Coccidioidomycosis in Infants: A Retrospective Case Series

Jessica M. Lee, MD,1,2* Ana Lia Graciano, MD,1,3 Lukasz Dabrowski, MD,1,4 Brenik Kuzmic, PharmD,5 and Mary Anne Tablizo, MD1,6

Summary. Introduction: In contrast to adults, coccidioidomycosis is a rare disease in infants and the mechanisms of disease acquisition are not well described in infants. The purpose of this study was to describe the clinical presentation, treatment, and outcome of pulmonary coccidioidomycosis in infants in an endemic area. Methods: We performed a retrospective observational study of all patients less than 12 months of age admitted to a tertiary free standing children's hospital from 2003–2012 diagnosed with coccidioidomycosis. Results: Thirteen infants were hospitalized during the study period. The majority of the patients presented with upper and/or lower respiratory tract infection. The most common presenting symptoms included fever (77%), cough (61%), and respiratory distress (38%). Disseminated disease, included pericardial effusion, neck abscess, and lesions in the cerebellum, basal ganglia and left temporoparietal skull. Fluconazole was the initial antifungal agent used. Amphotericin B was reserved for significant lung disease and disseminated cases. Failed response to fluconazole and amphotericin B were treated with a combination of voriconazole and caspofungin. Average length of treatment was 4 years. All patients survived to hospital discharge. The majority of the patients had resolution of chest radiograph and coccidiodal complement fixing antibody titers. Discussion: Infant coccidioidomycosis has a non-specific presentation and can mimic common infant respiratory illnesses. In endemic areas, coccidioidomycosis should be considered in the differential diagnosis of infants with pulmonary symptoms unresponsive to conventional treatment. Pediatr Pulmonol.

Key words: infections: pneumonia; infants; coccidioidomycosis.

INTRODUCTION

Coccidioidomycosis is a highly infectious disease, endemic to the southwestern United States including the low deserts of Arizona and the Central Valley of California. Other recognized endemic areas include Mexico and parts of Central and South America.1 From 2009 to 2012, the highest average annual incidence of coccidioidomycosis cases per 100,000 population in California were in Kern (205.1), Kings (191.7), Fresno (64.5), San Luis Obispo (47.2), Tulare (39.2), and Madera (20.7) counties.2

Coccidioidomycosis is acquired from inhalation of arthropores from soil inhabiting fungus, Coccidioides immitis/posadasii.3 The inhaled arthropores develop into spherules in the lung. These spherules mature in the bronchial mucosa and provoke an acute inflammatory response leading to the development of granulomas. Suppuration and microabcesses are also potential complications. Symptoms usually begin within 7–21 days from the inhalation of the arthropores.4 Asymptomatic disease is present in 60% of individuals infected with primary pulmonary coccidioidomycosis.5 The remaining 40% typically present with systemic symptoms including fever, headache, myalgia, and arthralgia.

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Conflict of interest: None.

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fever, diaphoresis, anorexia, malaise, arthralgias, cough, sputum production, or pleuritic chest pain. Erythema nodosum and erythema multiforme may also occur. Ninety-five percent of patients with primary pulmonary coccidioidomycosis undergo complete clinical resolution within 6–8 weeks from onset of symptoms. The other 5% develop disseminated disease or have residual pulmonary nodules that may persist months to years after resolution of initial symptoms.

Classification of coccidioidomycosis involves three major pulmonary syndromes: primary, disseminated, and residual. The disease severity can range from a self limiting community acquired pneumonia to significant morbidity and mortality with dissemination to the meninges, bones, skin, or genitourinary system. Residual pulmonary coccidioidomycosis represents a group of patients with symptoms or radiographically visible infiltrates that persist beyond 8 weeks. Nodules, cavities, persistent consolidation, chronic progressive disease, pleural disease, bronchiectasis, and adenopathy are manifestations of residual disease. Reactivation can occur at any time.

Patients with pulmonary coccidioidomycosis are often misdiagnosed as having a bacterial or viral respiratory infection. Delayed diagnosis can lead to more severe or disseminated disease. Current literature describing the clinical presentation, management, and treatment of coccidioidomycosis is largely based on adults and older children. There is limited information regarding coccidioidomycosis in infants.

