spontaneously over a few weeks. However, radiographic abnormalities remain in about 5%. One of the most common is the coccidioidal nodule (Fig. 5). Nodules are benign residual lesions of coccidioidal pneumonia but are problematic because of their radiographic resemblance to pulmonary neoplasms. Although they appear as single lesions on plain chest radiograph, multiple lesions

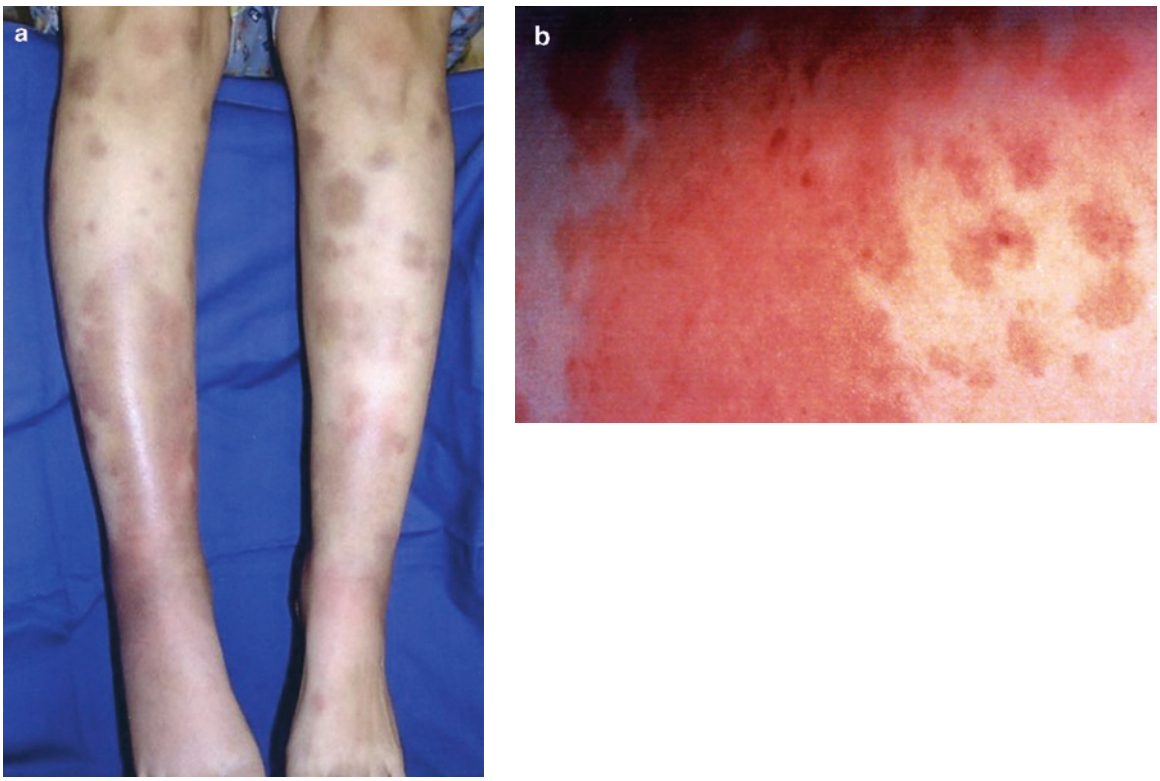

Fig. 3 Erythema nodosum (**a**) and erythema multiforme (**b**) in patients with primary coccidioidal pneumonia

