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Coccidioidomycosis: a review

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ABSTRACT

Coccidioidomycosis is a fungal infection of the Western hemisphere that is endemic to the soil in areas with limited rainfall. Human and animal infections result with inhalation of arthroconidia. Most often, this is an asymptomatic event. When illness occurs, it is primarily a pneumonic presentation. A small minority of infections eventuate in disseminated disease. Predominately, this presents as meningitis or osteoarticular or integumentary disease. Treatment may not be required for the mildest illness. Azoles are commonly prescribed. Severe infections may require amphotericin B.

INTRODUCTION

Coccidioidomycosis (CM) is an endemic diathermal dimorphic fungal infection of man and animals unique to the Western hemisphere.[1] The disease was first described in Argentina and subsequently in California. The disease is primarily a pneumonic illness often confused with community-acquired pneumonia (CAP).

In a small minority, the disease may disseminate to virtually any place in the body. Sites include soft tissues, bones, joints and meninges.[2]

Diagnosis is commonly made serologically. The sensitivity and specificity of these tests vary widely between laboratories. This is especially true in early primary infections (false negatives). Therapy currently consists of amphotericin B (AmB) compounds and azoles. Fluconazole is the most commonly used azole. Fluconazole failures result in the use of virtually all subsequently introduced azoles and AmB as rescue therapy.

EPIDEMIOLOGY

Coccidioides species occur in Southwestern USA and Northern Mexico. Additional foci are found in Utah, Eastern Washington, and Central and South Americas. Even in the most endemic areas, the fungus is sparsely distributed. It has commonly been found in association with animal and human middens.[3]

CM is infectious but not contagious. It is agreed that there are more than 150 000 infections per year in the USA.[4] Sixty per cent of infections are asymptomatic and 40% have a flu-like or pneumonic illness. Of these latter, a quarter is diagnosed. Approximately 1% of total infections disseminate. There is seasonality to the infection as reported from California and Arizona. In California, the highest incidence occurs in the fall. There was a large increase in cases in the southern San Joaquin Valley from 1992 to 1995. The reported cases declined subsequently but never to pre-1992 numbers. In the last decade, there has been a steady increase in reported cases year over year.[5] Some of this increase may be due to increased populations, increased soil disturbance (construction) changes in case definitions (lab only reporting) and increased diagnosis. In all probability, all of these do not account for more than a minority of the increased numbers. The annual incidence of infections in those living in the most endemic areas (Southern Arizona and Southern Central Valley, California) is probably 1%–3%. CM is increasingly found in individuals who live outside of the endemic zone due to increased leisure and work-related travel.

MYCOLOGY AND PATHOGENESIS

Coccidioides was originally described as one species *Coccidioides immitis*.[3] More recently, genetic analysis has defined two separate species with relatively distinct geographical distributions. *C. immitis* is largely found in California but also in Eastern Washington state.[6] Virtually all cases in Texas and Central and South America are *C. posadasii*.[7] At this juncture, there have been no distinct differences in the phenotypical behavior of the two species.

Coccidioides requires animal nutrients for growth; hence, its natural distribution is largely restricted to areas of previous human or animal habitation, particularly small rodent burrows.[3] It grows in soil (and on laboratory media) as a mycelium. After a variable period, mycelia septate and produce spores known as arthroconidia. The thin septations are fragile and the arthroconidia become airborne with minimal soil disturbance (wind and digging). The arthroconidia may travel 75 miles and occasionally a much greater distance.[8] Infection is almost always due to the inhalation of arthroconidia.

The majority of these inhalations either result in no infection (we have no data on this) or asymptomatic infections manifested as skin test conversion (60% of infections).[9 10] If not controlled, arthroconidium under the effect of temperature and other factors transform into spherules which subsequently internally divide into endospores. With spherule lysis, the

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endospores are released and become spherules, which result in exponential propagation of the pathogen.

