Pediatric Coccidioidomycosis in Central California: A Retrospective Case Series

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(See the Major Article by Levy et al on pages 1573–8 and Editorial Commentary by Galgiani on pages 1586–8.)

Background. Coccidioidomycosis, an endemic fungal infection seen throughout the southwestern United States, is not well described in children.

Methods. We performed a retrospective observational study of all children admitted to Children’s Hospital Central California with coccidioidomycosis from 1 January 2010 to 1 September 2011.

Results. Thirty-three children, aged 6 months to 17 years, were hospitalized during the study period. These included patients with pneumonia (n = 28), pleural effusion (n = 13), pleural empyema (n = 4), lung abscess (n = 7), pericarditis (n = 2), osteomyelitis (n = 5), meningitis/cerebritis (n = 2), and vocal cord infection (n = 1). Mediastinitis, with radiographic evidence of purulence and necrotic/abscessed lymph nodes in the mediastinum, was present in 7 patients (21%) and tended to occur more often in younger children (median age, 3 years [range, 0.5–11 years] vs 7 years [range, 0.6–17 years] for non-mediastinitis patients; P = .10). Seven patients were admitted to the intensive care unit and 10 required surgical intervention. One patient died of meningitis. Hospitalizations were longer for patients with mediastinitis (median, 130 days [range, 58–200 days] vs 43 days [range, 3–273 days for non-mediastinitis patients]; P < .01) and those with maximum coccidioidal complement fixation antibody titers ≥1:128 (median, 174 days [range, 53–273 days] vs 33 days [range, 3–200 days] for those with maximum titers <1:128; P < .01).

Conclusions. Coccidioidomycosis causes a substantial disease burden in the children of central California. Mediastinitis is common and tends to occur in younger children. Patients with mediastinitis or elevated coccidioidal complement fixation titers require longer hospitalizations. Further research is needed on the prevention and treatment of this disease.

Keywords. coccidioidomycosis; mediastinitis; complement fixation; pediatric.

Coccidioidomycosis (valley fever) is an infection caused by the fungus Coccidioides immitis/posadasii, which is endemic throughout the southwestern United States and is particularly common in the southern San Joaquin Valley of central California [1]. The incidence of coccidioidomycosis has increased over the past decade [2, 3]. Although most coccidioidal infections are asymptomatic, more serious presentations include acute and chronic pneumonia and disseminated disease, most frequently to skin, bones, and the central nervous system [4, 5]. While well described in the adult literature, there are few recent reports describing coccidioidomycosis in children [6–8]. Pediatric coccidioidomycosis comprises a substantial portion of the infectious diseases practice at Children’s Hospital Central California (CHCC).

The objectives of this study were to describe the clinical manifestations, natural history, diagnosis, treatment, epidemiology, and outcomes of pediatric patients hospitalized with coccidioidomycosis.

PATIENTS AND METHODS

Human Subjects Protection

Approval for this study was obtained from the Institutional Review Board of CHCC.
The study was conducted at CHCC, a 355-bed children’s hospital that serves as both a community hospital for the Fresno–Madera area and a tertiary referral center for 1.25 million children residing in 10 counties in central California.

Study Design and Population
We conducted a retrospective descriptive case series. We identified patients by a search of the CHCC medical records database for all patients admitted with a diagnosis of coccidioidomycosis between 1 January 2010 and 1 September 2011. Cases were also identified by review of laboratory records for positive coccidiodal serology or cultures demonstrating \(C. immitis/posadasii\). Patients were included if they had a clinical illness compatible with coccidioidomycosis and positive precipitin or complement fixation serology, cultures positive for \(C. immitis/posadasii\) from any source, or biopsy material demonstrating typical histology with the presence of coccidiodal spherules. All serologies were performed at the University of California, Davis Coccidioidomycosis Serology Laboratory [9]. Fungal identification was performed by the Fungus Testing Laboratory, Department of Pathology, University of Texas Health Science Center at San Antonio. Choice of antifungal drugs and duration of therapy were at the discretion of the attending physician.