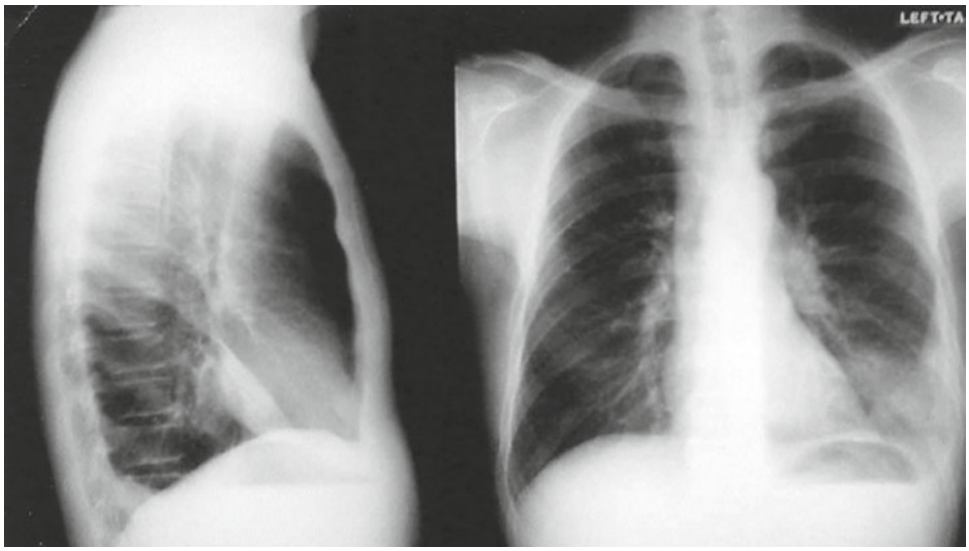

Fig. 4 Primary coccidioidal pneumonia. Note the dense infiltrate with evidence of atelectasis and ipsilateral small pleural effusion

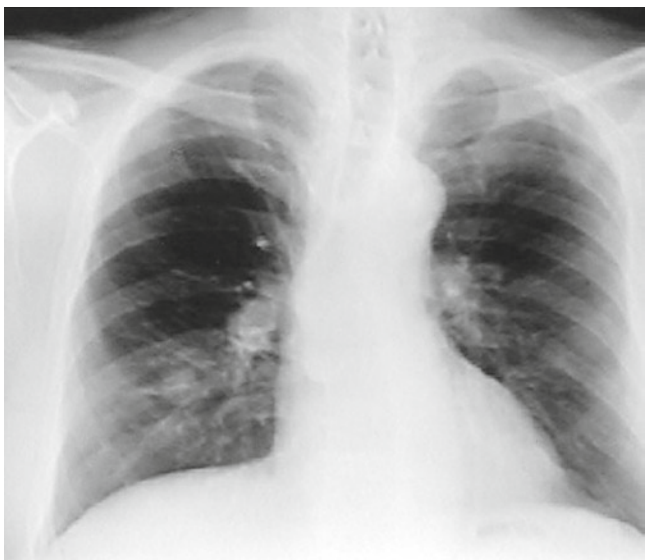

Fig. 5 Right lower lobe nodule due to coccidioidomycosis

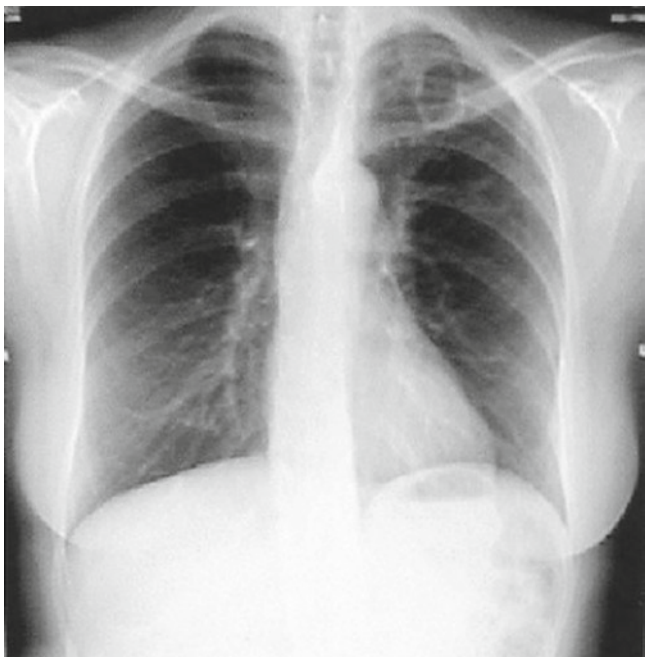

Fig. 6 Left upper lobe cavity. Patient acquired infection while working on an archeological site 2 years previously and complained of persistent cough and chest pain

are frequently seen on computed tomography (CT) of the chest, especially during primary pneumonia [116]. They range in size from a few millimeters to more than 5 cm in diameter and may be calcified. Currently, there is no radiographic way to clearly distinguish coccidioidal nodules from malignancies. Fine-needle percutaneous aspirate with histologic examination appears to be diagnostic in the majority of cases [117, 118].

Coccidioidal cavities occur when a pulmonary nodule excavates. In most cases, cavities are asymptomatic, between 2 and 4 cm in diameter, and their natural history is to close over time [119, 120]. Sputum cultures obtained from individuals with coccidioidal pulmonary cavities are frequently positive for *Coccidioides*. Radiographically, cavities are typically thin-walled but may have a surrounding area of infiltration (Fig. 6). Their course can be complicated. One syndrome is persistent chest pain and cough, often associated with an air-fluid level within the cavity. The symptoms may be due to coccidioidal infection per se or to secondary bacterial or fungal infection within the cavity. Even *Coccidioides* itself has been found to secondarily infect coccidioidal cavities [119]. Cavities have also occasionally been associated with significant hemoptysis. A unique complication is pyopneumothorax due to rupture of a cavity into the pleural space. Patients

complain of abrupt dyspnea, and the chest radiograph reveals a collapsed lung with an ipsilateral pleural effusion that is inflammatory in nature [121].

