Treatment of Pediatric Refractory Coccidioidomycosis With Combination Voriconazole and Caspofungin: A Retrospective Case Series

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(See the Major Article by McCarty et al on pages 1579–85 and the Editorial Commentary by Galgiani on pages 1586–8.)

Background. Coccidioidomycosis is a spectrum of diseases caused by the dimorphic fungi Coccidioides. Current regimens for severe or disseminated disease include fluconazole, itraconazole, or amphotericin; newer triazoles (ie, voriconazole, posaconazole) have been demonstrated to be useful in refractory disease. Previous reported experience with combination triazole and caspofungin therapy has been very limited; however, the utility of this combination for treatment of other invasive fungal diseases suggests potential benefit in refractory coccidioidomycosis.

Methods. We conducted a retrospective review of 9 pediatric patients treated with combination voriconazole and caspofungin (V/C) salvage therapy for refractory coccidioidomycosis at two children’s hospitals between January 2000 and June 2012.

Results. Nine children with refractory coccidioidomycosis were treated with V/C salvage therapy after failing conventional therapy consisting of a triazole, amphotericin B, or a combination of both. Eight of the 9 patients are currently in remission; 1 patient with central nervous system involvement continues to progress.

Conclusions. We report our positive clinical experience treating medically refractory coccidioidomycosis in the pediatric population with concurrent voriconazole and caspofungin therapy. Additional in vitro and in vivo evaluations are warranted to support the role of V/C salvage therapy for refractory coccidioidomycosis.

Keywords. refractory; coccidioidomycosis; voriconazole; caspofungin; pediatrics.

Coccidioidomycosis is a spectrum of disease caused by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii. The incidence of coccidioidomycois has increased over the past decade, particularly in Arizona and California where disease is endemic [1]. Primary infection is commonly asymptomatic, a self-limited febrile illness, or subacute pulmonary symptoms. Disseminated coccidioidomycosis is rare; children, pregnant women, persons of Filipino, Latino, Asian, and African American race, and immunocompromised individuals are at greater risk of extrapulmonary involvement [2].

Current recommended regimens for disseminated disease consist of itraconazole, fluconazole, or amphotericin B [2]. Both itraconazole and fluconazole have proven to be efficacious in rigorous studies [3–7]. However, if a patient is refractory to these initial treatments, there is no consensus regarding the most effective agents for salvage therapy; combination amphotericin...
B/triazole therapy is cited in the current 2005 Infectious Diseases Society of America (IDSA) guidelines, but is not recommended as superior to single-agent therapy [2]. Agents identified as potentially useful in refractory coccidioidomycosis include voriconazole, posaconazole, and caspofungin [8].

Monotherapy with newer triazoles, such as voriconazole or posaconazole, has been shown to have clinical efficacy as salvage therapy for refractory disease [9–11]. Caspofungin, an echinocandin antifungal, has demonstrated in vitro and in vivo murine activity, with case reports of success in patients with nonmeningeal refractory disease [8, 12–15]. There are reports of echinocandin failure when used as monotherapy, particularly in central nervous system disease; sterilization of serum or cerebrospinal fluid has not been achievable with caspofungin alone in murine models [16, 17].

Combination therapy with azoles and caspofungin has been shown to be effective against both Candida and Aspergillus species in vivo and in animal models of aspergillosis [18, 19]. Clinically, azole and caspofungin combination has had notable success as salvage therapy in invasive aspergillosis [20–22]. A literature search of English-language publications reveals only 1 case report detailing successful triazole (fluconazole) and caspofungin treatment for invasive coccidioidomycosis [14]. In this report, we summarize 9 pediatric patients with refractory coccidioidomycosis who, after failing traditional therapy, were treated with combination voriconazole and caspofungin (V/C).

**PATIENTS AND METHODS**

The pediatric patients included in this report were hospitalized at 1 of 2 children’s hospitals: University of California, San Francisco Benioff Children’s Hospital (UCSF), or Children’s Hospital Central California (CHCC). CHCC draws heavily from populations in California’s San Joaquin Valley where Coccidioides is endemic; UCSF has intermittent referrals from this area. Since 2002, infectious disease clinicians at UCSF have added caspofungin to triazole therapy in patients who were having significant disease progression despite aggressive use of standard therapies. CHCC began to add caspofungin to triazoles for salvage therapy on the basis of a prior abstract presented by clinicians at UCSF and clinician discussions [23].