The immunopathology of this host parasite interaction has been studied for several decades but is as yet incompletely understood. Both the innate and adaptive immune systems are involved. The response is sequential, multifaceted and very complex. Neutrophils, macrophages, and dendritic cells are all involved. T-cell responses based on T-helper (Th) cells, Th1 and Th2 ratio and Th17 and regulatory T cells ratio appear to be important. Antibodies are not demonstrably protective.

DIAGNOSIS

A diagnosis of CM is a combination of epidemiological, clinical, general laboratory, specific microbiological, serological, histopathological, and radiographical modalities. A single day trip to the endemic zone can result in clinical infection.

Non-specific laboratory markers include eosinophilia (>350 cells/mcL) in a minority of patients, polyclonal hyperglobulinemia, and hypoalbuminemia.[11 12] A full discussion of specific laboratory testing is beyond the scope of this review. It is noteworthy that a large number of errors in the diagnosis of CM is based on misinterpretations of serological testing. The enzyme immunoassay and IgM and IgG tests are commonly available. The sensitivity and specificity are dependent on the vendor. It is our recommendation that these tests should not be used to definitively diagnose or exclude CM. Immunodiffusion (ID) tests can be very sensitive and tend not to have significant false positives. The most sensitive ID testing available is at University of California, Davis, and Kern County Public Health laboratory, which use nearly identical procedures. A positive ID IgM or ID IgG test is essentially diagnostic. Compliment fixation for IgG antibody is both diagnostic and, from the two aforementioned laboratories, prognostic (figure 1).

Other diagnostics that are useful but not widely available are antigen detection and PCR.[13 14] Culture-based diagnosis is the most definitive, again based on accurate laboratory evaluations. It is important to inform the laboratory of a possible CM diagnosis. After a few days of growth in the laboratory, the mycelia will produce arthroconidia with the potential for a serous lab accident if not managed in an appropriate biosafety environment.[15] Appropriately interpreted histopathology can also be diagnostic. A well-collected sample with appropriate histology is also helpful. Generally, there should be granulomatous inflammation. There must be endosporulating spherules. Skin test positivity with Spherusol indicates past or present infection. Skin test conversion (negative to ≥5 mm bidirectional induration) indicates infection in the intervening time. False-negative skin test reactions suggest genetic or acquired failure of cellular immune response.

CLINICAL MANIFESTATIONS

Pulmonary

Primary: mild and moderate

Most encounters with *Coccidioides* result in an asymptomatic or undiagnosed respiratory infection. Those that are often misdiagnosed as CAP. Either a high index of suspicion based on a protracted clinical course, non-specific laboratory parameters or antibiotic treatment failure eventuates in clinical diagnosis of primary pulmonary CM. This then needs confirmation with specific laboratory. False-negative serological results early in the course are common. Sensitive ID or other tests can diagnose >90% of symptomatic infections, and this may take repeat testing for 6–8 weeks. Radiographical evaluation of the chest is mandatory, with a chest X-ray usually being adequate. Differential diagnosis sometimes mandates CT. Mild to moderate coccidioidal pneumonia will most often resolve without treatment. Certain individuals will develop persistent, progressive or complex