Coccidioidomycosis may result in chronic progressive disease, often associated with bronchiectasis and fibrosis. The patient usually has persistent cough, fever, positive sputum cultures for *Coccidioides*, and persistently elevated coccidioidal serology. The chest radiograph may reveal biapical pulmonary fibrosis, similar to that seen in tuberculosis or histoplasmosis. Without therapy, the process is often chronic and progressive [122].

Finally, primary coccidioidomycosis may present as a diffuse pulmonary process, similar to miliary tuberculosis. There are two mechanisms. The first is overwhelming exposure among immunocompetent persons. Larsen and colleagues reported two such cases where apparent inhalation of a large inoculum of organisms resulted in a diffuse pneumonic process and respiratory failure [47]. Arsura and colleagues reported their experience among eight immunocompetent patients, who represented 1% of all patients hospitalized for coccidioidomycosis [123]. Diffuse pulmonary coccidioidomycosis may also be a manifestation of dissemination and is often associated with fungemia, usually occurring among immunocompromised patients. The mortality rate for this form of coccidioidomycosis is exceedingly high [92, 124].

Disseminated Coccidioidomycosis

Dissemination is defined as the spread of coccidioidal infection beyond the thoracic cavity. In most cases, it portends a poorer prognosis than pulmonary coccidioidomycosis and is associated with a less vigorous cellular immune response to the fungus than occurs in those with pulmonary disease. Dissemination usually becomes clinically apparent within the first few months after pulmonary infection and may occur in individuals who are both symptomatic and asymptomatic at the time of initial infection. Indeed, evidence of antecedent pulmonary infection is apparent in only about 60% of individuals [125]. It is estimated that disseminated coccidioidomycosis occurs in fewer than 1% of all those infected, and the risk is increased in those with underlying immunosuppression as well as in males of African-American or Filipino descent [125]. Patients may have single or multiple sites of dissemination. Hypercalcemia is an uncommon complication of coccidioidal dissemination. The process does not appear to be related to vitamin D metabolism and frequently responds to antifungal therapy and fluid resuscitation [126].

The skin is the most common site of extrathoracic dissemination. Reports of large, verrucous lesions, particularly of the face, were prominent in the earliest reports on coccidioidomycosis. However, skin lesions can take on a variety of forms, including papules, plaques, ulcers, draining sinuses, and subcutaneous abscesses [127]. Early in the course of disease, skin lesions may appear to be particularly benign. Punch biopsies of any suspicious cutaneous lesion in a patient with coccidioidomycosis should be performed with material sent both for histopathologic examination and for fungal culture.

Bones are also frequent sites of coccidioidal dissemination, and the vertebrae are most commonly affected [128]. The patient notes persistent back pain and, on examination, there is point tenderness and, in some cases, overlying soft tissue swelling. Plain radiography generally reveals a well-marginated lytic lesion [129]. When a vertebral body is involved, there are usually one or more erosive lesions within the body; body height is preserved, and the intervertebral disk is not involved. MR imaging reveals signal abnormalities within the vertebral body (Fig. 7) and, often, paravertebral and epidural soft tissue swelling [130]. This mixture of bony and soft tissue inflammation can be very destructive and result in nerve root and spinal cord compression. Because of this, neurosurgical consultation is imperative.

Joints may be infected with or without underlying bone involvement. The knee is the most common site of coccidioidal synovitis. Patients present with chronic pain and swelling of

