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FUNGAL INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE (A BONIFAZ AND M PEREIRA, SECTION EDITORS)

Coccidioidomycosis in Children and Adolescents: an Update

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Abstract

Purpose of Review Coccidioidomycosis is a systemic fungal infection endemic in Southwestern United States, Northern Mexico, Central and South America. Coccidioidal infection is not well characterized in pediatric population; but due to an increasing incidence in this age group, a special interest had surged to further describe clinical findings, treatment and clinical course of pediatric patients with coccidioidomycosis.

Recent Findings In the last few years new data about coccidioidomycosis in children and adolescents has been published, including the report of increasing incidence in general population, making a high index of suspicion among healthcare providers important to avoid delays in diagnosis and treatment.

Summary This review focuses on coccidioidal infections in pediatric population, emphasizing on the epidemiology, clinical manifestations, natural history, diagnosis and management in children and adolescents.

Keywords Coccidioidomycosis · Pediatrics · Fungus disease

Introduction

Coccidioidomycosis or San Joaquin Valley fever is a systemic mycosis caused by inhalation of *Coccidioides* sp. fungal spores, which principally reside in Southwestern United States and arid areas of Mexico and Central and South America. However, cases in non-endemic areas have been reported and occur among persons who visit or temporarily relocate to endemic areas [1•, 2].

Coccidioidomycosis is characterized by a great variety of clinical manifestations, but up to 60% of persons exposed to the fungus are asymptomatic. Symptomatic persons usually have mild flu-like symptoms but also can present severe pulmonary disease or potentially fatal disseminated forms that can involve the skin, soft tissue, lymph nodes, bones, joints, viscera, and central nervous system [1•, 3].

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Epidemiology

Recent epidemiologic reports have documented an increased incidence since 1998, particularly in Arizona and California [3, 4, 5••].

Some of the factors that may be related to the rise in the number of cases are mainly climatic and environmental factors favorable to *Coccidioides* sp. proliferation, including occupational and recreational activities that disrupt the soil, dust storms, and earthquake activity. Other factors like improvement in surveillance methods, increased number of immunosuppressed individuals, more awareness of the disease, and improvement on diagnostic testing may also be playing a role [2, 5••].

Primary infections occur frequently after the rainy season in summer and fall affecting mostly construction and farm workers, military personnel, archeologist, and excavators. Also, in endemic areas, there is evidence of infection in animals like dogs, cats, rodents, cattle, and sheep [6•, 7].

Although most coccidioidal infections occur among adults between 40 and 59 years old, infection in people over 70 years old and in pediatric age groups does occur [3, 8••, 9••]. Coccidioidomycosis is reportable in 22 states of the United States of America (USA); approximately 65% of cases are

reported from Arizona and 30% from California; thus, its epidemiology in these states is well described [10•]. Cases that reported from states other than Arizona and California constitute 4% of total reported cases [10•].

In California, during 2000–2016, 49,986 cases were documented, of which 4582 (9.2%) occurred among persons aged ≤ 17 years [8••]. This resulted in an increase in incidence from 0.8 to 5.2 per 100,000 residents in pediatric age groups; and during 2015–2016, there was the sharpest increase in incidence by 148% among children and a 64% increase among adults (9.9 to 15.2 per 100,000) [8••]. In Arizona, in 2016, an incidence of 7.7 per 100,000 residents among 1 to 4 years of age and 209 per 100,000 in population over 70 years old was reported, the highest rates ever reported [9••]. Rates among adult and pediatric residents were 31.1 and 79.4 times higher in endemic regions than those in less endemic regions, respectively [8••].

Despite an increasing incidence, outcomes have improved and mortality rates declined from 5.2% in 2005 to 1.5% in 2012. The overall in-hospital mortality was 2.7% in adults and 3.2% in children, with a lower risk of mortality in male than in female children, contrary to adults in whom males > 65 years old have a higher risk of mortality [11•, 12].

Most infections in children occur between 12 and 17 years of age, and this is slightly higher in males than in females (3.1:2.7), as in adults. This may be due to age and sex differences in occupational or recreational activities, hormone production, or even immune response [8••].