In this manuscript, we describe the epidemiology, clinical manifestations, treatment, and outcomes of infants hospitalized with coccidioidomycosis.

METHODS

The study was conducted at Valley Children’s Hospital (VCH), a 356 bed free standing children’s hospital that serves the San Joaquin Valley of California, a region spanning multiple counties highly endemic for coccidioidomycosis including Kern, Fresno, Tulare, and Madera.

We conducted a retrospective chart review of all patients admitted to VCH from 2003 to 2012 and diagnosed with coccidioidomycosis. Coccidioidomycosis was diagnosed based on positive serology, and/or growth of *C. immitis*/posadasii from pleural fluid, bronchoalveolar lavage (BAL), endotracheal tube, or tissue specimens.

Data collected included demographic information, clinical presentation, radiologic findings, laboratory studies, clinical course, treatments, and outcomes. Complement fixation (CF) and immunodiffusion serology were all performed at the Coccidioidomycosis Serology Laboratory at the University of California at Davis.

This study was approved by the VCH Institutional Review Board.

RESULTS

From January 2003 to December 2012, 272 patients were hospitalized with coccidioidomycosis, 13 (4.8%) were younger than 12 months of age. Median age was 5 months (range 2–11 months). Eight patients were ≤6 months of age. The majority of the patients were Hispanic (77%). There were no known underlying medical problems identified except history of prematurity (32 weeks) in one patient. There was no maternal history of coccidioidomycosis in any patient. All cases were from the Central Valley (Table 1).

Onset of symptoms was between 2 days and 4 months prior to hospitalization.

The majority of patients (9/13) presented with respiratory symptoms including fever, cough, nasal congestion, and respiratory distress (Table 2). Two patients presented in respiratory failure requiring intubation and mechanical ventilation, one of them developed pulmonary hemorrhage. One patient presented with “chronic” stridor and was found to have a laryngeal abscess.

![Fig. 1. Coronal Computed Tomography chest of 6-month patient with pulmonary cocci and significant mediastinal disease.](image)

<table>
<thead>
<tr>
<th>TABLE 1— County of Residence, Ethnicity</th>
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<tbody>
<tr>
<td>County of residence</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Kern</td>
</tr>
<tr>
<td>Fresno</td>
</tr>
<tr>
<td>Tulare</td>
</tr>
<tr>
<td>Merced</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Other, not specified</td>
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</tbody>
</table>

Pediatric Pulmonology
Mediastinal lymphadenopathy with mass effect on adjacent structures including the carina, coronary sinus, and superior vena cava, was a common complication found in our patients. One of the infants developed superior vena cava (SVC) syndrome that required drainage of the obstructing lymphadenopathy (Figs. 1 and 2). Upper airway obstruction from laryngeal abscess, subglottic stenosis, and tracheal granuloma was also seen in our patient population.

Disseminated disease included cerebellar abscess, a depressed temporoparietal skull fracture from left parietal abscess, and basal ganglia lesions. Additional sequelae included deep neck abscesses and pericardial effusion. All patients presented with a pulmonary infiltrate including those who did not present with respiratory symptoms. Patients radiographic findings included mediastinal adenopathy (54%), pleural effusion (54%), hilar adenopathy (23%), lung abscess (23%), nodular lesion (23%), and cavitary lesion (23%) (Table 3).

Admission ESR had a median of 54 mm/hr (range 30–72). The CRP in this patient population had a median of 5.2 mg/dl (0.6–21.7).

Diagnosis was confirmed by serology, culture, or histopathology. Positive serum coccidiodal complement fixation (CF) titers were found in nine patients with a median titer of 1:40 (range 0–1:16384) on initial presentation. Two of the four patients with initial negative CF titers were positive on immunodiffusion. Three patients had positive CF titer on cerebrospinal fluid (CSF) (1:2–1:4).