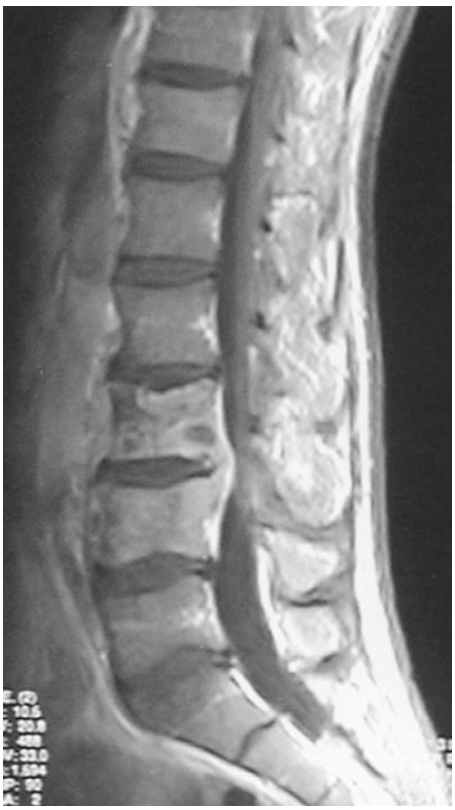

Fig. 7 Magnetic resonance image demonstrating coccidioidal vertebral osteomyelitis. Note nonhomogeneous enhancement in L3 and L4 with lack of involvement of disk space

the joint [131]. Magnetic resonance imaging (MRI) reveals a thickened and enhanced synovium and occasional underlying bone and cartilage loss [132]. Fluid from joint aspiration demonstrates an inflammatory process, but fungal culture is rarely positive. Synovial biopsy may be necessary to establish the diagnosis.

Meningitis presents with persistent headache and decreasing mental acuity. Lumbar puncture reveals a lymphocyte pleocytosis with an elevated protein and a markedly depressed CSF glucose concentration. A distinguishing characteristic is the presence of eosinophils in the CSF. Fungal culture is positive in only about one-third of cases [133]. Serum coccidioidal antibody tests are usually positive, and the specific diagnosis is most commonly established by the finding of anticoccidioidal antibodies in the CSF, although these may occasionally be negative [134]. Prior to the advent of antifungal therapy, coccidioidal meningitis was invariably fatal [135]. In one-half of patients, meningitis is the only clinically overt manifestation of disseminated coccidioidomycosis [133]. Coccidioidal meningitis should always be considered in the differential diagnosis of chronic lymphocytic meningitis, even outside the coccidioidal endemic region. A common complication is hydrocephalus, either communicating or noncommunicating. This may occur in the face of appropriate antifungal therapy. In all patients with coccidioidal meningitis, neuroradiography should be performed, with MRI the test of choice [136]. Some patients may develop encephalitis or stroke caused by cerebral vasculitis [137].

Special Hosts

Patients with conditions associated with depressed cellular immune function have been clearly identified as at increased risk for developing severe and disseminated coccidioidomycosis. Included are those with underlying lymphoma or cancer chemotherapy [138], those on chronic corticosteroids [92], and those with immunosuppression due to HIV infection [90]. Because of improved antiretroviral therapy and subsequent immune reconstitution, the severity of presentation and the number of cases of active coccidioidomycosis in association with HIV infection is declining [139]. The immune response inflammatory syndrome appears to occur very rarely in persons with concomitant HIV infection and coccidioidomycosis [139, 140].

There have been increasing reports of active coccidioidomycosis among those who have received solid organ transplants [141]. Most cases appear to be the result of a reactivated, previously acquired infection and emerge at a time of profound immunosuppression with resultant dissemination. Patients at risk usually have a history of prior active coccidioidomycosis or a positive coccidioidal serologic test just prior to transplantation. Antifungal prophylaxis with an azole appears to significantly reduce the risk of active coccidioidomycosis among such patients [142]. Four cases of donor-derived coccidioidomycosis have been reported [143–145]. However, a review of donors screened prior to transplantation within the endemic region found a low incidence of seropositivity and no instances of active coccidioidomycosis among the organ recipients, even when the donors had prior evidence of coccidioidomycosis [146].

Tissue necrosis factor-alpha (TNF-α) inhibitors have been associated with an increased risk of symptomatic illness with endemic fungi [147]. In a study performed among rheumatology clinics located in the coccidioidal endemic region [148], 13 cases of coccidioidomycosis were identified among patients receiving TNF-α inhibitors. Twelve cases occurred in those receiving the chimeric monoclonal antibody infliximab, and one occurred in a patient receiving the TNF-α receptor antagonist etanercept. All patients had pulmonary disease, and two had a history of prior coccidioidomycosis. While 10 patients had resolution of their pneumonia with antifungal therapy, 3 died after developing disseminated disease. In a cohort analysis, patients receiving infliximab had a fivefold higher risk of developing symptomatic coccidioidomycosis compared to patients on other rheumatologic medications. While it is unclear what proportion of cases in this group were due to acute infection compared to reactivation of previously acquired quiescent infection, there is a report of reactivation occurring outside the coccidioidal endemic region after the initiation of anti-TNF-α therapy [149]. Within the endemic area, it is reasonable to periodically obtain serology and chest radiographs for patients receiving monoclonal antibody TNF-α inhibitor therapy. Antifungal therapy should be considered for patients with evidence of active infection, and these patients must be closely monitored [150].