Ethnic differences in coccidioidomycosis have been reported; African American and Filipino adults and children are more likely to have extrapulmonary disease compared with other populations, and a 2 to 10 times higher rate of dissemination has been reported in African American children compared with Caucasians, suggesting a possible genetic predisposition to fungal dissemination [1•, 2]. Hispanic children are more likely to be admitted and to have prolonged hospitalizations related to coccidioidomycosis [1•]. The mechanisms behind variations in ethnic predisposition to dissemination have not been clearly established [13].

Disseminated disease occurs more frequently in infants [6•]. Underlying comorbidities in affected children have been reported in 34.2 to 41% among studies, such as deficiency anemia, cancer, HIV infection, diabetes mellitus, chronic pulmonary disease, renal failure, obesity, congestive heart failure, liver disease, drug and alcohol abuse, and connective tissue disease [1•, 10•, 11•, 14]. The percentage of immunocompromised children with coccidioidomycosis varied among reports, from 14% reported by Chu et al. to 41% reported by Connelly and Zarella [1•, 14, 15, 16]. Mortality in hospitalized children occurs in 1.5–8%, according to different studies [14, 16].

In Latin America, the number of reported cases of coccidioidomycosis also has increased, according to reports in Mexico, Guatemala, Honduras, Colombia, Venezuela, Brazil, Paraguay, Bolivia, and Argentina [17•]. The incidence in these countries is unknown. This may be because the disease is not reportable in some, primary infections that are not frequently diagnosed due to the lack of access to laboratory mycological diagnosis, or perhaps due to a high percentage of subclinical cases, low rate of suspicion, or misdiagnosis as tuberculosis, which is endemic [17•].

Pathogenesis and Immunity

Coccidioidomycosis is a deep mycosis caused dimorphic (biphasic) fungi *Coccidioides immitis* and *Coccidioides posadasii* [18]. The two species populate distinct geographic regions: *C. immitis* is found in central and southern California, and *C. posadasii* is present in parts of Mexico and Central and South America [2].

The fungal mycelia segment into arthroconidia, which are easily aerosolized when disturbed. Mycelia can survive in the desert soil at depths of 2–30 cm for months to years, and multiply rapidly after a rain [1•, 6•]. Infection usually occurs by inhalation of the arthroconidia (spores) in 98% of the cases, and in the rest (2%) may be secondary to direct traumatisms in the skin [18]. Arthroconidia undergo a morphologic change in the host's lungs and convert to multinucleate spherules filled with endospores. These spherules mature and rupture releasing hundreds of endospores into the surrounding tissue, and each one of them has the potential to form another spherule and repeat the cycle (Fig. 1). Endospore release is essential for lymphatic or hematogenous dissemination of the pathogen within tissues of the host [1•, 13, 19].

The innate immune system provides the first line of defense against *Coccidioides* sp. infection by expressing cell pattern recognition receptors (PRRs) like toll-like receptors (TLRs), C-type lectin receptors (CLRs), Nod-like receptors (NODs), and Rig-I-like receptors, which assemble to form pathogen-associated molecular patterns (PAMPs). It is known that TLRs and CLRs orchestrate the recognition of spherule wall components and initiate innate immunity, and subsequently trigger adaptative response against the fungus [19, 20••].

With regard to adaptative T cell responses to *Coccidioides* sp. infection, both CD4+ T-helper (Th) and CD8+ cytotoxic (Tc) lymphocytes contribute to protective pathogenic immune responses. CD4+ T cell subsets Th1, Th2, and Th17, and perhaps interleukin (IL)-10-producing cells play roles in cellular and humoral immunity upon *Coccidioides* spp. [20••].