Two patients presented with negative serology. One was a 5.5 month old who had history of recurrent stridor and presented in respiratory failure requiring intubation. Initial CF serology was negative and increased to 1:8 1 week after admission. Her endotracheal aspirate culture grew C. immitis/posadasii. The other patient was a 4.5 month old male with bilateral pneumonia, pleural effusion, and mediastinal adenopathy who grew C. immitis/posadasii on bronchoalveolar lavage, but whose titer remained negative despite extensive pulmonary disease and cerebellar edema.

Five of the infants grew C. immitis/posadasii from tissue biopsy (skull, tracheal granuloma, pericardium) and BAL. The two patients who presented in respiratory failure and required mechanical ventilation grew C. immitis/posadasii on endotracheal aspirate. The patient with cerebellar involvement had a negative cerebrospinal fluid culture and negative CF titers in CSF but had a positive endotracheal aspirate culture for C. immitis/posadasii.

Antifungal therapy was used in all patients. Fluconazole was the primary antifungal agent used. Patients who presented with significant lung disease and with disseminated infection were treated initially with amphotericin B. Patients who did not respond to fluconazole or amphotericin B received combination of voriconazole and caspofungin. The mean length of antifungal treatment was 4 years (1.5–7 years).

All patients survived to hospital discharge. Mean hospital length of stay was 62 days (range 8–202 days). Three patients (23%) were lost to follow up. Seven patients had complete resolution of abnormal CXR findings despite extensive adenopathy and infiltrates on presentation. CF titer returned to 0 on seven patients. The

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**TABLE 2—Presenting Symptoms by Percentile of Prevalence Among Patient Population**

<table>
<thead>
<tr>
<th>Presenting symptom</th>
<th>Number of patients</th>
<th>Percentile of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>61</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Stridor</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Occipital mass</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Right neck mass</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

**TABLE 3—Radiographic Lung Findings by Percentile of Prevalence Among Patient Population**

<table>
<thead>
<tr>
<th>Radiographic finding</th>
<th>Number of patients</th>
<th>Percentile of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrate</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Mediastinal adenopathy</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>Hilar adenopathy</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Lung Abscess</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Nodular lesion</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Cavitary lesion</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

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*Fig. 2. Axial CT of same patient demonstrating pulmonary abscess and pleural nodules.*
patient with the cerebellar lesion showed resolution on follow up MRI (Table 4).

**DISCUSSION**

The diagnosis of coccidioidomycosis is accomplished via serologic, histopathologic, and/or culture methods. Serologic tests include detection of anticomplement antibodies via enzyme immunoassay (EIA), immunodiffusion, or CF methods. In approximately 50% and 90% of primary infections, immunoglobulin M (IgM) is detected in the first week and third week, respectively. Immunoglobulin G (IgG) response can be detected by immunodiffusion, EIA, or CF tests. Serum CF antibodies usually are low and transient in mild disease. Persistently high titers (≥ 1:16) can be found in severe and disseminated disease. In immunocompromised hosts or individuals with immature immune systems (i.e., infants), CF titers may not be reliable.

The definitive method of establishing the diagnosis is by isolating the fungus from clinical specimen. *Coccidioides* readily grows on most media used in clinical microbiology laboratories. The presence of a mature spherule with endospores is pathognomonic of infection. A species specific DNA probe can identify *Coccidioides* species in cultures.

Establishing the diagnosis of coccidioidomycosis among infants is difficult, in part, due to their immature immune system. Infants may have a speciously negative titer, which may lead to misdiagnosis. Culture from a BAL sample or a biopsy specimen may confirm the diagnosis. By 6 months of age, serologic testing may be more reliable.

The negative titers seen in young infants at the initial presentation of the disease, with signs and symptoms indistinguishable from a bacterial or viral illness, may lead to errors in diagnoses and may lead to extensive pulmonary and disseminated disease because of delay in appropriate therapy. Thus, coccidioidomycosis should be suspected in infants with persistent pulmonary symptoms and abnormal chest x-ray findings who reside in or have traveled to an endemic area.

In our patient population, infants who initially presented with negative titer were diagnosed with coccidioidomycosis based on growth from BAL and tissue culture. Ultimately, the majority of the infants in the study had the diagnosis confirmed by both a positive CF and immunodiffusion result.