With approval from both hospitals’ institutional review boards for human subject research, we conducted a retrospective review of the medical records of pediatric patients <21 years of age at the time of diagnosis and who were treated with V/C for medically refractory coccidioidomycosis between January 2002 to June 2012. The diagnosis of coccidioidomycosis was based on culture, serum complement fixation (CF) >1:16, radiographic studies, and cerebrospinal fluid–positive CF when applicable. The definition of refractory was applied based on failure of standard therapy (verified by clinical and radiographic findings, with serologic data providing additional confirmation) for ≥4 weeks. We included all pediatric patients <21 years of age who had been treated with V/C for 4 weeks. We excluded patients who had been treated with V/C for <4 weeks and patients who had a third agent (such as amphotericin B or interferon-γ) included in the V/C salvage regimen.

Detailed chart review was performed for the duration of the patients’ care at either UCSF and CHCC. For 1 UCSF patient, the most recent clinical status and CF titer was obtained from a follow-up provider at another institution.

**RESULTS**

**Illustrative Case Report**

A 15-year-old Filipina presented to UCSF in January 2003 with disseminated coccidioidomycosis including fever, weight loss, multifocal osteomyelitis, pleural effusions, and multiple skin nodules and abscesses (case 1). At diagnosis, her CF serum titers were 1:256. The patient received 4 days of intravenous amphotericin, followed by 2 months of outpatient oral fluconazole, initially 12.5 mg/kg/day then 20 mg/kg/day. She had disease progression with an enlarging mediastinal mass and cervical spine instability requiring fusion and was rehospitalized for intravenous liposomal amphotericin. Two months into hospitalization, CF titers persisted at 1:256 and the patient worsened clinically with progression of bone lesions, development of a new pericardial effusion, and mediastinal mass compression of her trachea and superior vena cava.

After 4 months of conventional therapy failure, combination intravenous voriconazole (7.5 mg/kg/day divided twice daily) and intravenous caspofungin (loading dose of 1 mg/kg/day followed by a maintenance dose of 0.7 mg/kg/day) was given. The patient experienced marked clinical improvement; within 1 week, she became afebrile, and within 1 month, she had radiographic improvement of her abscesses and bone lesions. Following 8 months of therapy, CF titer was 1:128, and down-trended to 1:32 at 12 months. Following 13 months of V/C therapy, intravenous caspofungin was discontinued; the patient continued on oral voriconazole. Four months later, CF titer was 1:16. One year later, serum CF titer was 1:2. Four years after V/C discontinuation, CF was negative, and the patient self-discontinued voriconazole.

In May 2012, 9 years after initial diagnosis, the patient presented to the clinic with complaint of intermittent symmetric neck and bilateral iliac pain although she had no systemic symptoms such as fever, night sweats, or weight loss. At that time she had a negative CF, normal complete blood count with differential, normal erythrocyte sedimentation rate, and normal C-reactive protein. Her pain appears to be mechanical and is currently managed with a nonsteroidal anti-inflammatory agent.
## Table 1. Pediatric Refractory Coccidioidomycosis Case Summaries