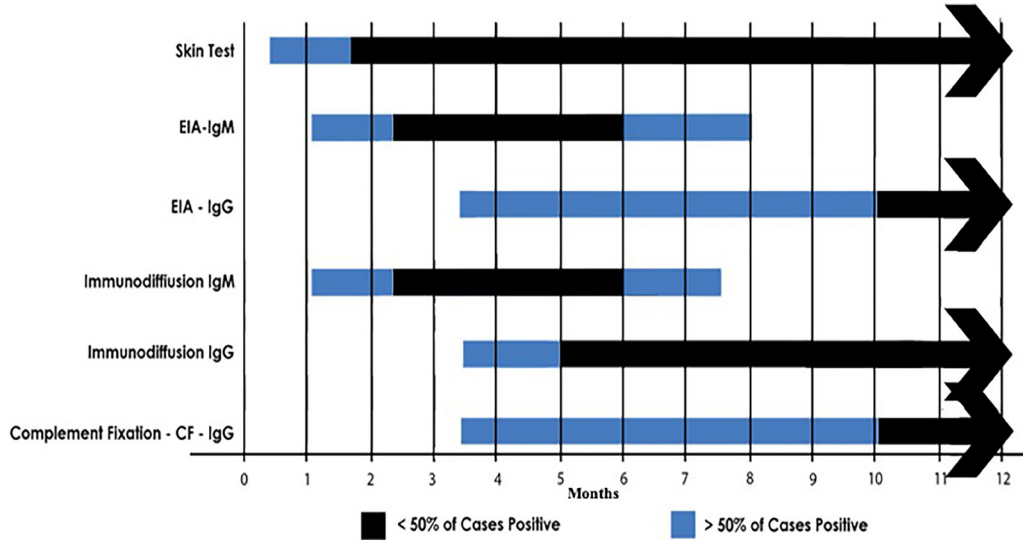

Figure 1 Immunological diagnostics commonly used in coccidioidomycosis. Immunodiffusion IgM and IgG, are represented on this figure as performed at Kern County Public Health Department and Department of Medical Microbiology, University of California Davis. These tests may be accessed at the Department of Medical Microbiology at University of California Davis. There is a substantial variability in the duration of positive tests. CF, complement fixation; EIA, enzyme immunoassay.

pulmonary disease, and an additional small percentage of apparently healthy individuals will develop disseminated disease (see further). For this reason, it is the policy of the Valley Fever Institute (VFI) to discuss risks and benefits of treatment options with our patients. Greater than 90% opt for treatment.

Primary: severe

A small percentage of pulmonary patients present with multilobe alveolar infiltrate disease of miliary (hematogenous disseminated pulmonary) disease. If the PaO_2 is ≤70 mm Hg or the A-a O_2 gradient is ≥35 or the PaO_2-FiO_2 ratio is ≤330, we define the patient as severe. These patients are hospitalized and initiated on lipid preparation AmB. VFI policy is also to initiate glucocorticoids on a schedule identical to that recommended for pneumocystis (methylprednisolone/prednisone 40 mg two times per day for 5 days, 40 mg/day on days 6–11, 20 mg/day through day 21).[16] Usually AmB is for 1 month (inpatient to outpatient and then transitioned to an azole; see treatment as follows).

PULMONARY COMPLICATED

Pleural effusion

Exudative pleural effusion occurs in approximately 10%. This is most often associated with pneumonic disease but may be the sole clinical focus of infection. Often, no separate diagnostic approach is required and serological diagnosis is adequate. A complex patient or differential diagnosis may require thoracentesis. Culture is diagnostic but insensitive if not from biopsy. Surgical therapy is seldom if ever required (see coccidioidal empyema as follows).

Nodules

Coccidioidal pneumonia can resolve to a normal chest X-ray or may leave residue, such as a scar. A nodule is in most circumstances a satisfactory result. If a patient has a known diagnosis and is closely followed up and an infiltrate resolves to a nodule, no further evaluation is required. The problem occurs when an isolated nodule is found and there is no track record, hence a differential diagnostic problem. If the nodule is calcified, it is unlikely malignant. If the nodule is quite small, it may be reasonable in a low-risk (for cancer) individual to follow with repeat CT imaging. Larger nodules (>1 cm) may require biopsy. The serological status of the patient is not of great help in decision making.

Cavitary and fibrocavitary

Cavitary lung disease has a complex differential diagnosis, including infections and autoimmune and malignant diseases. In CM, one may find cavitary disease that is noted as a sequela of primary pulmonary infections or as an incidental or clinical presentation of varying significance. The the most common is the incidental 'thin-walled' cavity.[17] Approximately 50% will resolve in 2 years. The role of antifungal treatment, if any, is unclear.

