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MAJOR ARTICLE

Challenges in the Long-term Management of Patients With Coccidioidal Meningitis: A Retrospective Analysis of Treatment and Outcomes

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Background. Coccidioidal meningitis (CM) is the most severe form of disseminated coccidioidomycosis. Despite years of clinical experience, it remains a difficult condition to treat, often requiring surgical procedures, such as placement of a ventriculoperitoneal shunt, in addition to lifelong antifungal therapy.

Methods. We performed a retrospective analysis of patients with CM seen in a large referral center in Central Valley, California, from 2010 to 2020. Data pertinent to CM were collected and analyzed.

Results. Among 133 patients with CM identified in the 10-year period, nonadherence to antifungal therapy was noted in 43% of patients. Of the 80 patients who underwent ventriculoperitoneal shunt placement for management of intracranial pressure, shunt failure requiring revision surgery occurred in 42 (52.5%). Rehospitalizations due to CM-related reasons occurred in 78 of 133 patients (59%). Twenty-three percent of patients (n = 29) died due to complications from CM, on an average 22 months after the diagnosis of CM. Encephalopathy at presentation was associated with a significantly higher risk of death.

Conclusions. Patients with CM in central California are predominantly rural agricultural workers with elevated levels of poverty and low health literacy and many barriers to care, leading to high rates of medication nonadherence and loss to follow-up outpatient care. Management challenges are frequent, such as failure of antifungal therapy, high rates of rehospitalization, and the need for repeated shunt revision surgeries. In addition to the development of curative new antifungal agents, understanding the barriers to patient adherence to care and antifungal therapy and identifying means to overcome such barriers are of paramount importance.

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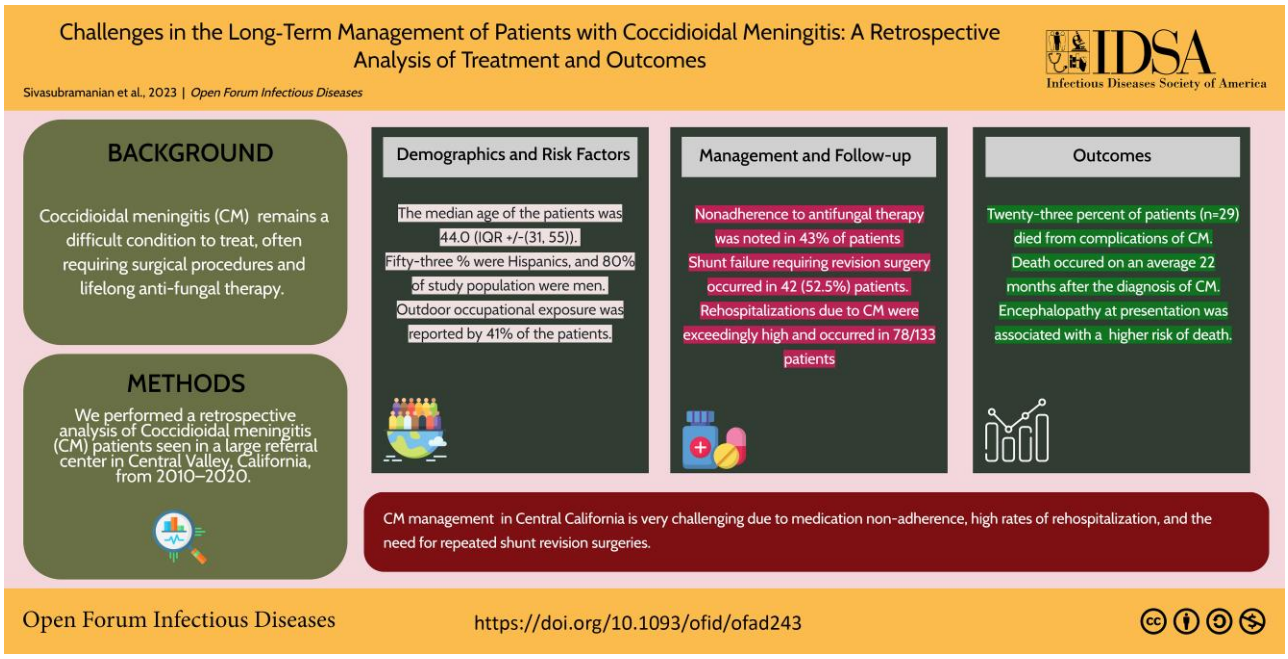
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/challenges-in-the-long-term-management-of-patients-with-coccidioidal-meningitis-a-retrospective-analysis-of-treatment-and-outcomes

Keywords. central nervous system; coccidioidal meningitis; coccidioidomycosis; disseminated coccidioidomycosis.

