Diagnosis and Initial Management of Musculoskeletal Coccidioidomycosis in Children

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Dedication:

This thesis is dedicated to my father Patrick Ho, to my mother Patricia Ho, and to my sister Renita Ho. Simply, I would not be here but for their love, support and sacrifice.

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Abstract:

Coccidioidomycosis is an invasive fungal infection caused by the inhalation of aerosolized spores of *Coccidioides* spp., which reside in the arid soil of the southwestern United States and northern Mexico. Dissemination of coccidioidomycosis is rare, and can lead to extrapulmonic diseases including meningitis, osteomyelitis, and skin and soft-tissue involvement. The purpose of this study is to report our experience with musculoskeletal coccidioidomycosis in children. We retrospectively reviewed the charts of patients with musculoskeletal infection with *Coccidioides* spp. at our institution from 1997 to 2010. Demographic and clinical data were collected from medical records, including the age of the patient, gender, white blood cell count, immunocompetence, length of stay, location of involvement, and initial treatment. In total, we identified 20 children with musculoskeletal coccidioidomycosis. The mean age was 12.3 years (range: 2 to 17) at time of diagnosis. Diagnostic criteria included positive imaging tests (usually MRI), serological positive titers, and/or biopsy with positive cultures. The most common presenting symptom was bone pain (100%) and just 3 (15%) patients had accompanying signs/symptoms of pulmonary infection. Only 2 (5%) patients had a white blood cell count > 15×10^9/L (5%). Locations of infection included the foot (24%), knee (14%), spine (19%), forearm (10%), lower leg (7%) and other sites (26%). Fluconazole was the most common antifungal agent used (75%). Surgical intervention was required in 12 (60%) of patients. This is the first series that has described musculoskeletal coccidioidomycosis exclusively in children. This study suggests that the initial presentation of this disease can be nonspecific and difficult to recognize in children. Clinicians should consider this diagnosis when faced with a musculoskeletal infection in children from the southwestern United States and northern Mexico.

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Introduction:

Background:

Coccidioidomycosis is an invasive fungal infection endemic to the southwestern United States and parts of Latin America[1,2]. Of an estimated 150,000 new cases of coccidioidomycosis each year in the United States[3], the majority of cases occur in Arizona and California[4], where the incidence has increased steadily over the past 20 years[5,6]. Coccidioidomycosis is caused by inhalation of the airborne arthroconidia of soil-dwelling fungi of the genus *Coccidioides*[7]. This genus is comprised of two nearly identical species, *Coccidioides immitis* and *Coccidioides posadasii*, also referred to as the "Californian" and "non-Californian" species, respectively, due to their geographic distributions[8,9]. There is no apparent clinical difference between the disease states caused by the two species, neither in disease presentation nor in response to treatment[3,10].

Primary coccidioidomycosis is asymptomatic in approximately 60% of those infected, and the remaining 40% commonly present with an acute pulmonary infection characterized by vague flu-like symptoms[2,7,11]. In 1% to 5% of patients, primary respiratory infection may progress to disseminated disease and involve any organ system, a serious complication with considerable morbidity and mortality[12-16]. Dissemination of *Coccidioides* spp. can lead to meningitis, osteomyelitis, hematogenous infection and skin and soft tissue involvement[16]. Extrapulmonary infection can also occur independent of the primary infection[17]. Musculoskeletal manifestations of coccidioidomycosis are estimated to occur in 20% to 50% of cases of disseminated disease[14,17-19]. Disseminated musculoskeletal coccidioidomycosis is a chronic destructive disease that requires aggressive medical and surgical management[15].

Coccidioidomycosis was first reported in 1892 by Posadas, an intern at the time who described a skin lesion in an Argentinian soldier that was thought to have been caused by a protozoan organism[20]. In 1896, Rixford and Gilchrist reported the first two cases of coccidioidomycosis in the United States, naming the organism *Coccidioides* ("resembling *Coccidia*") *immitis* ("not mild")[21]. The spectrum of disease presentation was first appreciated in 1929, when Chope, then a second year medical student, accidentally inhaled a cloud of spores

while studying *C. immitis* in the Dickson laboratory at Stanford University. Within 9 days of the exposure, he developed a right upper lobe pneumonia and severe pleuritic chest pain, fever, productive cough and hemoptysis. Four weeks later, he developed erythema nodosum and was found to have spherules in his sputum samples. The prognosis was considered extremely poor, however he recovered over the following months, and his ordeal provided major insight to coccidioidomycosis. It was only in 1936, when Dickson and his colleagues in the Health Department of Kern County, California were able to link the cases of acute cough, fever, pneumonia and erythema nodosum, collectively referred to as "San Joaquin Valley fever", with the causal organism *C. immitis*[7].