More complex cavitary and fibrocavitary disease occurs. Chronic therapy with azoles probably has a salutary effect on symptoms and course. The most dreaded complication of cavitary disease is massive hemoptysis. This needs to be managed by a team of pulmonary, thoracic surgery and interventional radiology on an emergent basis.

Empyema

The aforementioned cavitary disease is often clinically silent and unrecognized for years. Unrecognized or recognized pleural-based cavities may rupture into the pleural space, resulting in a hydropneumothorax often with bronchopleural fistula. This and only this is a coccidioidal empyema. The pathogenesis and pleural fluid are distinct from coccidioidal effusion. The culture is commonly positive. Treatment at a minimum requires chest tube drainage and, if there is a persistent air leak, surgical intervention. Medical therapy has a lesser role but is routinely provided. Azoles usually suffice.

DISSEMINATED

By convention, *Coccidioides* that is not pleural/pulmonary is disseminated. There are two basic types: lymphatic and hematogenous. The former is exemplified by pericarditis and supraclavicular lymphadenitis, the latter by meningitis. Clearly, hematogenous disease is more common. There is reason to believe that at least some 'uncomplicated pulmonary infection' is in fact asymptomatically disseminated.[7] Most commonly, dissemination is categorized by the site of clinically evident disease.

Virtually every part of the human body has been described with coccidioidal infection. The sites discussed will be limited to the more commonly encountered.

Osteomyelitis

Infection has been described in almost all bones. The axial skeleton is of particular importance. The lumbar spine being the most common. The pelvic bones and long bones are commonly involved. A total body technetium pyrophosphate bone scan is routinely accomplished on all cases of osteomyelitis and all other patients where any dissemination is identified. CT and more commonly MRI with gadolinium are used to evaluate the extent and the severity of disease.[18] Surgical intervention is commonly needed to debulk extensive disease or to preserve or restore structure or function.

Life and limb-threatening disease are usually treated with lipid preparation AmB for 12 weeks and then transitioned to azole for a total of 3 years. Lesser disease may be treated with an azole primarily.

Synovitis

Synovitis may occur as a separate entity but not uncommonly in association with osteomyelitis. In this latter circumstance, the osteomyelitis takes precedence. The knee is most commonly affected; other sites are the wrist and ankle. Treatment is largely medical; azoles alone are usually effective. Occasionally, lipid preparation AmB or surgical interventions are required for severe or refractory disease. If adjacent (or distant) bones are involved, treat as osteomyelitis.

Lymphadenitis

This most commonly occurs as lymphatic spread from pneumonic disease to hilar lymph nodes and can be found on chest X-ray or chest CT. Subsequent spread to mediastinal lymph nodes may occur but seldom presents clinically. Subsequent spread to subclavicular, supraclavicular and suprasternal lymph nodes may occur. Hematogenous spread

to lymph nodes occasionally occurs. In the setting of known coccidioidal disease one may make a clinical diagnosis. More commonly and especially if a presenting problem, a lymph node biopsy is required. A surgical biopsy is much preferred over needle biopsy for sensitivity and specificity of diagnosis. Azole therapy for 3 years usually produces a salutary effect.

Soft tissue infections

This is a heterogeneous group of infections. Perhaps most severe is an intramuscular infection often associated with osteomyelitis. Prevertebral abscesses are associated with vertebral osteomyelitis/discitis. These may require drainage by an interventional radiologist or surgery. Lipid preparation AmB is often used initially followed by 3 years of azole therapy. Psoas abscess and gluteal abscesses are also noted. The latter is often associated with sacroiliitis.

Another relatively common presentation is subcutaneous abscess. This may be small or quite large (10 cm). Commonly, these are culture positive. One is tempted to drain these; however, even if called 'abscess', they do not behave anything like a bacterial abscess. If opened, they will drain for weeks and create an unpleasant management problem. Better are large volume aspirations, which might need to be repeated over time. Medical management is usually with azoles.