Risk Factors for Disseminated Coccidioidomycosis

There have been identified rare human genetic mutations that can cause susceptibility to disseminated coccidioidomycosis

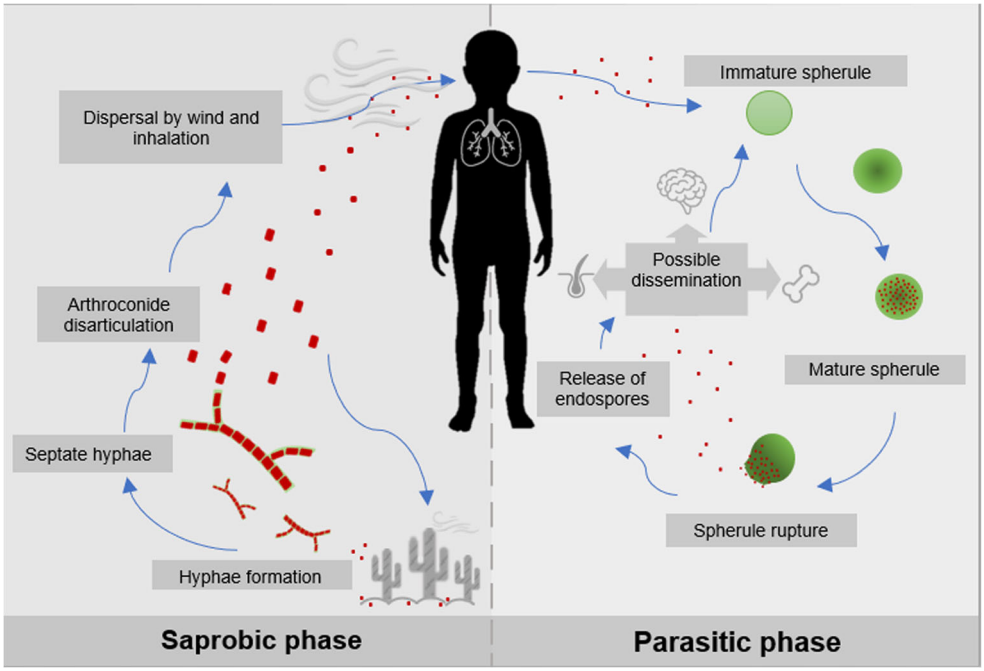

Fig. 1 Life cycle of *Coccidioides* spp.

such as mutations in genes involved in the IL-12-interpheron (IFN)-γ signaling pathway (*IFNGR1*, *IL12RB1* (*AR*), *STAT3*, *STAT1*, *IL12RB2*, *STAT4*, *IFNAR2* (*AR*)), innate immune sensing (*DDX58*, *IFIH1*, *TLR4*, *TLR5*), phosphoinositide-3-kinase pathway (*PIK3R3*, *PIK3R5*, *PIK3CG*), NFκB signaling (*IRF5*, *IKBKB*, *RIPK2*, *NFKBIA*), and IL-17 signaling (*IL17RA*, *IL17RC*, *TRAF3IP2*) [20••]. Also, some human leukocyte antigen (DRB*1301) influences risk of dissemination in Hispanics [6•, 18].

Persons with impaired cellular immunity, such as those infected with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), recipients of solid organ or hematopoietic stem cell transplants, and those receiving biologic response modifiers (tumor necrosis factor [TNF] antagonists—infliximab, etanercept, adalimumab, certolizumab, golimumab; inhibitors of T cell activation—abatacept; inhibitors of downstream signaling and other cytokines—ustekinumab, tocilizumab) are more likely to have severe infection, disseminated infection, and higher mortality rates [21••, 22•].

Other risk factors that have been identified for disseminated coccidioidomycosis are pregnancy, males, and race/ethnicity with also an increased risk of mortality [10•, 22•, 23].

Clinical Manifestations

Coccidioidomycosis occurs at any age, but information about clinical manifestations in pediatric patients is limited as compared with adults. It is estimated that 60% of patients with coccidioidomycosis will develop an asymptomatic or minimally symptomatic infection. The remaining 40% will be symptomatic in a *variable* manner, most commonly with pulmonary manifestations, and only in a small proportion of cases progressive pulmonary or disseminated infection occurs [5••, 7].

Most pediatric patients with coccidioidomycosis were previously healthy but can still develop severe and sometimes life-threatening disease [1•, 3, 5••, 24••]. Differences in disease severity may be related to variations in immunologic responses to the infection among individuals [24••].