In the United States, *Coccidioides* spp. are found in the semiarid desert soil of the San Joaquin Valley of California, and regions of Arizona, Nevada, Utah, New Mexico and Texas[16,22,23]. This geographic region is characterized by high summer temperatures, less than 20 inches of rainfall a year, and alkaline soil[22]. Coccidioidomycosis is associated with a seasonal pattern in Arizona, demonstrated by increased rates of infection in early winter from October to January, and a smaller summer peak from May to August[24]. The incidence in Arizona has increased over the past decade, and may be due to climate change, influx into the endemic region of susceptible persons, and increased physician and laboratory reporting[5]. In Mexico, coccidioidin skin test surveys suggest a high endemicity in the Northern, Pacific Coast and Central regions of the country[25], although epidemiologic data are limited since coccidioidomycosis is not a reportable disease[26]. Coccidioidomycosis is also endemic to parts of Guatemala and Honduras, where skin test surveys in the Comayagua Valley showed a 25% prevalence[27]. Disease prevalence extends down to South America; indeed, it was in Argentina where Alejandro Posadas described the first known case of coccidioidomycosis in 1892[20]. A review of all reported cases of coccidioidomycosis in Argentina from 1892 to 2009 showed that incidence was highest in the semi-arid region of the Sierra Pampeanas with an incidence of 2.1 cases per 100,000 population in 2008[28]. In Brazil, the disease is endemic to the northeastern states of Bahia, Piauí, Ceará and Maranhão[29,30], where several small outbreaks have been associated with the digging of armadillo burrows and subsequent inhalation of aerosolized arthrospores[31]. *Coccidioides* spp. are also found elsewhere in South America including in regions of Venezuela and Paraguay[32].

Furthermore, travel and tourism to endemic regions have contributed to the increasing presentation of coccidioidomycosis in nonendemic areas such as New York and as far as Japan[33-35], making this a disease of national and worldwide importance[32,36].

The cytology and ecology of *Coccidioides* spp. are well-described in the literature[3,16,37-40]. Briefly, *Coccidioides* spp. are dimorphic, existing in a saprobic mycelial phase in the soil of endemic regions and in spherule form in tissue. In the soil, arthroconidia develop along branching septate hyphae that readily disarticulate as the organism matures. The arthroconidia are barrel-shaped and easily aerosolized, measuring less than 4µm in width and 6µm in width. Once inhaled, the arthroconidia are ingested by pulmonary macrophages and then transform to a round cell that eventually becomes a spherule. The spherule is a thick-walled structure ranging from 8 to 30µm in diameter that contains hundreds of asexual endospores, each typically measuring 2 to 4µm in diameter. Rupture of the spherule leads to dispersion of the contained endospores, inducing an inflammatory response that produces the systemic manifestations of the disease. Endospores may form new spherules and propagate in the lung, or spread hematogenously resulting in disseminated coccidioidomycosis.

Impact:

The incidence of coccidioidomycosis has increased over the last decade and has reached epidemic proportions in Arizona[24]. Arizona alone accounts for nearly 80% of all reported cases of coccidioidomycosis[4,41], and the Arizona Department of Health Services reported a rate high of 91 cases per 100,000 population in 2006, representing a 246% increase since 1999[24]. Disseminated coccidioidomycosis occurs at all ages[17,42], however manifestations in the pediatric population have received very little study as compared to adults[43,44]. In Arizona, while coccidioidomycosis is more likely to be reported in persons older than 60 years[45], the incidence in patients younger than 20 years increased 121% from 1998 to 2001, a larger increase than in any other age group in that period[6]. A study in the American Indian population reported increased susceptibility to coccidioidal dissemination in children younger than 5 years old as compared to other age groups[46]. Disseminated coccidioidomycosis resulting in musculoskeletal involvement requires long-term medical therapy and often aggressive surgical debridement for

effective management[47]. Skeletal infection is an uncommon presentation of coccidioidomycosis, and therefore may be neglected in the initial differential diagnosis[48].