<table>
<thead>
<tr>
<th>Case</th>
<th>Race/Ethnicity, Age, Sex</th>
<th>Presentation</th>
<th>Initial CF</th>
<th>Chronological Therapy Prior to Salvage V/C</th>
<th>Length of Standard Therapy</th>
<th>Clinical Progression Prior to V/C</th>
<th>CF Pre-V/C</th>
<th>Length V/C</th>
<th>CF Post-V/C</th>
<th>Maintenance Therapy and Duration</th>
<th>Follow-up Time</th>
<th>Most Recent CF</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (UCSF)</td>
<td>Asian (Filipina), 15 y, F</td>
<td>Sternal lesion, cough and night sweats, multiple vertebral abnormalities, unstable C-spine, 30-lb weight loss.</td>
<td>1:256</td>
<td>IV Amp PO Fluc IV Amb</td>
<td>4 mo</td>
<td>Mediastinal mass compressing trachea/ superior vena cava and pericardial effusion; progression abscesses and bony lesions.</td>
<td>1:256</td>
<td>13 mo</td>
<td>1:16</td>
<td>Vori PO x 5 y; no medication x 4 y</td>
<td>9 y</td>
<td>Negative</td>
<td>Now age 24 y. Discontinued prophylaxis in 2008; at that point CF negative. Currently healthy and off prophylaxis x 4 y with no disease recurrence.</td>
</tr>
<tr>
<td>2 (UCSF)</td>
<td>White (Portuguese), 14 y, M</td>
<td>Patient was initially on high-dose oral steroids for respiratory symptoms. Presented with worsening laryngeal tracheobronchitis and biliary tree symptoms; sites involved: gallbladder, liver, bone marrow.</td>
<td>1:256</td>
<td>IV Amp + PO Fluc IV Amp + IV Fluc PO/V Itra PO Fluc PO Vori</td>
<td>5 y</td>
<td>Progressive biliary and hepatic fibrosis, stenting of the biliary tree, repeated GI bleeds, ascites, hepatic failure. Vori and Caspo started in conjunction with liver transplant.</td>
<td>1:16</td>
<td>8 mo</td>
<td>1:2</td>
<td>Vori PO x 8 y (until current)</td>
<td>9 y</td>
<td>&lt;1:2</td>
<td>Now age 24 y. No progression of fungal disease. 2009 attempt made to discontinue Vori, CF titers increased to 1:4, declined to 1:2 after Vori resumed.</td>
</tr>
<tr>
<td>3 (UCSF)</td>
<td>White, 2 mo, F</td>
<td>Self-limited pneumonia at 2 mo; 6 mo later developed hydrocephalus requiring ventriculoperitoneal shunt. Shunt infection; peritoneum and CSF grew Enterobacter and Coccidioides.</td>
<td>&gt;1:256; CSF 1:8</td>
<td>PO Fluc IV Fluc</td>
<td>13 mo</td>
<td>Worsening pulmonary involvement, refractory ascites.</td>
<td>Serum 1:32; CSF negative</td>
<td>12 mo</td>
<td>1:16</td>
<td>Vori PO x 2 y, then changed to Fluc PO x 5 y (until current)</td>
<td>8 y</td>
<td>Serum 1:4; CSF negative</td>
<td>Now age 8 y. In school and intellectually normal; requires crutches to walk. Normal MRI in 2011. On Fluc PO.</td>
</tr>
<tr>
<td>4 (CHCC)</td>
<td>Pacific Islander (Samoan), 12 y, F</td>
<td>Cough for 2.5 mo, dyspnea, low-grade fever. CT demonstrated lobar pneumonia, mediastinal adenopathy, and microabscesses.</td>
<td>1:2</td>
<td>PO Fluc IV Amb</td>
<td>4 mo</td>
<td>No improvement clinically, renal toxicity from Amb, increasing titers.</td>
<td>1:32</td>
<td>8 wk</td>
<td>1:4</td>
<td>Vori PO (until current)</td>
<td>9 mo</td>
<td>Negative</td>
<td>Improving radiographically and clinically.</td>
</tr>
<tr>
<td>5 (CHCC)</td>
<td>Asian (Laotian), 16 y, M</td>
<td>Cough for 3 mo, fever, night sweats, weight loss. CXR showed lobar pneumonia and hilar adenopathy.</td>
<td>1:8</td>
<td>PO Fluc IV Amb</td>
<td>6 wk</td>
<td>Progressive pneumonia radiographically and clinically, now with bronchial narrowing, paratracheal, hilar and subcarinal adenopathy, worsening fever, worsening oxygenation.</td>
<td>1:128</td>
<td>3 mo</td>
<td>1:64</td>
<td>Vori PO x 6 m (until current)</td>
<td>9 mo</td>
<td>1:8</td>
<td>Gradual improvement, afebrile with radiographic and clinically pulmonary improvement. Polyp removed from distal trachea with spherules noted on pathology.</td>
</tr>
<tr>
<td>6 (CHCC)</td>
<td>Latino, 11 mo, M</td>
<td>Fever, cough, RLL cavity, right hilar and extensive mediastinal adenopathy.</td>
<td>1:8</td>
<td>IV Amb PO Vori PO Fluc IV Amb</td>
<td>3 mo</td>
<td>Worsening disease, narrowing of bronchus intermedius.</td>
<td>1:32</td>
<td>9 wk</td>
<td>1:8</td>
<td>Vori PO x 8 mo (until current)</td>
<td>8 mo</td>
<td>1:8</td>
<td>Now age 1.5 y. Continues to improve on Vori PO.</td>
</tr>
<tr>
<td>7 (CHCC)</td>
<td>Asian (other), 14 y, F</td>
<td>Fever, cough, headache, night sweats, weight loss, bilateral reticular nodular lung disease, extensive mediastinal involvement, and lytic bone lesion at T10.</td>
<td>1:256</td>
<td>IV Amb IV Amb + IV Vori</td>
<td>8 wk</td>
<td>Worsening left side effusion, progression of pulmonary lesions on CT, increasing titers.</td>
<td>1:16 384</td>
<td>3 mo</td>
<td>1:2048</td>
<td>Itra and Caspo x 3 wks; then Itra PO x 4 mo (until current)</td>
<td>8 mo</td>
<td>1:512</td>
<td>Now age 15 y. Stable as an outpatient; clinically improving.</td>
</tr>
</tbody>
</table>
Following case 1, an additional 8 pediatric patients (2 additional at UCSF and 6 at CHCC) received V/C therapy for refractory coccidioidomycosis (Table 1). Mean age of presentation was 10.5 years (SD, 7.3 years) and ranged from 2 months to 20 years. At initial presentation, 6 of the patients had fever and a cough, 2 had bony lesions, 3 had night sweats and weight loss, and 2 had neurologic symptoms (some with overlapping symptom categories). Of the 9 children, 5 had disseminated disease (cases 1, 2, 3, 7, and 8), including 4 (cases 1, 2, 3, and 7) with both extrapulmonary and pulmonary involvement, and 2 (cases 3 and 8) with central nervous system involvement. The remaining 4 children had refractory pulmonary disease without significant extrapulmonary involvement.