Cutaneous disease

Cutaneous CM is one of the most common and usually the most benign form of dissemination. Depending on the circumstance, the diagnosis can be simple, as in a new skin lesion in someone with recently diagnosed CM. More difficult are patients presenting primarily with an unidentified skin lesion. The visual appearance of cutaneous CM is quite variable. Small cutaneous abscesses or verrucous lesions are common and ulcerated lesions may occur. Diagnosis is usually by biopsy. In some circumstances, clinical suspicion and serology may suffice.

Peritonitis

When it occurs in isolation, coccidioidal peritonitis can be a subtle and difficult diagnosis. While rare, many of our infectious disease colleagues in California have diagnosed these patients; presentation is varied but most commonly ascites of uncertain origin.[19] Paracentesis yields fluid consistent with an inflammatory/malignant process. Laparoscopic evaluation shows peritoneal 'studding' that is grossly identical to carcinomatosis and tuberculosis peritonitis. Serum cocci serology is almost always positive. Peritoneal fluid titers add nothing, and culture of the fluid is low yield. Histopathology is the the most common positive diagnostic.

Meningitis

This is the most devastating complication of coccidioidal infections. Both morbidity and mortality are higher than any other disease manifestation. Untreated, it is universally fatal. It may copresent with primary disease, appear some weeks or months after primary infections or in persons with no notable primary infection. The latter is 30%–50% of disseminated infections. In our institution, coccidioidal meningitis is more common than bacterial, viral, tuberculous (Tb) and cryptococcal meningitis combined.

The most common presentation is headache. Persistent and progressive confusion, focal neurological deficits, gait disturbances (especially tandem gait) are other presentations seen separately or in parallel. A high index of suspicion and early lumbar puncture either with or without antecedent neuroimaging are paramount. The diagnosis can be suspected on the basis of MRI with gadolinium in 50% of cases (differential diagnosis Tb).[12] CT is of far lower sensitivity. The lumbar puncture is the diagnostic of choice. The lumbar puncture, if at all possible, should be completed in the traditional lateral recumbent position. An opening pressure of 180–200 mmH_2O is normal. An opening pressure ≥250 mmH_2O requires cerebrospinal fluid (CSF) removal to obtain pressure of <50% of the opening pressure or 200 mmH_2O, whichever is greater. CSF should be analyzed for cells, differential (cytospin), glucose, protein, coccidioidal titers and fungal culture.[20] Additional studies for tuberculosis, *Cryptococcus*, *Brucella*, syphilis and others are often warranted. A diagnosis is made if there is CSF pleocytosis, usually lymphocytic with decreased glucose, elevated protein and a positive culture (best but low frequency). A positive CSF complement fixation (CF) titer at a reliable laboratory also is helpful but frequently negative. A positive serology (blood) with ID IgG or CF antibody is the most common way the diagnosis is made. Presence of CSF antigen is diagnostic but not rapidly available.[21 22]

Severe increased intracranial pressure (ICP) is defined as ≥250 mmH_2O. This needs to be considered a separate problem with separate management.[7] In persistent or severe cases, placement of a shunt might be essential.

Azoles are the primary medical therapy. Duration of treatment is currently construed to be lifelong. The reason for this is lack of available proof of cure and the significant morbidity and mortality of relapse.

Complications of coccidioidal meningitis are manifold. Included are hydrocephalus, vasculitic infarctions, focal neurological deficit of cranial nerves, arachnoiditis, syrinx, paraplegia, bowel, bladder and erectile dysfunction. Coccidioidal meningitis is best managed by those with experience. More complete discussion of diagnosis, complications and treatment is beyond the scope of this review.[23–26]

THERAPY

Some aspects of treatment are discussed previously in broad terms. There are no currently used antifungal drugs that have a specific indication for CM. Most treatments are based on observational studies, anecdotes and expert opinion. The key properties of antifungals are found in table 1.