Aim:

To the best of the authors' knowledge, there have not been any previous studies specifically examining musculoskeletal coccidioidomycosis in the pediatric population. The goal of this project is to retrospectively examine musculoskeletal coccidioidomycosis and characterize the initial presentation and management of a disease in a population that has received little study as compared to adults. A greater understanding in the context of pediatric patients may allow for earlier detection, potentially mitigating complications and improving resolution. Moreover, this descriptive study will provide data for future investigations and hypothesis development. Herein, we present our experience with pediatric musculoskeletal coccidioidomycosis at the largest children's hospital in the hyperendemic state of Arizona.

Methods:

This is a retrospective chart review of patients who were seen and treated at Phoenix Children's Hospital from 1997 to 2010 for musculoskeletal coccidioidomycosis. Patients were included if they were under age 17, and had an ICD-9-CM discharge diagnosis code of at least one of the following: primary extrapulmonary coccidioidomycosis (114.1), other forms of progressive coccidioidomycosis (114.3), and coccidioidomycosis, unspecified (114.9). A transition in 1997 to a new hospital records filing system prohibited investigation prior to that year. 20 patients with musculoskeletal involvement of coccidioidomycosis were identified. Medical records were reviewed for age, sex, race, date of admission and date of discharge, status of immunocompetence, presence of pulmonary symptoms on clinical presentation, serologic and microbiologic findings, radiographic findings, location of involvement, and method of treatment and surgical intervention. Attempts to obtain follow-up data were made, however were unsuccessful. This is primarily due to PCH lacking an out-patient Infectious Diseases clinic where the patients could be followed, as the Infectious Diseases physicians serve only on an in-patient consult service. Unfortunately, most of the patients were simply lost to follow-up, and some were seen by non-PCH orthopaedic surgeons, limiting our access to the data due to institutional policies. Collected patient data were de-identified and stored electronically on an encrypted server. This study was approved by the Phoenix Children's Hospital Institutional Review Board as well as the University of Arizona Institutional Review Board.

Results:

A total of 20 patients with musculoskeletal coccidioidomycosis were identified in the 13 year study period (January 1997 to December 2010). See Table 1 on page 7 for selected clinical data. The average age at time of diagnosis was 12.3 years (range: 2 to 17 years). The majority of patients were male, 13 (65%) and 7 (35%) were female. Caucasians were most represented at 11 patients (55%), followed by Hispanic 5 (25%) Hispanic, and 3 (15%) were Black and 1 (5%) was of Middle Eastern descent. 3 (15%) of the patients were immunocompromised with comorbid hematologic malignancy, 2 with pre-B cell acute lymphocytic leukemia and one with systemic lupus erythematosus and hemolytic anemia. All patients had geographic risk factors in that they lived in Phoenix, Arizona and the surrounding regions. The average length of hospital stay was 8.8 days, with 3 patients requiring hospitalization for more than 2 weeks. 2 (5%) patients required treatment in the ICU.

Among the 20 patients in this study, there were 42 musculoskeletal lesions distributed throughout the body, with 8 (40%) patients having involvement in multiple locations. There were 10 lesions in the foot and ankle. There were 8 lesions of the knee, 2 of the tibia, 1 of the fibula, 2 of the femur and one of the pelvis. The elbow was involved 1 time, the forearm 3 times, and the hand 2 times. There were 8 lesions in the spine, 2 lesions involving the skull, 1 of the sternum and 1 of the rib.

Table 1. Selected Clinical Data

Case #	Age (years)	Gender	Immunocompetence	Location of disease
1	17	Male	Competent	Right femur
2	15	Female	Competent	Spine T12
3	13	Female	Competent	Left navicular bone, cuboid bone
4	5	Male	Competent	Spine L5, T6, calvarium
5	12	Male	Competent	Right knee
6	15	Female	Competent	Left proximal ulna
7	12	Male	Competent	Right radius and ulna
8	2	Male	Competent	Right knee
9	5	Male	Competent	Right third and middle phalanx, spine T6, T7, T10, T11
10	12	Female	Competent	Right cuboid bone
11	10	Male	Competent	Right knee
12	7	Male	Pre-B-cell ALL	Spine T7
13	17	Female	SLE, hemolytic anemia	Left sternum
14	11	Female	Competent	Right wrist, Left fibula, Right tibial metaphysis, calcaneus, base of the 5^{th} and 1^{st} metatarsals, Left patella, Left cuboid, Left olecranon, Left 5^{th} metacarpal, Left 1^{st} metatarsal
15	16	Male	Competent	Right tibial epiphysis
16	5	Male	Competent	Right cranium, Left lateral 4^{th} rib
17	16	Male	Pre-B-cell ALL	Left distal femur, Left knee
18	16	Female	Competent	Right knee, Left knee
19	10	Male	Competent	Left knee
20	7	Male	Competent	Right hip