Baseline demographic, clinical, radiographic, and laboratory data, including method of diagnosis and maximum coccidiodal complement fixation titers, were collected. The antifungal medications used, duration of therapy, reasons for changes in therapy, complications of therapy, and disease outcomes were recorded. Outcomes were defined as follows: cured, therapy completed with no signs or symptoms of disease; improved, patient discharged, receiving ongoing outpatient antifungal therapy with continued clinical improvement; relapsed, inpatient therapy completed followed by a return of signs or symptoms of coccidioidomycosis requiring repeat inpatient treatment; and fatal, death due directly to coccidioidomycosis. All data were entered into a secure database and patient identifiers removed prior to database analysis. Data presented here represent follow-up as of 1 October 2012.

Statistical Analysis
Statistical analysis was performed using Stata software, release 12 (StataCorp, College Station, Texas). Differences between groups for continuous variables were compared with the Wilcoxon (Mann-Whitney) test. Differences with \(P\) values <.05 were considered significant.

RESULTS
Patient Population
Thirty-three children were admitted during the study period (Table 1). There was an even distribution by sex (17 males, 16 females). The age at admission ranged from 6 months to 17 years (median, 6 years). Five patients were <2 years of age. One 13-year-old had stable, uncomplicated trisomy 21, but no patients had serious underlying medical conditions, immunosuppression, or diabetes mellitus. Twenty-one patients were Hispanic, 3 Asian, 2 African American, and 7 Caucasian, an ethnic distribution similar to that of our overall patient population. The majority of patients (30/33 [91%]) resided in the southern San Joaquin Valley and no histories of intense dust exposure were noted in any. All surviving patients have been discharged and continue to be followed as outpatients.

Presenting Symptoms
Children presented with a variety of symptoms (Table 2), with fever (82%), cough (73%), and localized pain (58%) being the most common. Fever was present for a median of 9 days at the time of admission (range, 2–60 days). The median duration of

Table 1. Patient Demographics According to Coccidioidomycosis Disease Process Distribution

<table>
<thead>
<tr>
<th>Demographic</th>
<th>All Patients</th>
<th>Pulmonary Coccidioidomycosis</th>
<th>Mediastinitis</th>
<th>Disseminated Coccidioidomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Total in category</td>
<td>33 (100)</td>
<td>28 (84.8)</td>
<td>7 (21.2)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>Male sex</td>
<td>17 (51.5)</td>
<td>14 (42.4)</td>
<td>5 (15.2)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range), y</td>
<td>6 (0.5–17)</td>
<td>6 (0.5–17)</td>
<td>3 (0.5–11)</td>
<td>8 (0.6–14)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>21 (63.6)</td>
<td>18 (54.5)</td>
<td>5 (15.2)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7 (21.2)</td>
<td>6 (18.2)</td>
<td>0 . . .</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Asian non-Filipino</td>
<td>3 (9.1)</td>
<td>2 (6.1)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (6.1)</td>
<td>2 (6.1)</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
</tr>
</tbody>
</table>
all symptoms prior to diagnosis was 17 days (range, 1–120 days). Erythema nodosum was seen in only one (3%) of patients.

Clinical Manifestations
Most patients presented with pulmonary disease (Table 3). Twenty-eight (85%) patients had pneumonia, many with pleural effusion or empyema, while 7 (21%) had disseminated disease, including 5 (15%) with osteomyelitis and 2 (6%) with meningitis. Mediastinitis, with radiographic evidence of purulence and necrotic/abscessed lymph nodes in the mediastinum, was present in 7 patients (21%). Four of these patients developed airway narrowing (Figure 1), requiring intensive care unit admission. Mediastinitis tended to occur more often in younger children (median age, 3 years [range, 0.5–11 years] vs 7 years [range, 0.6–17 years] for non mediastinitis patients; P = .10).

Osteomyelitis occurred in 5 patients from all age groups, with several patients having widespread bony disease. Bones involved included the skull, vertebrae, phalanges, ribs, calcaneus, tibia, and radius. Surgical drainage was required in 4 of these patients. One 11-year-old patient with multiple bone involvement, including 9 vertebrae, had disease considered too widespread for operative intervention and responded to long-term medical management with liposomal amphotericin B followed by oral itraconazole.

One 18-month-old female with tracheoaryngeal coccidiodomycosis presented with a 3-week history of progressive stridor, requiring laryngoscopy, bronchoscopy, and debridement of vocal cord and subglottic laryngeal and tracheal granulomatous lesions. Pathology demonstrated chronic active mucosa inflammation, with silver stain demonstrating spherules and endospores typical of coccidioidomycosis. She responded well to debridement, liposomal amphotericin B, and later oral fluconazole and is considered cured.