Male sex and increasing age, particularly over 60 years, have been associated with increased risk of developing symptomatic coccidioidomycosis but not necessarily disseminated disease [151–154]. Diabetics may have an increased risk of severe pulmonary disease with cavitation [13]. Numerous studies have found that African-American men are at markedly increased risk for the development of disseminated coccidioidomycosis when compared to other groups [41, 151, 153, 155, 156]. For these patients, the clinical presentation is often stereotypical, with widely disseminated disease typically involving the skin, subcutaneous tissue, and vertebrae (Fig. 8). Filipino men have also been suggested to be at similar risk [13].

Finally, women who acquire coccidioidomycosis during the second and third trimesters of pregnancy are at increased risk of developing severe, symptomatic, and often disseminated coccidioidomycosis, although morbidity and mortality appear to have declined markedly from the past [157]. Women

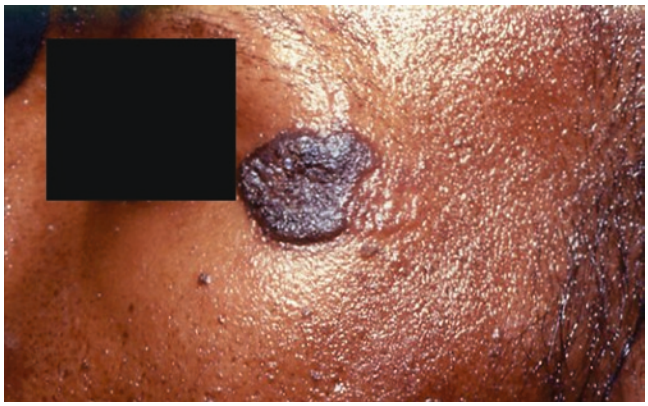

Fig. 8 Disseminated coccidioidomycosis in an African American man. Typical verrrucous skin lesion on the face

who have stable or asymptomatic coccidioidomycosis prior to pregnancy do not appear to develop worsening disease as pregnancy advances. Congenital anomalies have been observed in the newborns of women who received high-dose fluconazole for coccidioidal meningitis during their pregnancy [158]. Although recent studies have not found a clear association [159], high-dose azole therapy during pregnancy should be avoided, particularly during the first trimester.

Diagnosis

There are three mainstays for the diagnosis of coccidioidomycosis: culture, histopathology, and serology. *Coccidioides* grows as a nonpigmented mould, usually after 3–7 days of incubation at 35 °C on a variety of artificial media, including blood agar. Any growth suspicious for *Coccidioides* can be formally identified using a commercially available chemiluminescent probe that hybridizes with coccidioidal-specific DNA sequences. It has a sensitivity and specificity of 99% and 100%, respectively [160]. Sputum or other respiratory secretions are frequently culture-positive in primary coccidioidomycosis, cavitary disease, and chronic or persistent pulmonary coccidioidomycosis. Biopsy specimens from disseminated sites are less likely to reveal growth. When coccidioidomycosis is suspected, cultures should always be obtained. If positive, they provide absolute confirmation of the diagnosis. As previously mentioned, the growth of *Coccidioides* on artificial media represents a laboratory hazard and suspected samples should be handled accordingly [161].

Histopathologic identification of spherules is another method for establishing the diagnosis of coccidioidomycosis (Fig. 9). In some instances, such as biopsy of pulmonary nodules, it appears to have greater sensitivity than culture [117, 118], while in other instances, such as respiratory secretions, it appears to be less sensitive [162, 163]. For routine biopsies, the Gomori methenamine silver (GMS) stain or the periodic acid–Schiff (PAS) stains are preferable to the hematoxylin-eosin method, because spherules stand out from tissue with these stains. Microscopic examination of specimens treated with 10% potassium hydroxide (KOH) has been used in the past to identify spherules in respiratory samples. However, it has a very low sensitivity. The Papanicolaou stain is more sensitive [163].