The most common presenting symptom was bone pain (100%) and 3 (15%) patients had accompanying pulmonary symptoms. The mean body temperature on presentation was 37.2°C (range: 36.3-39.6°C) and only 3 (15%) were febrile (temperature ≥38.1°C). The mean white blood cell count was 8.3×10^9/L (range 1.6-17.7×10^9/L) and only 2 (5%) patients had a white blood cell count > 15×10^9/L (5%). The mean value of erythrocyte sedimentation rate was 70.5 mm/h, and <20 mm/hr in only 1 of the 8 patients for which that data were available. The mean value of serum c-reactive protein concentration was 52.6 mg/L in the 9 patients for which the data were available. Complement fixation antibody titers were available for 6 patients, and were equal to or greater than 1:16 in 5 patients, with a range of 1:4-1:256. Of note, the patient with the complement fixation antibody titer of 1:4 had already received prolonged antifungal therapy. All patients had positive cultures or histologic evaluation of surgical biopsy or debridement samples, and all underwent radiologic examination, most commonly magnetic resonance imaging.

All patients were treated with antifungal medication, most commonly fluconazole used in 15 (75%) patients, followed by itraconazole in 2 patients, voriconazole in 2 patients, and amphotericin B in 1 patient. Both patients treated with voriconazole had previously been treated with fluconazole. Surgery was required in 12 (60%) patients, 8 (40%) of whom underwent surgical debridement, and the others biopsy. All surgical operations were performed by a pediatric orthopaedic surgeon.

Discussion:

Primary coccidioidomycosis is asymptomatic in approximately 60% of patients, and the remainder usually develop vague influenza-like symptoms[49]. Approximately 95% of all cases in the United States occur in Arizona and California[24], however cases have been reported in non-endemic areas such as New York, as far away as Korea and Japan[33,35,50]. In Tucson, Arizona, a study reported that 29% of patients with community-acquired pneumonia had coccidioidomycosis[51]. In Phoenix, Arizona, it was reported that 17% of patients with community-acquired pneumonia had evidence of acute coccidioidomycosis[52]. Musculoskeletal dissemination is uncommon, occurring in less than 5% of all infections[22], and can lead to significant morbidity and mortality if not properly managed[17]. Patients with musculoskeletal involvement require long-term antifungal suppression, often lifelong, as studies have shown relapse can occur in more than one-third of patients after discontinuation of antifungal treatment[14,53].

Our data suggest that the initial presentation of disseminated musculoskeletal coccidioidomycosis in children can be diverse, and is often nonspecific. Although a primary pulmonary infection, all of our patients had musculoskeletal complaints as a presenting feature, and only 3 patients had respiratory symptoms. Just 3 patients were febrile on presentation. Males have been shown to be at increased risk for dissemination[17], and in this study, 65% of the patients were boys. A prior study done in the adult population showed a male majority of 77% in those with disseminated disease at-large[14]. Although immunosuppression is a significant risk factor for disseminated infection in adults[17,54], 85% of patients in this study were immunocompetent. It has been reported that people of African or Pacific Islander descent are at higher risk for disseminated disease[22,54]. Because of the small sample population, the association of race and disease presentation cannot be determined in this study. Laboratory findings may also be varied and potentially misleading. Consistent with prior findings in the adult population[55], the overwhelming majority (90%) of children in this study had a normal white blood cell count, and only 2 patients had a white blood cell count of $>15\times10^9$/L. An

elevated erythrocyte sedimentation rate and elevated serum c-reactive protein concentration were the most consistently remarkable clinical laboratory abnormalities noted.