Two patients had coccidoidal meningitis, both with significantly advanced disease at the time of admission. One meningitis patient had refractory progressive disease and died after 95 hospital days. Of note was that he had been ill with symptoms of meningitis for 16 days at a referring institution before a diagnosis was made and antifungal therapy initiated. The second patient developed basilar meningitis with focal cerebritis and widespread spinal cord disease, was hospitalized for 241 days, and remains stable on oral azole therapy.

Table 2. Most Frequent Signs and Symptoms Experienced By Hospitalized Pediatric Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Patients</th>
<th>Duration of Symptoms, d, Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>27 (81.8)</td>
<td>9 (2–60)</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (72.7)</td>
<td>10 (1–60)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (24.2)</td>
<td>7 (1–17)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9 (27.3)</td>
<td>14 (7–30)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>6 (18.2)</td>
<td>9 (5–14)</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>1 (3.0)</td>
<td>21</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>1 (3.0)</td>
<td>8</td>
</tr>
<tr>
<td>Nonspecific erythema</td>
<td>5 (15.2)</td>
<td>14 (5–30)</td>
</tr>
<tr>
<td>Localized paina</td>
<td>19 (57.6)</td>
<td>10 (1–120)</td>
</tr>
<tr>
<td>Localized swellingb</td>
<td>5 (15.2)</td>
<td>30 (7–120)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7 (21.2)</td>
<td>14 (7–35)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (27.3)</td>
<td>9 (1–28)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (15.2)</td>
<td>14 (7–30)</td>
</tr>
</tbody>
</table>

* Includes back, chest, extremities, head, joints, trunk.

* Includes extremities, skull, joints.

Table 3. Patient Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (%) of Patients</th>
<th>Age, y, Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumoniaa</td>
<td>28 (84.8)</td>
<td>6 (0.5–17)</td>
</tr>
<tr>
<td>Pneumoniaa with pleural effusion</td>
<td>11 (33.3)</td>
<td>7 (0.5–15)</td>
</tr>
<tr>
<td>Pneumoniaa with empyema</td>
<td>3 (9.1)</td>
<td>7 (6–10)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (3.0)</td>
<td>8</td>
</tr>
<tr>
<td>Pleural empyema</td>
<td>1 (3.0)</td>
<td>5</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>7 (21.2)</td>
<td>3 (0.5–11)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>5 (15.2)</td>
<td>8 (0.6–14)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (6.1)</td>
<td>8 (3.5–12)</td>
</tr>
</tbody>
</table>

* Pneumonia defined as the presence of miliary disease, focal consolidation, cavity, or nodule on chest radiography.

Figure 1. Chest radiograph demonstrating mediastinitis with severe airway compromise in a 6-year-old boy.
Radiographic Features
Abnormal chest radiographs were present at the time of admission in 31 patients and a wide variety of findings was noted in patients, with many patients having multiple abnormalities. Most patients (82%) had focal consolidation. Mediastinal adenopathy (49%), hilar adenopathy (39%), pleural effusion (36%), pleural empyema (12%), mediastinitis (21%), and focal lung abscess (21%) were all common. All lung abscess patients had concomitant pneumonia. All 5 patients with osteomyelitis had radiographic evidence of pulmonary disease at admission, whereas the 2 patients with meningitis had normal chest radiographs.

Diagnostic Studies
Coccidioidomycosis was diagnosed by serology, culture, and/or biopsy in patients who presented with suggestive clinical findings. Complement fixing antibodies were present in 32 patients (97%), while 26 (79%) had precipitin antibodies, demonstrating the presence of immunoglobulin M antibodies to C. immitis/posadasii on immunodiffusion testing. Ten patients grew C. immitis/posadasii from biopsy or respiratory tract specimens whereas 8 had tissue biopsies revealing granulomatous inflammation with typical fungal spherules of coccidioidomycosis. Eosinophilia (>500 eosinophils/μL of blood) was present in 4 patients (12%).