Case 2 had large doses of steroids prior to presentation; however, it is unclear if the “asthma” the steroids were meant to address was actually early presentation of pulmonary coccidioidomycosis; no other patient had any form of immunosuppression. Self-described races and ethnicities included 4 Asians (1 Filipino, 2 Laotian, 1 other), 4 white (2 non-Hispanic, 2 Hispanic/Latino), and 1 Pacific Islander (Samoan).

Conventional therapy length ranged from 6 weeks to 5 years; however, case 2, who was treated for 5 years prior to salvage therapy, also had a liver transplant at V/C initiation. Excluding this patient, the range of standard therapy was 6 weeks to 13 months. Seven patients received both fluconazole and amphotericin monotherapy before V/C initiation. Two patients were treated with combination amphotericin and azole (fluconazole or voriconazole) prior to V/C initiation. Four children received voriconazole therapy without success prior to the addition of caspofungin.

V/C therapy ranged from 8 weeks to 13 months; voriconazole and caspofungin were given at standard dosages and adjusted for appropriate levels. Most patients had a decrease in CF titers during or immediately after therapy. Eight patients experienced clinical improvement following V/C initiation and, at the time of submission, are in remission. Case 8 continues to deteriorate neurologically, although laboratory titers are now negative. Five patients, including case 8, currently receive oral voriconazole maintenance (typically approximately 10 mg/kg/day or 400 mg/day; trough levels titrated to maintain between 1–5 μg/mL), 2 receive oral itraconazole and 1 oral; one patient has not continued on maintenance therapy.