Coccidioidomycosis is classified into primary and secondary diseases, depending on whether there was direct inoculation or dissemination from a primary focus, respectively. Most cases of primary disease are acquired by inhalation of arthroconidia; thus, the lungs are the most common site involved. Primary involvement of the skin is quite rare and is acquired by direct cutaneous inoculation. Secondary disease can affect any organ, most commonly the skin, bones, joints, and nervous system (Table 1) [18, 25].

Primary Pulmonary Coccidioidomycosis

It is the most common type of infection [5••]. It occurs 1–3 weeks after the inoculation. The patient may present a flu-like syndrome called "the Valley fever of San Joaquin" with cough, fever, headache, fatigue, and arthralgias, or develop a more severe lower respiratory tract disease, including pneumonia [6•, 7]. Actually, in endemic regions, primary coccidioidal pneumonia may account for 25% of all community-acquired pneumonia [7]. Local progression can

Table 1 Clinical manifestations of *Coccidioides* sp. infections

	Incubation period	Clinical findings	Complications
Asymptomatic infection (60%)	Not applicable	Not applicable	Rare (pulmonary sequelae, reactivation)
Primary pulmonary coccidioidomycosis (40%)	1–3 weeks	Flu-like syndrome (the Valley fever of San Joaquin): fever, cough, headache, night sweats Pneumonia (localized) Diffuse pulmonary disease Other: rheumatologic complaints, reactive cutaneous involvement (erythema nodosum, erythema multiforme, acute generalized exanthema, Sweet syndrome, and interstitial granulomatous dermatitis)	Pulmonary complications: pleural effusion, empyema, lung abscess, pericarditis, and mediastinitis Chronic and progressive pulmonary disease Reactivation
Disseminated disease/extrathoracic coccidioidomycosis (20–40%)			
Skeletal system	Weeks–months	Chronic osteomyelitis (tibia, vertebrae, skull, metatarsals, and metacarpals)	Periosteal or intraosseous abscess, intramuscular abscess, and septic arthritis
CNS	Weeks–months	Meningitis: headaches, seizures, blurry vision, photophobia, meningismus, cognitive decline, hearing changes, and focal neurologic deficits	Hydrocephalus, vasculitis, cerebral ischemia, infarctions, vasospasm, and hemorrhage
Skin	Weeks–months	Widely heterogeneous cutaneous lesions (papules, nodules, gummas, pustular lesions, ulcerated and verrucous plaques, scars, abscesses, and fistulas) more frequently in the neck, armpits, and inguinal region	

lead to pleural effusion, empyema, lung abscess, pericarditis, and mediastinitis [26]. Diffuse pneumonia is a more severe form of the disease that can happen if there is a high inoculum exposure or if the patient is immunosuppressed [7].

Chest radiographic features are not specific, the most common finding being focal consolidation. Others include mediastinal adenopathy, hilar adenopathy, pleural effusion, pleural empyema, mediastinitis, and focal lung abscess. However, the x-ray can also be completely normal [5••, 26].

Chronic and progressive pulmonary disease, presenting with persistent cough, hemoptysis, and weight loss, occurs in a small percentage of cases [25].

Cutaneous Coccidioidomycosis

Up to 50% of primary pulmonary coccidioidomycosis cases have reactive cutaneous involvement, manifesting as erythema nodosum, erythema multiforme, acute generalized exanthema, Sweet syndrome, and interstitial granulomatous dermatitis. These represent a favorable prognostic sign because they are due to a robust immune response that decreases the risk of dissemination [7, 18, 25].

Erythema nodosum is the most frequent manifestation within this group; it is a self-limited, inflammatory disorder characterized by multiple erythematous, painful indurated nodules usually limited to the extremities. It is associated with less dissemination and chronicity rates [25].

The skin is one of the most common sites of disseminated infection, or secondary cutaneous coccidioidomycosis. Up to 70% of patients with disseminated disease have skin involvement. It typically presents within weeks or months after the infection or can be the initial manifestation. Clinical appearance of lesions is widely heterogeneous (papules, nodules, gummas, pustular lesions, ulcerated and verrucous plaques, scars, abscesses, and fistulas) and can be located in the face, neck, scalp, and chest wall (Fig. 2a, b). Due to the wide clinical manifestations, secondary cutaneous coccidioidomycosis is included in the group of "great imitators" [25].