Polyenes

There was no effective therapeutic prior to the introduction of AmB deoxycholate.[27 28] This drug had a profound effect on the morbidity and mortality of CM. The drug was used for severe and persistent pneumonic disease, most forms of disseminated disease and intrathecally for coccidioidal meningitis.[23–26]

AmB deoxycholate has largely been supplanted by lipid preparations (AmB liposomal and AmB lipid complex) because of demonstrable improved tolerability and

Table 1 Antifungal drugs used in the treatment of CM[18 24 29 30 42–47]

Class	Drug	CNS penetration	Dose	Food requirement	Half-life	TDM target	Toxicity	ADR	MOA
Polyene	Intrathecal AmBd*	100%	Initial dose: 0.1 mg, 3×/week then titrate (CNS)	N/A	Terminal half-life 127–152 hours after multiple doses	N/A	++++	Headache, nausea and vomiting, neurotoxicity (ophthalmoplegia, hearing loss, ataxia, paraplegia, neurogenic bladder and erectile dysfunction)	Binds to ergosterol in cell membrane and causes leakage and rapid cell death
	L-AmB	Nearly undetectable	Intravenous: 5 mg/kg/day	N/A		N/A	++++	Infusion-related reaction (fever, rigors and hypotension), nephrotoxicity, electrolyte abnormality (hypokalemia and hypomagnesemia)	
Azole†	Fluconazole	50%–100%	Intravenous/tab: 800 mg daily (non-CNS), 800–1200 mg/day (CNS)	No food requirement	~30 hours	Non-CNS: random 30–60 µg/mL CNS: random 40–80 µg/mL for CNS	+++	Ectodermal (dry lips, skin, eyes, anterior nares) (epistasis), arthralgias (shoulder most common), headache, elevated liver enzyme, QTc prolongation	Inhibit demethylation of lanosterol to ergosterol, leading to compromised membrane integrity
	Itraconazole	<1%	Cap/solution: 200 mg two times per day	Cap: with fatty meal and acidic drink (Coke) Liquid: empty stomach	~30 hours	Random: 3–6 µg/mL	+++	Sodium retention, black box warning: negative inotropic effect, elevated liver enzyme, QTc prolongation	
	SUBA-itraconazole	ND	Cap: 130 mg/day	With food	~30 hours	Random: 3–6 µg/mL	+++	Same as itraconazole	
	Voriconazole	22%–100%	Tab: 4 mg/kg two times per day	Empty stomach 2 hours before and after	~6 hours	Random: 3–6 µg/mL Trough 1.0–5.5 mg/L	++++	Visual disturbance, neurotoxicity, periostitis, QTc prolongation, severe photodermatitis and possibly related cutaneous malignancy, including melanoma and squamous cell carcinoma, elevated liver enzyme	
	Posaconazole	<1%	Tab: 400 mg/day Suspension (only if unable to take tab): 400 mg two times per day	DR-tab: take with food Suspension: take with fatty food or acidic drink	~25 hours	Random: 3–6 µg/mL	+++	Aldosterone-like effect: hypokalemia, hypertension, elevated liver enzyme, QTc prolongation	
	Isavuconazonium	ND	Cap: 372 mg/day	No food requirement	80–120 hours	Random: 3–6 µg/mL	+	Nausea, vomiting, diarrhea, headache, hypokalemia, elevated liver enzyme	

Serological methods for diagnosis of primary CM, modified from Ron Talbot, Kern County Public Health Department.
*Historically used as primary therapy with great success, currently it is most often used as rescue therapy after failure of one or more azole therapies.
†All the aforementioned azoles have been used successfully in CM meningitis, and the presence or lack of CSF penetration does not appear to be substantiative.
ADR, adverse drug reaction; AmBd, amphotericin B deoxycholate; cap, capsule; CM, coccidioidomycosis; CNS, central nervous system; CSF, cerebrospinal fluid; DR, delayed release; L-AmB, liposomal amphoterin B; MOA, mechanism of action; N/A, not applicable; ND, no data; QTc, Corrected Q-T interval; tab, tablet; TDM, therapeutic drug monitoring.