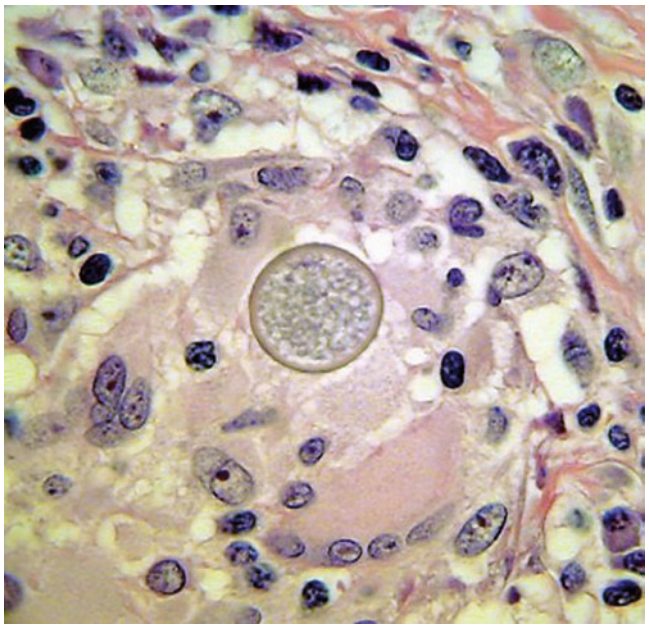

Fig. 9 Hematoxylin–eosin stain of lung tissue containing a coccidioidal spherule. Note surrounding inflammatory cells

Serologic tests identifying anticoccidioidal antibodies were initially developed by Smith and his colleagues nearly 50 years ago [164]. They remain important today both in the diagnosis and the management of coccidioidomycosis [165, 166]. Because of changes in nomenclature and methodology, coccidioidal serologic tests can be confusing. The tube precipitin (TP) assay employs a heat-stable antigen now known to be a β-glucosidase [167], detects IgM antibodies, and is generally positive very early during infection or during acute reactivation [166]. The complement fixation (CF) assay uses a heat-labile antigen that is a chitinase [168], detects IgG antibody, and is positive during early disease and remains positive in cases of severe illness and dissemination. Rising serum titers suggest more severe clinical disease, and detection in the CSF is usually diagnostic of coccidioidal meningitis. A modification of these assays employs immunodiffusion (ID) and the same antigen preparations to detect the presence of specific antibodies [169, 170]. The IDTP and IDCF are comparable to the standard assays [171] and have few or no false-positive results.

A commercial enzyme immunoassay (EIA) that detects IgM and IgG antibodies using proprietary antigens is also available. While it may be more sensitive than the TP and CF assays, its specificity has not been established, and there has been concern about false-positive results [172]. However, one report that examined the utility of an isolated IgM EIA result found it to be very specific after results were compared with clinical and laboratory follow-up [173].

Serologic tests are problematic in that they depend on host response, which may be dampened due to immunosuppression [174, 175]. Recently, assays that directly detect *Coccidioides* have become available. Following a report that some patients with coccidioidomycosis have *Histoplasma capsulatum* antigenuria [176], a specific assay that detects coccidioidal galactomannan was developed [177]. While not fully evaluated, it appears useful for patients with immunosuppression coexisting with severe and disseminated disease. Recently, there has been a series of reports on genomic detection of *Coccidioides* from a variety of samples [178–182]. While none are currently commercially available, they hold out the promise of a rapid, sensitive, and specific diagnostic tool for the future.

Treatment

Antifungal Options

Treatment alternatives for coccidioidomycosis must be tempered with the knowledge that there has never been a placebo-controlled trial of any antifungal agent in coccidioidomycosis and only one comparative trial. Amphotericin B, formulated with deoxycholate, has been used for the management of severe coccidioidomycosis for nearly 50 years [8]. While no formal study has ever been done, a review of published cases suggests that amphotericin B induces clinical improvement in up to 70% of patients treated [183]. Unfortunately, the well-known adverse events of amphotericin B have limited its usefulness. In addition, intravenous amphotericin is ineffective in coccidioidal meningitis, and intrathecal therapy is required. Because of these problems, the use of amphotericin B for the management of coccidioidomycosis has generally been supplanted by the oral azole antifungals. However, many clinicians still use intravenous amphotericin B as initial therapy for severely ill patients, and some patients will require amphotericin B if they fail to respond to azole antifungals. There are several lipid formulations of amphotericin B. To date, none has been shown to have superior efficacy to the deoxycholate formulation in the treatment of coccidioidomycosis, and at this time these newer formulations should be reserved for patients at risk for or with renal dysfunction.

Oral azoles have become the mainstay of therapy for most cases of coccidioidomycosis that require therapy. Because of reduced efficacy and toxicity, ketoconazole has been supplanted by the newer agents, particularly fluconazole and itraconazole. Initial studies performed by the Mycoses Study Group suggested that the minimum azole dose should be 400 mg daily and that relapses are frequent once therapy is discontinued [184, 185]. A landmark comparative trial of fluconazole and itraconazole completed among patients with pulmonary and nonmeningeal disseminated coccidioidomycosis demonstrated that the drugs were comparable in both efficacy and relapse rate, but the response rate was higher with itraconazole, particularly with bone disease [186]. Oral fluconazole and itraconazole have both demonstrated efficacy in the treatment of coccidioidal meningitis [187, 188].