Most immune-competent patients with coccidioidomycosis recover without medical intervention. Chronic and disseminated coccidioidomycosis warrants treatment with antifungal agents. These include amphotericin B, voriconazole, fluconazole, or itraconazole. There is no consensus regarding which patients to treat and duration of treatment. Management strategies vary widely from patient to patient, largely contingent on the disease type, severity, and the integrity of patient’s immune system.

As recommended by the American Academy of Pediatrics, Redbook 29th edition, current antifungal treatment recommendations for children with severe primary infection include fluconazole or itraconazole for 3–6 months. Severe primary infection is manifested by CF titers of 1:16 or greater, significant pulmonary infiltrates, weight loss of greater than 10%, marked chest pain, severe malaise, intense night sweats, or respiratory symptoms that persist for more than 2 months. Antifungal treatment in cases of uncomplicated primary infection is controversial. Although the majority of cases are self limiting, some experts contend antifungal treatment may reduce illness duration or risk for severe complications.

For disseminated infection, initial therapy includes oral itraconazole or fluconazole. Amphotericin B is recommended as alternative therapy if lesions are progressing or are in critical locations (i.e., vertebral column). For CNS infections, initial therapy is oral fluconazole. However, in cases of poor response to oral azoles or with severe basal ganglia inflammation, intrathecal amphotericin B can be used. The role of newer azole antifungal agents, such as voriconazole, posaconazole, and echinocandins, in treatment of coccidioidomycosis has not been established. These newer agents may have a role in severe coccidioidal disease (e.g., meningitis) when conventional therapy has failed.

The duration of antifungal therapy is variable. Disseminated coccidioidomycosis should be treated with antifungal therapy for at least 6 months up to 1 year. Therapy is continued until clinical and laboratory evidence indicates that active infection has resolved.

In our cohort, all patients received antifungal therapy. Fluconazole was the initial antifungal agent used. Amphotericin B was used in patients who presented with significant lung disease and with disseminated infection. Patients with poor response to fluconazole or amphotericin B received voriconazole and caspofungin. Previous reports of combination therapy of a voriconazole and caspofungin are limited. A retrospective case series conducted by Levy et al. in 2013 found a positive clinical experience treating medically refractory coccidioidomycosis in the pediatric population with both voriconazole and caspofungin.
and caspofungin therapy. In their study, nine patients with refractory coccidioidomycosis were treated with voriconazole and caspofungin salvage therapy and eight of the nine are currently in remission. In our patient population, the average length of antifungal treatment was 4 years. The average length of treatment of 4 years in our study population is significantly longer than the 6 month to 1 year treatment recommended by the Redbook. The need for longer duration of treatment in our study population may be suggestive of a more persistent and severe course of the disease among young infants.

Our study highlights the need to monitor for coccidioidomycosis in patients with persistent respiratory symptoms who live in endemic areas. Misdiagnosis and lack of treatment can lead to a more severe pulmonary disease and in many cases to disseminated disease. Our patients presented with multiple extrapulmonary locations, including skin, lymphatics, skull, and cerebellum.

The results of this study are consistent with findings of a similar study conducted in 2013 by McCarty et al., that looked at coccidioidomycosis among a broader pediatric population ages 6 months–17 years over approximately 20 months. Both our study and the McCarty’s et al. study describe the most common presenting symptoms of pediatric coccidioidomycosis as cough, fever, and dyspnea. However, McCarty found disseminated disease spread to the bones in older children with a 15.2% incidence of osteomyelitis. One patient in our study population grew C. immitis/posadasii on skull mass biopsy. Areas of concerns include the study’s small patient size and a potential reporting bias, as 3 or 23% of the patients were lost to follow up.

Infant coccidioidomycosis is a complex disease demonstrating a wide variety of clinical and radiologic manifestations. The variability of clinical course and presentation of infant pulmonary coccidioidomycosis is similar to previous studies in adults and older children. The presentation of infant coccidioidomycosis among our patient population showed significant pulmonary involvement at the time of diagnosis.

Suspicion for coccidioidomycosis should be raised in endemic area for infants with pneumonia not responding to conventional treatment. Further studies examining the course of illness and treatment protocols are needed among pediatric patients.

REFERENCES