decreased nephrotoxicity.[29–31] Nonetheless, intrathecal AmB deoxycholate still has a role in coccidioidal meningitis.[23]

For severe pneumonic disease, VFI usually initiates AmB lipid preparation on a daily basis for two or more weeks, depending on response. Subsequently, the dose is decreased to three times a week for two or more additional weeks. Then the patient is then transitioned to an azole.

The treatment for severe non-meningeal disseminated disease is similar. Initial AmB lipid preparation is given 6 or 7 days/week in the hospital and transitioned to 3–5 days/week outpatient infusion center for the first 30 days of treatment. Thrice weekly therapy is continued for approximately 90 days and occasionally longer. Monitoring consists of complete blood count (CBC) with differential, basic metabolic panel (BMP), liver function test (LFT), serum magnesium (Mg^{++}), and phosphate (PO_4). At least weekly. BMP, Mg^{++} is monitored at every infusion.

Azoles

The first oral therapy for CM was introduced in 1981, ketoconazole. This was in its time a major advance. This drug is not currently recommended due to perceived inferior efficacy and increased toxicity.[32 33] Subsequently, fluconazole was introduced and rapidly supplanted its antecedent and is still the most widely used anticoccidioidal antifungal. The Food and Drug Administration (FDA)-approved maximal dose (adults) is 400 mg.[34] It was soon discovered that this dose had significant failures, some of which could be salvaged by an increased dose.[35] At the VFI, we seldom use doses less than 800 mg/day.

Fluconazole is used as a primary treatment for mild to moderate pneumonic disease and in non-life and limb-threatening disseminated disease (skin, soft tissue, and small bones). Toxicity is modest but can be problematic. Ectodermal toxicity, including dry lips, skin, eyes, and anterior nares (epistaxis), is common.[36] Focal or diffuse arthralgias may be confused with that of the primary disease (desert rheumatism) and has the inexact moniker of 'fluconazole shoulder syndrome' despite the fact that it can present throughout the musculoskeletal system. Perhaps a better name is fluconazole arthropathy. Fluconazole can cause headache that is usually mild but may be persistent and therefore can be confused with coccidioidal meningitis. This can definitely be distinguished by lumbar puncture. In a stable clinical circumstance, a drug holiday of 5–7 days may resolve the issue with reasonable clarity. Another concern with all azoles is the issue of hepatotoxicity and drug-induced hepatitis. Fluconazole does cause transaminitis but very rarely leads to drug-induced hepatitis or death.[37] Nonetheless, laboratory monitoring on a periodic basis is recommended.

Itraconazole was introduced shortly after fluconazole. These drugs were compared in a randomized controlled trial.[38] Itraconazole is usually dosed at 100 mg, two capsules two times per day, and this is the dose most commonly used at the VFI. Absorption is problematic (see table 1).[39 40] Side effects include sodium retention and decreased cardiac contractility.[41 42] Therefore, at the VFI, we generally endeavor not to use this drug in persons at increased risk of heart failure. When used in those individuals, we monitor brain natriuretic peptide.

Voriconazole was introduced in 2002. It was observed that this drug could rescue individuals who failed fluconazole.[43] The FDA-approved dose of 200 mg orally every 12 hours was not found to be optimal; hence, at the VFI, the usual starting dose is 4 mg/kg of body weight every 12 hours with no food 1 hour predose and postdose. The originally reported toxicity of 'flashing lights' based on the drug's ability to activate retinal cells has been found to be of limited significance.[44] The originally noted side effects did not include photodermatitis. This has proven to be a major concern. Changes in skin color and severe sunburn with limited sun exposure were noted early in this drug's use.[45] Subsequently, multiple cases of melanoma and squamous cell carcinoma have been associated with these changes.[46] Currently, the VFI does not recommend this drug on a routine basis.