In extremely rare cases, there is direct cutaneous inoculation and primary cutaneous infection occurs. It is usually seen in adults but very few cases have been reported in children. It presents as a painless, indurated nodule with ulceration on an extremity. It has good prognosis, usually with spontaneous resolution [18, 27].

Disseminated Coccidioidomycosis

Disseminated disease occurs in 1–3% of patients affected by coccidioidomycosis, but 30–50% of immunosuppressed persons [10•]. It results from hematogenous spread, most likely following a primary pulmonary infection, but it can occur even in the absence of significant respiratory disease [1•, 5••].

In children, there is an increased risk of dissemination of the disease [18]. A retrospective study conducted by Dimitrova et al. reported sixty-four children with coccidioidomycosis, of whom 60% had only pulmonary disease and 40% disseminated disease [1•]. In 2019, Lee et al. reported a high frequency of disseminated coccidioidomycosis among

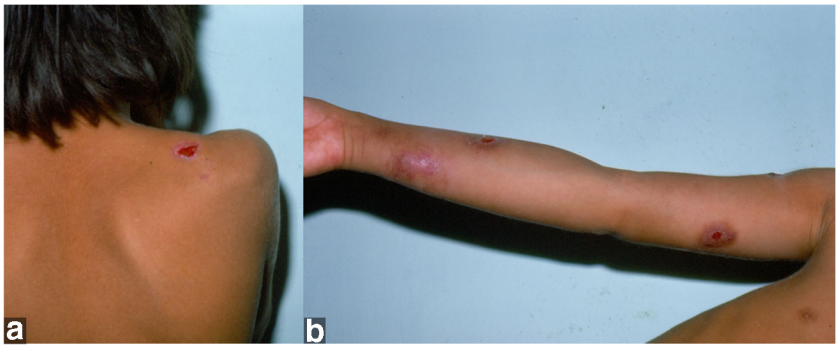

Fig. 2 **a**, **b** Secondary cutaneous coccidioidomycosis in a child manifesting as disseminated ulcerated infiltrated plaques

pediatric patients at an infectious disease clinic in California, where almost 20% of the cases had disseminated infection at the time of the diagnosis or later in the course of the disease [5••].

Most pediatric patients with disseminated coccidioidomycosis are immunocompetent. Naeem et al. reported that 80% of the children with extrapulmonary coccidioidomycosis were previously healthy, and only 6% were immunocompromised patients [24••]. Immunosuppression is not necessarily associated with greater propensity of disseminated disease [1•].

Disseminated disease manifests clinically within 2 years of exposure. Patients have longer delays in diagnosis, with a median of 57 days after symptom onset versus 16 days in patients with pulmonary disease [5••]. In children, disease can present with a variety of symptoms: they frequently have constitutional symptoms like fever, weight loss, or pain localized to the affected sites [5••]. Dissemination to any organ can occur, either one or multiple sites. Naeem et al. reported that patients 10 years or older at the time of the diagnosis are more likely to have more than 1 organ involved and experience relapses or progressive, fatal disease compared with those < 10 years old [24••]. Extrapulmonary organ involvement includes the bones, joints, mediastinum, central nervous system (CNS), cervical lymph nodes, larynx, and skin [24••].

The skeletal system is the most common affected site, followed by the CNS [24••]. Bone involvement most frequently involves the tibia, vertebrae, skull, metatarsals, and metacarpals [6•]. The infection can result in chronic osteomyelitis, radiologically presenting with lytic lesions and cortical destruction [28].

Central nervous system (CNS) involvement is the most deleterious site of extrapulmonary infection; it may be part of widespread dissemination or may be the only manifestation of the disease. One-third of pediatric patients with disseminated coccidioidomycosis have CNS involvement, underscoring the importance of early evaluation for the presence of disease at this site [1•]. It most commonly causes meningitis, manifesting frequently as headaches, seizures, blurry vision, photophobia, meningismus, cognitive decline, hearing changes, and focal neurologic deficits [7]. Cerebrospinal fluid (CSF) analysis typically shows an elevated white blood cell count with mixed or lymphocytic pleocytosis, high levels of protein, and low levels of glucose. When left untreated, this infection is uniformly fatal. The most common life-threatening complications include hydrocephalus, vasculitis, cerebral ischemia, infarctions, vasospasm, and hemorrhage [6•, 7].