The role of newer azole antifungals, such as posaconazole and voriconazole, has yet to be determined. Three small, nonrandomized clinical trials of posaconazole [189–191] suggest that it can be useful in patients who have failed previous azole therapy for coccidioidomycosis. For voriconazole, there are only individual case reports indicating efficacy in patients that have failed other treatments [192–194].

Other classes of antifungals hold promise for the future. The 1,3-β-D-glucan synthase inhibitor caspofungin, an echinocandin, was found to have efficacy in the treatment of murine coccidioidomycosis [195] and there are case reports of clinical use [196, 197], although efficacy remains unclear. Nikkomycin Z, a chitin synthase inhibitor, also may find a use in the future treatment of coccidioidomycosis [198]. Although it might be predicted that immune modulating agents would be useful adjuncts in the management of severe coccidioidomycosis, there is only a single report of possible efficacy using IFN-γ [199].

Antifungal susceptibility testing has gained credence as a useful technique for the management of some fungal infections, but there is no standardized method for performing such an assay with *Coccidioides*. While there are not enough data to advocate its general use, there are reports of consistency [200] and utility [201].

Although surgery plays a smaller role in the management of coccidioidomycosis than it did in the past, it still is vital as an adjunctive therapy in certain instances. It remains the major part of therapy in the management of pyopneumothorax and is occasionally required for extirpation of problematic pulmonary cavities. In addition, surgery is useful for drainage and debridement of extrapulmonary sites that fail to resolve with antifungal therapy [202] and in the placement of shunt catheters in patients with hydrocephalus due to coccidioidal meningitis [203]. Finally, many patients with coccidioidal vertebral osteomyelitis will require surgery in addition to chemotherapy [204].

Management of coccidioidomycosis is notoriously difficult because of the tremendous variability in the course of illness among patients with similar types of disease and because of the multifarious nature of the disease in any given patient. In spite of this, useful clinical guidelines have been recently updated [150].

Primary Pneumonia and Pulmonary Residuae

The goal of therapy for primary pneumonia is to ameliorate symptoms. There are no data that such therapy will prevent dissemination. It is clear that the vast majority of cases of primary pulmonary coccidioidomycosis will not require any therapy [205]. It is prudent to follow up with all such patients for at least 1 year to document resolution of the initial process and to ensure that dissemination has not occurred. Therapy should be considered in those patients with severe symptoms, including prostration, night sweats, and weight loss, in those with elevated serum CF titers (>1:16), or in those with underlying conditions that increase their risk of severe coccidioidomycosis, such as HIV infection with depressed peripheral blood CD4 cell counts, treatment with corticosteroids or TNF-α inhibitor therapy, Filipino or African-American race, and pregnant women who acquired infection during the second or third trimester. If treatment is initiated, it should be continued for at least 3–6 months [150]. An oral azole antifungal at a minimum daily dose of 400 mg is recommended.

Management of pulmonary residuae is more complex. Pulmonary nodules require no therapy. Most pulmonary cavities will also require no therapy, but antifungal therapy should be considered in those with persistent symptoms, including cough, chest pain, and hemoptysis. In cavities with an air-fluid level, treatment for a secondary bacterial infection is warranted. In rare cases, surgery may be required because of persistent hemoptysis or an enlarging cavity despite therapy. The mainstay of management of pyopneumothorax is surgical, but most clinicians would also use adjunctive antifungal therapy. For most cases where therapy is indicated, oral azole therapy similar to that for primary pneumonia is appropriate.

Diffuse Pneumonia and Chronic Pulmonary Disease

Diffuse pulmonary coccidioidomycosis, whether due to high inoculum exposures or to fungemia in an immunocompromised host, should always be treated. Because of the severity of this manifestation of coccidioidomycosis, most clinicians begin with intravenous amphotericin B with a concomitant azole antifungal as initial therapy and then change to an oral azole antifungal alone once the patient is clinically stable [150]. Antifungal therapy should be continued for at least 1 year, and many clinicians recommend life-long therapy, particularly for the immunocompromised patient.