The diagnosis of coccidioidomycosis is based on clinical suspicion supported by a combination of microbiologic, histopathologic, immunologic or radiographic evidence[49]. Culture is the most definitive diagnostic method, and while the organism grows readily in about 5-7 days, it is extremely dangerous in the laboratory and handled using Biosafety Level 3 containment[56]. Serologic testing can be important in the diagnosis and management of coccidioidomycosis. It should be noted, however, that serological data alone cannot rule out the disease, as one study showed the overall sensitivity of serologic studies to be 82%[57]. IgM antibody can be detected within the first few weeks of infection using immunodiffusion with the tube precipitin antigen assay. Immunodiffusion complement-fixation antibody testing measures IgG antibodies to complement-fixing antigen, and usually becomes positive after several months of infection[49]. The antibody titer can be correlated with the extent of disease, with elevated titers typically being associated with progressive disease[58,59], however studies have shown that elevated serum titers may persist after clinical resolution[60]. The enzyme-linked immunosorbent assay for coccidioidal IgG and IgM antibodies is commonly used as well, and maybe the most sensitive of the methods[57]. Radiologic imaging is an important component in the diagnosis of musculoskeletal coccidioidomycosis. On plain radiographs, the majority of lesions exhibit a punched-out lytic appearance. On computed-tomography, lesions are of low attenuation and often appear bubbly and expansive. The magnetic resonance imaging appearance of coccidioidomycosis typically shows decreased signal on T1-weighted images and a corresponding increase in T2-weighted images[61].

This study demonstrates that the surgical burden of disseminated musculoskeletal coccidioidomycosis in the pediatric population is significant. Of the 20 children in this study, 8 (40%) required surgical debridement, which is consistent with published literature in the adult population[62]. Surgical intervention recommendations for disseminated musculoskeletal coccidioidomycosis are relatively nonspecific, but generally follow the principles of surgical treatment of tuberculosis osteomyelitis[3,13]. Surgery can be a critical component in management

of cases with extensive destructive lesions, large abscesses, progressive tissue destruction, bony sequestrations, vertebral instability or impingement on critical organs[3,63]. Patients with a high complement fixation titer (≥1:128) are more likely to fail to medical therapy alone[13]. Surgical debridement should include thorough curettage of all grossly involved bone, and in cases of spinal disease, radical debridement with drainage of paravertebral fluid collections and fusion with or without instrumentation[64,65]. Musculoskeletal coccidioidomycosis has been reported to involve the axial skeleton most frequently[14,17,61], however in this study, as in others[13,62], the lower extremity was most commonly affected, and involvement of multiple bones was not uncommon.

Management of all cases of disseminated coccidioidomycosis with bony involvement requires aggressive antifungal therapy[3,15]. The most common antifungal agent used in this series was fluconazole, which is consistent with the current guidelines published by the Infectious Diseases Society of America[3]. Fluconazole is a triazole antifungal agent with an established favorable safety profile and high tolerability in pediatric patients[66]. Triazole agents share a five-membered azole ring with a complex side chain, and promote fungal cell lysis and death by inhibiting the conversion of lanosterol to ergosterol, the main sterol in the fungal cell membrane[67]. Fluconazole clearance is more rapid in the non-neonatal pediatric population than in adults, with a mean plasma elimination half-life of approximately 20 hours in children and 30 hours in adults. Therefore, relative to weight, higher doses of fluconazole are required in children, generally a maintenance dose of 12 mg/kg daily[68,69]. Side effects are uncommon, but include vomiting, diarrhea, and rarely increases in hepatic transaminases[66]. Due to its excellent blood-brain barrier penetration, it is also the drug of choice for meningeal coccidioidomycosis in both adult and pediatric populations[70]. Response rates of musculoskeletal coccidioidomycosis to fluconazole are varied, with one study reporting a rate of 26%[53] and a smaller study reporting an 86% response rate[71].

Itraconazole is another effective triazole antifungal medication that is used to treat adults and children with musculoskeletal coccidioidomycosis[60], though it has been studied less extensively than fluconazole in the pediatric population[72]. Two of the patients in this series

were treated with itraconazole as initial therapy. A randomized controlled trial comparing itraconazole with fluconazole in primarily adult patients with a range of manifestations of nonmeningeal coccidioidomycosis demonstrated superior efficacy of itraconazole over fluconazole, particularly in subgroup analysis of skeletal infections[53]. The fluconazole dosage of 400 mg daily in this trial may have been inadequate, however, as some experts recommend dosages of fluconazole up to 2000 mg daily for the treatment of progressive disease[3]. Itraconazole undergoes significant hepatic biotransformation involving the cytochrome P450 system, and as a result, the pharmacokinetics profile is highly variable[73]. Routine monitoring of serum drug levels is recommended, especially in cases of concomitant treatment with other medications with which there may be a drug interaction[69,74]. The recommended pediatric starting dose range of itraconazole for invasive fungal infections is 2.5 - 5 mg/kg twice daily[69], and successful management has been reported with a dose of 10 mg/kg daily in two cases of musculoskeletal coccidioidomycosis[72].