Other sites are less frequently affected and include the mediastinum, lymph nodes, larynx, skin, heart, and intraabdominal cavity [1•, 24••]. Symptoms of extrathoracic coccidioidomycosis are indistinguishable from infection due to other pathogens, cancer, or other medical conditions.

Naeem et al. recently reported that CNS and skeletal diseases were more frequent in older children whereas laryngeal and mediastinal diseases occurred in younger children [24••]. Intraabdominal and cardiac involvement is more frequent in immunocompromised patients [1•]. Mediastinitis is a common finding in children, but rarely reported in adults with coccidioidomycosis [3]. For the above reasons, there is a need of careful and prompt evaluation of specific extrapulmonary disease in each age group [24••].

The risk of dissemination is higher in immunosuppressed patients (HIV/AIDS, hematologic malignancies, recipients of immunosuppressive drugs), those with cardiopulmonary disease, pregnant women in the third trimester, males, African American and Filipino ethnicity, those with age > 65 years, children < 1 year, and those with other conditions such as systemic lupus erythematosus and diabetes mellitus [5••, 7, 25, 28].

Previously, studies performed in adults reported that higher *Coccidioides* sp. complement fixation (CF) titers indicate more extensive infections, a need for longer duration of antifungal therapy and an increased risk of relapse. The above applies to pediatric cases [3], in whom CF titers greater than 1:32 at the time of diagnosis are associated with disseminated disease in pediatric patients. Nevertheless, negative coccidioidal CF titers cannot completely exclude disseminated disease, and about 10% of cases had negative serology early in the course of the clinical disease [5••, 24••]. If there is clinical suspicion despite a negative serology test, clinicians should consider repeating tests or obtain cultures and/or tissue for diagnosis [5••]. On the other hand, an elevated titer is not always indicative of disseminated disease [5••].

Mortality rates associated with disseminated coccidioidomycosis have been reported to be as high as 28%, but early diagnosis and treatment can decrease the likelihood of morbidity and mortality [29].

Diagnosis

The diagnosis is made with a good medical history including travel history, a high index of suspicion for the disease, and obtaining of the appropriate diagnostic studies [6•]. The diagnosis can be made with a combination of serological, histopathological, and microbiological methods.

Serologic findings can be detected after 1 week in 50% of patients, specifically immunoglobulin (Ig) M antibodies known as tube precipitin (TP), which are positive in 90% by the third week of illness and can remain positive after 5 months [6•]. Past studies indicated that only 2.4 to 9.3% of patients with non-disseminated infections developed maximal titers of > 1:16, while 58 to 65% of patients with disseminated infections developed titers of > 1:16; thus, the latter were considered a specific indication of possible dissemination [30]. Actually, even uncomplicated infections can develop higher titers; currently CF titers above 1:32 indicate severe primary or disseminated disease, and become positive at 2 to 28 weeks and can remain positive for 6 to 8 months [6•, 30]. They are quite specific, but even this cutoff value has a 16.5% of false positive rate and 34.4% of false negative rate, especially in immunocompromised patients [6•, 30].

Examination of sputum, bronchial washes, exudate, or scales can be performed using different techniques like smear with 20% potassium hydroxide (KOH) and fluorescent calcofluor white (CFW) stain, revealing multiple spherules with endospores inside, considered a pathognomonic finding (Fig. 3a). Periodic acid-Schiff (PAS) and Grocott-Gomori stains are also used to demonstrate the spherules in tissue (Fig. 3b). These parasitic structures have a spherical shape with double membrane; they measure approximately 20 to 70 μm in diameter with average endospores of 2–5 μm in diameter; nevertheless, if the spherule is in early stages, it has a smaller size, and it has no endospores and can be confused with some other fungal structures such as *Blastomyces dermatitidis* cells [18]. An unusual case of chronic coccidioidomycosis in a patient with diabetes was reported, where hyphae and arthroconidia were found in pulmonary tissue sections with no typical endospore-forming spherules found on histopathology evaluation [31, 32].