Treatment
All patients were initially treated with intravenous liposomal amphotericin B (5 mg/kg/day) (17) or fluconazole (16), with liposomal amphotericin B initiated in those patients with more severe illness present at the time of admission. Twenty-five (76%) of these patients responded to single-drug therapy and, when signs and symptoms of their disease showed improvement, were discharged home on oral azole therapy. Eight patients (47%) failed to respond to liposomal amphotericin B and had progressive disease, which was considered life-threatening in 6, and were treated with salvage therapy consisting of combinations of antifungal drugs (Table 4). Three patients—1 with fatal meningitis, 1 with life-threatening mediastinitis, and 1 with refractory vertebral osteomyelitis—required 3 drug combination therapy with liposomal amphotericin B, caspofungin and voriconazole. All patients treated with combination therapy responded well, with the exception of the patient with fatal meningitis, and were ultimately discharged on oral azole therapy. Interferon-γ 1b was used as adjunctive salvage therapy in 3 patients with life-threatening disease. Two patients with mediastinitis and severe airway compromise received anti-inflammatory therapy with systemic corticosteroids. A 6-year-old boy with near total occlusion of the trachea (Figure 1) was treated with dexamethasone 2 mg/kg for 2 days followed by a tapering dose over a period of 23 days, whereas a 1-year-old female with near total occlusion of the left mainstem bronchus was treated with methylprednisolone 4 mg/kg for 1 day followed by a tapering dose over a period of 30 days. Both responded well to systemic corticosteroids with resolution of respiratory distress. Complications of antifungal therapy were seen in many patients, the most common being renal dysfunction, anemia, and transaminitis in those receiving liposomal amphotericin B and transaminitis in those receiving azole therapy. Photosensitivity occurred in 2 patients treated with voriconazole.

Surgical drainage and/or debridement was performed on 10 patients, including bone debridement (n = 4), chest tube drainage (n = 2), vocal cord debridement (n = 1), pericardiectomy (n = 1), and placement of ventriculoperitoneal shunts (n = 2 meningitis patients).

Outcomes
Hospitalizations were often prolonged, particularly for younger children, and ranged in length from 3 to 273 days (median, 54 days). Patients <4 years of age had median hospital stays of 68 days (range, 5–273 days) versus 37 days (range, 3–200) for patients ≥4 years of age, although these results were not statistically significant (P = .13). Mediastinitis resulted in more prolonged hospitalizations (median, 130 days [range, 58–200 days] for mediastinitis patients vs 43 days [range, 3–273 days] for non-mediastinitis patients; P < .01). Seven patients (21%) required intensive care, primarily for respiratory compromise or altered mental status, with median intensive care unit stays of 14 days (range, 2–90 days). Patients with maximum complement fixation titers ≥1:128 had significantly longer hospitalizations than those with maximum complement fixation titers <1:128 (median, 174 days [range, 53–273 days] vs 33 days [range, 3–200 days]; P < .01).

With the exception of 1 patient with fatal meningitis, all patients hospitalized with pediatric coccidioidomycosis were discharged home on oral azole therapy. Two patients relapsed on oral fluconazole therapy, requiring readmission and treatment with liposomal amphotericin B, and both were subsequently discharged. As of 1 October 2012, 21 patients have completed treatment and are considered cured, whereas 11 are improved and continue to receive oral azole therapy at home.

DISCUSSION
Most patients with coccidioidomycosis have asymptomatic or clinically mild infections [1, 4, 5]. However, as demonstrated in this case series of previously healthy children, pediatric patients hospitalized with coccidioidomycosis often have severe and sometimes life-threatening disease. Coccidioides immitis/posadasii can cause both serious pulmonary disease and can also disseminate from the lungs, most often to the bones and central
nervous system [1]. It can be an acute or indolent disease in children. Most patients in our series presented with fever, cough, and localized pain, usually in the chest and back, or in the case of osteomyelitis, in the extremities.

Unlike recent reports of coccidioidomycosis in children, our patients were younger, lacked significant comorbid conditions, and had longer hospital stays [6–8]. Intensive care unit admissions were common and response to treatment was often slow. While both meningitis patients in our series required intensive care, most of the intensive care unit admissions were for patients with airway compromise, some with severe disease, including 2 who required systemic steroid therapy to manage extrinsic airway compression. Mediastinitis, with radiographic evidence of widespread purulence and multiple necrotic/abscessed lymph nodes throughout the mediastinum, was a common finding in our patients. This is rarely reported in adults with coccidioidomycosis [10, 11]. Most of our mediastinitis patients responded to medical management alone, although 1 patient with pericarditis did require surgical drainage. Our surgeons who operate on children with mediastinal coccidioidomycosis comment on the extremely difficult and hazardous nature of the procedures, noting that the inflammatory process in the mediastinum seen with coccidioidomycosis obliterates the normal anatomic planes, making it difficult to identify landmarks and easier to violate structures such as the great vessels, tracheobronchial tree, or esophagus. Pulmonary coccidioidomycosis in children is also notable for the number of patients with pleural effusions and empyemas. Two patients with empyemas required chest tube drainage, but most responded to medical management alone.