The next azole to become available was posaconazole. It originally was available as a liquid formulation that had poor absorption. Despite therapeutic successes, the VFI no longer recommends this formulation except for individuals unable to ingest a tablet. The tablet formulation has improved absorption, is once a day and less dependent on coadministration of fatty food. Posaconazole is used as a rescue therapy when fluconazole has failed in pneumonic and disseminated disease. Side effects include hypokalemia and hypertension based on an aldosterone-like effect.[47] This may limit use of this drug in some patients. The FDA-approved dose of the tablet formulation is 100 mg, three times a day, every 24 hours. At th VFI, the recommended dose is 400 mg every 24 hours.

Isavuconazonium is the latest azole that has become available. VFI has used this drug preferentially due to its tolerability and efficacy in the last 5 years in all forms of infection, particularly when fluconazole has failed. The VFI has only used the FDA approved dose of 372 mg every 24 hours to date.

DURATION OF TREATMENT

For pneumonic disease other than miliary, the treatment duration varies from no treatment to several years. For those requiring treatment, the signal to discontinue treatment is based on resolution of symptoms, improved chest X-ray and improvement of the CF titer (University of California, Davis, or Kern County Public Health Department) to 1:2 or <1:2. This most often takes 3–12 months.

For disseminated disease, including miliary pulmonary disease, the VFI recommends treatment duration of a minimum of 3 years with clinical and radiographical stability and a CF titer of <1:2 for at least 6 months (table 2).

MONITORING TREATMENT

During treatment with azoles, CBC differential, BMP and LFTs are monitored periodically. Attention to hypokalemia, anemia, malnutrition and glucose control is paramount. There are no data that prove therapeutic drug monitoring is an adjunct to care for CM. However, the VFI finds it to be useful due to substantial variations in the absorption and metabolism of all the azoles and a tool to assess adherence in the setting of lack of response.

Table 2 Clinical manifestations of primary CM and treatment*[18 43–47]

Clinical presentation	Antifungal therapy	Duration of therapy
No significant respiratory distress	Azoles	3 months–1 year
Respiratory failure	Liposomal AmB Long-acting azole	Daily for 14 days 1 year or occasionally longer
Skin lesions	Azoles	≥3 years
Abscess lesions	Azoles	≥3 years
Synovitis (without adjacent osteomyelitis)	Azoles	≥3 years
Axial skeleton long bones, other critical bones	Liposomal AmB Azoles	Daily for 14 days Three times a week for 12 weeks or occasionally longer ≥3 years
Osteomyelitis (non-critical bones)	Liposomal AmB/azoles	≥3 years
Peritonitis	Azoles Liposomal AmB (rare)	≥3 years
Lymphadenopathy	Azoles Liposomal AmB (rare)	≥3 years
Other sites	Azoles Liposomal AmB (rare)	≥3 years
Meningitis	Azoles Intrathecal AmB (for treatment failure)	Lifelong therapy
Intracranial hypertension/ hydrocephalus	Repeated lumbar puncture/ventricular shunting	

Spherusol—conversion from negative to positive is diagnostic and also used as a marker for delayed hypersensitivity. False negatives and false positives are a potential with all the aforementioned tests.
*Mallow, Joshua J Clinical Micro Vol 55 March 2017 3.0 University of Arizona.
CM, coccidioidomycosis.

Targeted therapeutic drug levels can be found in table 1. For itraconazole, levels of itraconazole and its active metabolite hydroxyitraconazole should be combined.

POST-THERAPY FOLLOW-UP

At the VFI, it is endeavored to follow up all patients for 2 years if not treated or post-therapy if treated. They are evaluated with declining frequency for clinical or serological relapse and dissemination.

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