There were 8 additional patients who received V/C therapy but met exclusion criteria. Reasons for exclusion included co-receipt of liposomal amphotericin [4], interferon-γ [1], or interferon and amphotericin [2], or a shortened course (3 weeks) of V/C therapy (1 patient, a 6-month-old female with mediastinitis, pneumonia, and empyema). Seven of the 8 excluded patients are currently in remission; 1 patient who received liposomal amphotericin and interferon with V/C therapy died of progressive meningitis.
Current IDSA guidelines for coccidioidomycosis recommend oral triazoles (itraconazole and fluconazole) for disseminated disease and amphotericin B as an alternative [2]. Combination therapy with amphotericin B and a triazole is cited as a potential treatment for severe disease, although this regimen is not recommended as superior to single-agent therapy. There are limited recommendations regarding salvage therapy for progressive disease in those receiving standard treatment. Recent case reports illustrate some success with voriconazole or posaconazole for salvage treatment of refractory coccidioidomycosis [11, 24, 25]. However, despite caspofungin’s in vitro efficacy against Coccidioides and the success of V/C salvage therapy in other fungal diseases, there is little known regarding combination azole and caspofungin treatment for coccidioidomycosis [13, 14, 17, 20, 21, 26].

In this case series, we describe 9 children with refractory coccidioidomycosis who failed conventional antifungal therapy, 8 of whom experienced clinical, radiologic, and laboratory responses to V/C salvage therapy. Of the 2 patients with central nervous system disease, 1 had continued clinical deterioration despite serologic improvement following V/C therapy. This could be an indication that V/C therapy is not adequate for central nervous system involvement, or could be attributable to delayed initiation of optimal therapy and overall severity of disease.

We did not observe a difference in response time or treatment outcome in patients who had extrapulmonary vs isolated pulmonary disease. In our experience, many children with disseminated coccidioidomycosis also have significant pulmonary involvement, in contrast to adults, who often have either pulmonary or extrapulmonary disease. Thus, we do not believe that the combination of pulmonary and extrapulmonary lesions in several of our cases was related to refractory infection, as this distribution is more common in pediatric patients.

Although the patients in this case series were managed at 2 independent institutions, their presalvage regimens were very similar. Because of the descriptive retrospective nature of this case series, we cannot definitively attribute the observed clinical and laboratory improvements to the addition of caspofungin to voriconazole salvage therapy. It has been shown elsewhere in the literature that many patients respond to salvage voriconazole monotherapy [11]. However, we find it striking that 4 of the patients had disease progression while receiving voriconazole (cases 2, 6, 7, and 8) and then subsequently responded favorably to combination V/C therapy. These children were managed at 2 California hospitals over a span of 12 years. The decade of follow-up data suggests that transition to voriconazole monotherapy for maintenance is an effective strategy after combination therapy; although continued remission might be possible with any azole [27].

DISCUSSION

Considerable debate regarding the clinical application of in vitro observations of antagonism with antifungal combination therapies exists [19, 28]. Regarding combination of echinocandins and azoles, there is clinical and in vitro evidence showing no antagonism in other fungal diseases [20, 22, 26]. We did not observe decline in clinical response following implementation of combination therapy in our cases. On the contrary, 8 of 9 of patients experienced marked clinical improvement on combination therapy.

This case series had several limitations. First, it is the combined retrospective experience of 2 institutions, and we describe “real-life” treatment strategies and our experiences with salvage therapy in our pediatric patients. The patients had a multitude of different disease manifestations; initial treatment choices and durations were varied because the current standard of care leaves much room for clinician judgment [2]. In addition, the patients were treated at different times over the past decade, creating an inequality in our overall follow-up time. Therefore we are unable to comment on the long-term outcome of the more recent cases or if there is an optimal single-drug therapy for patients once they have stabilized on the combination.

Finally, we are unable to say whether voriconazole alone would have been adequate treatment for the 5 patients who did not receive it before the combination, and whether the addition of caspofungin would have had efficacy if we had used a different triazole. Demonstration that V/C combination therapy is superior to salvage voriconazole monotherapy is not possible in a case series; however, we do present evidence that V/C therapy improved the clinical picture when used in the setting of prior voriconazole monotherapy. Additionally, the clinical improvement suggests that there is no in vivo antagonism.

In conclusion, this case series describes the success we observed clinically using V/C salvage therapy in children with refractory coccidioidomycosis. Based on the clinical successes we have observed, we feel that additional in vitro and in vivo evaluations are warranted to support the role of V/C salvage therapy for refractory coccidioidomycosis.

Note

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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