Culture remains the best method for definitive diagnosis but should only be performed in specialty laboratories with Biosafety Level 3 containment [18]. Growth is usually apparent in 4 to 8 days in Sabouraud agar culture media plus antibiotics; colonies are non-pigmented hairy, dry mold but may acquire brown colors as they age. Direct examination of the culture reveals abundant arthroconidia [18] (Fig. 3c).

Regarding molecular testing, polymerase chain reaction (PCR)–based testing is performed after culture growth, with favorable results in pulmonary samples, but poor results in cerebrospinal fluid [31].

Complementary imaging studies like X-ray, computed axial tomography (CAT) scans, and magnetic resonance imaging (MRI) are crucial in the diagnosis of pulmonary and musculoskeletal involvement.

Treatment

In general, coccidioidomycosis is a self-limited illness in more than 90% of children and adults. Antifungal therapy is indicated to reduce the severity of the primary infection and to prevent and treat dissemination [6•].

Both in children and in adults, it is important to measure CF antibody titers before starting therapy and every 3–6 months so treatment response, prognosis, and disease evolution can be evaluated. The aim is to achieve levels below 1:8 to consider a clinical and mycological cure [18].

Current regimens for meningeal and non-meningeal coccidioidomycosis include fluconazole, itraconazole, and amphotericin B [33•]. Monotherapy with second-generation triazoles, voriconazole, and posaconazole has been shown to have clinical efficacy as salvage therapy for refractory disease (Table 2) [34].

Fluconazole has become the drug of choice for meningeal disease and the usual first choice for disseminated non-meningeal disease because of its excellent bioavailability, tolerability, blood-brain barrier penetration, and lack of toxicity. Itraconazole is equally effective in patients with non-meningeal disease [35].

Amphotericin B is considered first-choice therapy for serious infections, but later it can be considered to change to azole therapy when the response to treatment is good [18]. Amphotericin B can be found in different formulations that differ in the degree of toxicity and side effects. Amphotericin B has been associated with a significant improvement in survival but is associated with significant side effects, and its intrathecal administration can be complicated by headache, nausea, vomiting, chills and fever, and arachnoiditis, similar to relapse manifestations [6•]. Combination therapy with amphotericin B and a triazole is an option for severe disease, although this regimen is not recommended as superior to single-agent therapy [34].

Musculoskeletal involvement requires long-term antifungal suppression, even for life, due to reported high rates of relapse after its discontinuation. Fluconazole is the drug of choice, with an established favorable safety profile and high tolerability in pediatric patients. Moreover, patients with high

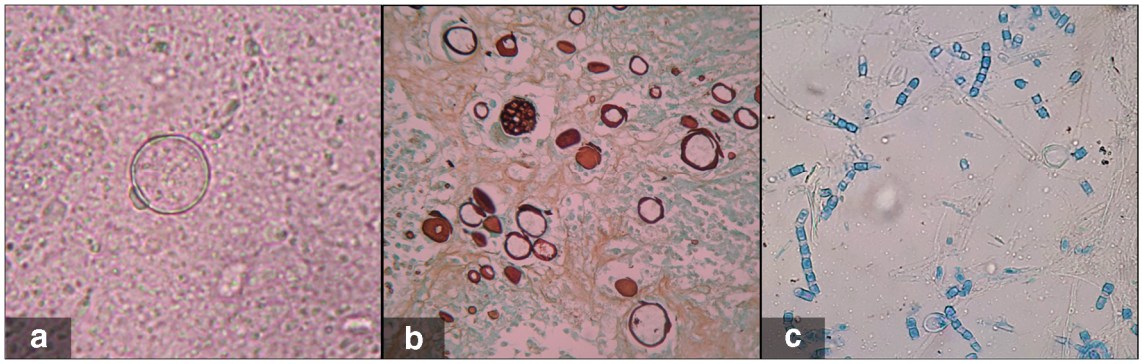

Fig. 3 **a** Coccidioidal spherule observed in direct exam stained with KOH. **b** Coccidioidal spherules in a tissue sample stained with Grocott-Gomori. **c** Arthroconidia from culture of *Coccidioides* spp. stained with lactophenol cotton blue. Image courtesy of Alejandro Bonifaz

complement fixation titers (≥ 1:128) will require surgical debridement because of the high rates of incomplete response to medical treatment alone, similar to the adult population [36].