Chronic persistent pneumonia, consisting of cough, fevers, inanition, and other symptoms for 6 weeks or more, also requires therapy. Treatment with an oral azole antifungal at 400 mg daily is usually adequate. Therapy for months to years is the rule. Monitoring symptoms, periodically rechecking sputum cultures for growth of *Coccidioides*, and repeated assessment of serum CF titers is helpful in determining response. Similar therapy is also recommended for those patients with fibrocavitary disease. However, many of these patients will have minimal pulmonary symptoms. In such cases, in the absence of a positive sputum culture and without elevated CF serologies, it may be appropriate to withhold antifungal therapy and observe the patient over time.

Disseminated Non-meningeal Coccidioidomycosis

With rare exceptions, all forms of extrathoracic disseminated coccidioidomycosis require antifungal therapy. For nonmeningeal disseminated coccidioidomycosis, the type of antifungal therapy will depend on the clinical severity of disease. In those hospitalized because of coccidioidomycosis, intravenous amphotericin B should be initiated. Many clinicians experienced in the management of coccidioidomycosis combine amphotericin B at the outset with an oral azole antifungal at 400 mg or more daily. While there is a theoretical risk of antagonism between these two classes of drugs [206], antagonism has not been observed clinically in coccidioidomycosis nor in other mycoses [207], and many patients have been observed to improve on such combined coverage. Once the patient has clinically stabilized, usually over 4–6 weeks, the amphotericin B can be tapered and stopped, leaving the patient on oral azole therapy alone. Some patients fail azole therapy after responding to amphotericin B. In such cases, reinstitution of amphotericin B will be required. Because relapse is frequent, particularly with oral azoles [184, 185], therapy should be continued for a prolonged period, often years. Patients should be periodically monitored for evidence of disease activity at the site of dissemination, either through direct clinical observation or through imaging. In addition, CF serology should be obtained at 3–6-month intervals. Assessment of coccidioidal-specific cellular immunity at similar time points is helpful. There are no strict guidelines for discontinuing therapy in patients with disseminated nonmeningeal coccidioidomycosis, and some patients

may require life-long therapy. In a retrospective study, Oldfield and colleagues found that relapse was more frequent in those with a peak CF titer of ≥ 1:256 and in those who had persistently negative coccidioidal skin tests. End-of-therapy CF titer was not predictive [208]. The risk of relapse is between 15% and 30% after azole therapy is discontinued. Relapses usually occur at the site of initial disease and within 1 year of stopping therapy [184, 185, 209]. It is reasonable to taper and then stop antifungal therapy in a patient with disseminated nonmeningeal coccidioidomycosis if there is minimal or no evidence of clinical disease, if the CF titer is <1:2, and if there is evidence of return of cellular immune response. Such patients should be followed at 3-month intervals to ensure that relapse does not occur.

Coccidioidal Meningitis

Intrathecal amphotericin B was the first effective treatment for coccidioidal meningitis [210]. Unfortunately, it was associated with numerous adverse reactions, including discomfort due to repeated injections, arachnoiditis, myelitis, inadvertent brain stem puncture, and secondary bacterial infection. In 1993, a noncomparative study of oral fluconazole at 400 mg each day demonstrated a nearly 80% response rate to therapy, including in subjects previously on intrathecal amphotericin B [187]. In an earlier study, itraconazole also appeared to have efficacy [188]. Currently, the vast majority of patients receive oral azoles as their sole treatment for this form of disseminated coccidioidomycosis. Some clinicians will initiate therapy with doses higher than 400 mg daily and then reduce to this dose once the patient is stable [150]. Current data suggest that the risk of relapse is exceedingly high if azole therapy is discontinued in patients with coccidioidal meningitis [211]. Therefore, therapy should be life-long. If hydrocephalus occurs during treatment, a shunt is indicated, but no change in medication is required [150]. Some clinicians feel that clinical cure may be possible with the combination of intrathecal amphotericin B and oral azole therapy [212]. A recent report describes a novel approach to administering intrathecal amphotericin B by using a subcutaneous programmable pump [213].

Prevention

Because coccidioidomycosis is usually acquired environmentally, there are no established methods to prevent infection within the endemic area. Measures that reduce dust have been shown to be useful [36]. While it might be presumed that new construction might lead to an increase in risk, this has not been definitively proven [39]. Individuals who wish to reduce their risk of becoming infected should avoid activities that cause them to be exposed to soil or dust in endemic areas, since such activities have been shown to increase the risk of infection [49, 50]. In addition, efforts at predicting climatic conditions associated with the risk of symptomatic illness [38, 39] might prove useful in the future.

As noted above, several subunit antigens have been identified that have been demonstrated to protect animals from experimental coccidioidomycosis [102–105] and a live vaccine has shown promise in a murine model [106]. In the future, these efforts may lead to the development of a human vaccine.

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