Fifteen percent of our hospitalized patients had osteomyelitis and all of them had concomitant pulmonary disease at the time of diagnosis. The diverse nature of the bones involved is in keeping with other reports of coccidioidal osteomyelitis [12]. Patients with coccidioidal osteomyelitis often require surgical intervention to achieve cure, although we were able to successfully manage 1 patient with widely disseminated bony disease with medical management alone [13]. Of note is that he did not have evidence of abscess formation in any bones at the time of diagnosis.

Delay in diagnosis of coccidioidomycosis, even in endemic areas, is common and was seen in many of our patients [14, 15]. Delays in diagnosis can, in our opinion, have clinical significance and may have contributed to the severity of disease and prolonged hospital stays in some of our patients.

Coccidioidomycosis is noted to disseminate more frequently in patients who are immunocompromised or of Filipino or African American ancestry [4, 16, 17]. None of our patients were known to be immunocompromised. We have performed routine immunology workups in many children hospitalized with coccidioidomycosis and have not identified any with
undiagnosed immunodeficiencies. While our numbers are small, the ethnic distribution of our patients reflects the overall distribution of patients seen in our facility. The 2 African American patients in our series had particularly severe disease, one with life-threatening mediastinitis and one with refractory, multifocal vertebral osteomyelitis. They were hospitalized for 175 and 158 days, respectively. Also of note is that 30 of 33 (91%) of our patients resided in the southern San Joaquin valley, an area known to have a high rate of endemic coccidioidomycosis [1].

There is very little information from prospective controlled trials on the treatment of coccidioidomycosis in adults and none in children [18, 19]. While azole therapy is commonly used as initial treatment, the Infectious Diseases Society of America treatment guidelines for coccidioidomycosis recommend amphotericin B as an alternative agent for rapidly progressive infection or disease in critical locations [20]. Liposomal amphotericin B was used in many of our patients, given the severity and rate of progression of their disease and the known frequency of nephrotoxicity seen with amphotericin B deoxycholate [21]. We saw a poor response in some patients treated with liposomal amphotericin B, including treatment failures and/or progression of disease. Given the disease severity in these patients and concerns about permanent morbidity and/or mortality, it was elected to treat a number of children with severe disease with salvage therapy consisting of various combination regimens of antifungal drugs. Combination antifungal therapy is not routinely used in coccidioidomycosis because of a lack of data as well as theoretical concerns about the possibility of antagonism [22]. However, with the exception of one patient with advanced meningitis who died, all children treated with combination therapy responded favorably and were ultimately discharged from the hospital. Based on a case report, 3 patients with severe refractory disease were treated with interferon-γ 1b [23]. Although none of the 3 had any obvious adverse effects from interferon, it was difficult to detect any benefits and this treatment must be considered investigational.

Finally, patients with maximum coccidioidal complement fixation titers ≥1:128 required longer hospitalizations than those with maximum complement fixation titers <1:128. Studies performed in adults suggest that higher titers indicate more extensive infection, a need for a longer duration of antifungal therapy and an increased risk of relapse [24, 25]. Our data suggest that an elevated complement fixation titer also indicates more severe disease in children.

Our investigation has several limitations. This is a retrospective case series that relied on passive surveillance of medical records, which may have inconsistently or incorrectly reported important patient information. Also, pediatric patients from central California are admitted to other children’s hospitals in the state and we may have underreported severe coccidioidomycosis in children in our region. Finally, our cohort of patients is limited to one hospital in one geographic area, and the clinical findings here may not be representative of all children hospitalized with coccidioidomycosis.

In summary, coccidioidomycosis can cause severe and life-threatening disease in previously healthy children. Although rare in adults, mediastinitis with evidence of multiple necrotic, abscessed medistinal lymph nodes, sometimes accompanied by airway compression, is common. Hospitalizations are often prolonged and treatment can be difficult. Further research is needed on the prevention and treatment of this disease.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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