Bilateral reticulonodular infiltrates or miliary patterns on chest radiographs suggest underlying immunosuppression or a high inoculum size and are an indication for therapy. These patients are typically treated with amphotericin B because it shows a faster response than azoles in severely ill patients. Therapy should be continued for at least 1 year, followed by secondary prophylaxis [6•].

Coccidioidal meningitis is treated with fluconazole. Therapy is continued for a lifetime because of the high rate of relapse among patients treated with azoles [6•].

The role of corticosteroids in treatment of coccidioidomycosis is controversial; nevertheless, some studies show favorable results in severe pulmonary and central nervous system diseases with reduced inflammation as therapy is initiated [37].

Surgical intervention is commonly necessary as an adjuvant to medical therapy in patients with coccidioidomycosis [14]. Connelly and Zarella reported that 54% of their hospitalized pediatric patients required surgical intervention, and Fisher et al. reported that 41% of their patients underwent surgical intervention [14, 16]. Most of the procedures involved pulmonary and cerebral infections. Indications for surgical management for pulmonary infections include enlarging peripheral cavity, severe hemoptysis from cavitation, empyema, and bronchopleural fistula [15].

The uses of echinocandins and azoles do not cause antagonism in fungal diseases and this combination has good results. A retrospective study of Levy at al. evaluated a concurrent voriconazole and caspofungin therapy, with good results; however, due to the retrospective nature of the study, it cannot make a certain recommendation of this combination therapy as salvage therapy [34].

Prevention of coccidioidomycosis relies primarily on limiting exposure. Vaccines that would boost cell-mediated immune responses are desirable. A trial of killed spherule vaccine has been inconclusive. Multiple candidate vaccines are being evaluated in animal models and seem to be promising. Recombinant peptides, synthetic peptides, and adjuvants such as recombinant interleukin-12 are being investigated as possible vaccines [6•].

Table 2 Pediatric dosing for the treatment of coccidioidomycosis

Antifungals	Dosing in pediatric age group
Fluconazole	6–12 mg/kg/day (dose up to 15–23 mg/kg/day for meningitis)*
	Adult dosing 400–800 mg/day (dose up to 1200 mg/day for meningitis)*
Itraconazole	5–10 mg/kg/dose 2 times daily for 3 days, followed by 2–5 mg/kg/dose 2 times daily
	Adult dosing 200 mg 2 to 4 times daily
Liposomal amphotericin B	3–5 mg/kg/day
Lipidic amphotericin	2–6 mg/kg/day
Amphotericin B deoxycholate	0.25 a 0.75 mg/kg/day (3 doses in a week, maximum dose 30 mg) for 2–3 weeks (sometimes a break period is necessary)
Amphotericin B colloidal dispersion	3–4 mg/kg/day

Duration of treatment is typically 6–12 weeks for mild-to-moderate diseases and 12–24 weeks for severe diseases, but also depends upon underlying condition and site of infection

*For meningitis, therapy should be continued for life

Conclusions

In summary, coccidioidomycosis is a systemic fungal infection that affects all ages, and mainly presents with mild respiratory symptoms but in some cases, dissemination can occur with great clinical variability and life-threatening infections. Pediatricians need to be aware of coccidioidal infections in children and adolescents, including risk factors, clinical presentation, diagnosis, and treatment, due to an increased incidence both in endemic and in non-endemic areas.

Compliance with Ethical Standards

Conflict of Interest Maria Teresa Garcia-Romero reports personal fees from Pierre Fabre Mexico, personal fees from Sanofi Mexico, and personal fees from Pfizer Mexico outside the submitted work. Mariana Maza-Morales, Marian Kristalia Rivas-Calderón and Elsa Eduwiges Barrón-Calvillo declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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