Voriconazole and posaconazole are newer triazole antifungal agents that have been used to treat musculoskeletal coccidioidomycosis[15]. Two patients in this series was treated with voriconazole after failing to respond to fluconazole. Voriconazole is a synthetic derivative of fluconazole that, similar to itraconazole, has wide inter-patient variability in serum concentrations largely due to genetic variance in the cytochrome P450 system[67]. Experience with voriconazole in children for disseminated coccidioidomycosis is limited[75], however its highly favorable efficacy in the management of other invasive mycoses including *Aspergillus* spp. and *Candida* spp. in the pediatric population is well described in the literature[76-81]. In a retrospective study involving adult patients with coccidioidomycosis who were intolerant of or refractory to fluconazole, it was noted that treatment with voriconazole showed improvement in 14 of 21 (67%) patients[82]. Posaconazole is a second-generation triazole with similar in vitro activity against *C. immitis* to that of amphotericin B[83], and was found to be significantly more potent than fluconazole and itraconazole in a murine model of disseminated coccidioidomycosis[84]. Experience with posaconazole treatment in the pediatric population is limited[67,85]. Studies in primarily adult groups examining posaconazole as salvage therapy

following failure of conventional coccidioidomycosis therapies show response rates of 70% to 85%[82,86,87], suggesting the need for further investigation in the treatment of children.

The use of amphotericin B was once the mainstay of medical treatment, given primarily intravenously but sometimes locally as well, especially in cases of joint involvement[55,88-91]. Amphotericin B is still recommended as an alternative therapy if disseminated disease is rapidly progressive or refractory to the azole antifungal agents[3]. In cases of coccidioidomycosis of the spine, the use of amphotericin B as a first-line medication has been recommended[47], however successful management in adult patients with the azole derivatives has also been reported[92]. In our study in children, those with spinal involvement were also initially treated successfully with fluconazole. In a retrospective chart review, it was found that treatment of osseous coccidioidomycosis with amphotericin B was associated with fewer cases of relapse as compared to azole therapy[14]. Lipid formulations of amphotericin B, including amphotericin B colloidal dispersion, amphotericin B lipid complex and liposomal amphotericin B are associated with less renal toxicity and fewer infusion-related side effects than the conventional amphotericin B deoxycholate[93].

Future Directions:

Disseminated musculoskeletal coccidioidomycosis is a chronic disease in which relapse is common[14,94], and obtaining long-term follow-up data is important. Despite efforts to that end, the lack of follow-up data in this study is a limitation, the significance of which is not lost on the authors. The appropriate clinical responses to the initial management strategies outlined in this report are encouraging, however it will be important to obtain follow-up data in order to assess the relative long-term efficacies of the initial treatment methods. In particular, it is suggested that in adults, a combination of surgical and medical management leads to better long-term outcomes[62]. It would be interesting to assess the relapse rates in those children treated with surgical debridement and antifungal treatment and in those treated with medical therapy alone. In addition, the study size will need to be increased in order to allow for further analysis of risk factors and to correlate specific demographic characteristics with disease severity and response to treatment. As with all retrospective studies, there are also limitations regarding

available data. For example, more often than not, positive serological studies for each case were referenced in the discharge summaries, without the accompanying primary documentation in the paper charts. As such, details such as titer levels were not available. In a prospective trial, one can stipulate which data are important for each project aim, and therefore have a more scientifically robust study.

Conclusions:

Coccidioidomycosis is an invasive fungal infection that affects all ages, however there are relatively few studies in the literature addressing coccidioidomycosis in the pediatric population[44]. This is the first study examining disseminated musculoskeletal coccidioidomycosis exclusively in children. Our data suggest that the initial presentation of this disease process can be relatively nonspecific, requiring the clinician to maintain a high index of suspicion in order to avoid delays in diagnosis. In addition to antifungal therapy, surgical debridement is often necessary in the management of this disease. Clinicians should consider disseminated musculoskeletal coccidioidomycosis in any child living in an endemic area, or with a positive travel history.

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