Coccidioidomycosis, also known as Valley fever or San Joaquin Valley fever, is a fungal infection endemic to the southwestern United States, including California and Arizona [1]. It is caused by the soil-dwelling fungi *Coccidioides immitis* and *Coccidioides posadasii*. The annual number of cases has increased tremendously over the last 2 decades. The age-adjusted incidence of coccidioidomycosis in endemic areas increased from 5.3 cases in 1998 to 42.6 per 100 000 people in 2011 [2]. In California alone, the incidence has increased more than 213% from 2014 to 2017 [3]. More than 60% of the cases are either asymptomatic or have mild self-limited respiratory infections. Disseminated disease occurs in 1%–3% of the cases, with a higher risk in Filipino or African Americans, people with uncontrolled diabetes, pregnant people, smokers, and people with immunocompromising conditions such as human immunodeficiency virus (HIV) infection [4].

Coccidioidal meningitis (CM) is the most severe and fatal form of this disease. It is characterized by chronic basilar meningitis with resultant complications such as hydrocephalus and stroke [5]. CM is a difficult condition to treat, often requiring surgical procedures, such as placement of ventriculoperitoneal (VP) shunts to relieve elevated intracranial pressure, in addition to antifungal therapy [6, 7]. Intrathecal amphotericin was the agent of choice before the advent of azoles [8]. Since the 1980s, azoles have largely replaced intrathecal amphotericin for the treatment of CM [9, 10]. However, lifelong therapy is required, and relapses with serious complications are known to occur in patients who stop treatment [11–13]. We conducted a study to analyze the long-term follow-up and treatment outcomes of patients with CM in central California.

METHODS

We retrospectively reviewed cases of CM seen at Community Regional Medical Centers (CRMC) and affiliated clinics from 1 January 2010 to 31 December 2020. CRMC is a 750-bed tertiary referral center in Fresno, California, and the primary teaching hospital for the University of California, San Francisco at Fresno. It is a primary referral center for several cities in central California's San Joaquin Valley, an area endemic for coccidioidomycosis.

Patients were identified using *International Classification of Diseases, Ninth Revision* or *Tenth Revision* codes. Each medical record was then reviewed to determine whether patients met criteria for CM to be included in the study. CM was defined as (1) positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR), cultures, or detection of complement-fixing antibodies to *Coccidioides* antigen in the CSF; (2) typical CSF abnormalities with detection of serum complement-fixing antibodies with compatible clinical illness; or (3) typical CSF abnormalities with compatible clinical illnesses and *Coccidioides* recovered from another site. Compatible clinical illnesses

include fever, chills, headache, changes in mentation, and ataxia. Typical CSF findings include pleocytosis (white blood cell count >5 cells/μL), elevated protein levels, and/or reduced glucose levels. Serum and CSF complement fixation and immunodiffusion tests were performed locally at the CRMC laboratory and referred to the University of California, Davis laboratory for confirmation. The study was approved by the CRMC institutional review board.

Data were extracted from patient medical records from the initial diagnosis of CM and subsequent hospitalizations and clinic visits. Baseline information was collected, including demographics (age, ethnicity, race, and occupational exposure) and underlying medical conditions (diabetes, HIV infection, pregnancy, immunocompromising conditions, smoking, alcohol consumption, and drug use). Clinical, laboratory, and imaging data pertinent to CM, including clinical symptoms and signs, cultures, serology, PCR, brain imaging results, antifungal therapy, intracranial pressure management, follow-up visits, treatment course, serological trends, response to therapy, change in antifungal management, and outcomes, were collected. The *C immitis* real-time PCR assay was developed in our center's laboratory using the BD Max system [14].

Statistical Analysis

Descriptive statistics were used to describe the sample characteristics of the patients based on outcome measures. Measures of association were tested using the χ^2 or Fisher exact test for categorical measures and the Wilkson-Rank sum test for continuous measures. A Cox regression model was used to examine the factors associated with the death rate while counting for the time of observation. The assumption of proportional hazards was tested. Logistic regression was used to examine the factors associated with shunt failure, serological failure, and rehospitalization. Unadjusted models (ie, bivariate models) were used to test the association of each factor with categorical outcome measures. The adjusted model was subsequently used to test the unique association of each factor with the outcome, while controlling for the other covariates.

RESULTS

We identified 133 patients with CM who were admitted to our center between 1 January 2010 and 31 December 2020.

Demographics and Clinical Features

The median age of the patients was 44.0 years (interquartile range [IQR], 31–55 years). Fifty-three percent of the patients were Hispanic, and 80% were men. Outdoor occupational exposure was reported by 41% of the patients (Table 1). Underlying medical conditions included diabetes mellitus (25%), HIV or other immunocompromising conditions (8%), and cancer (4%). The most common presenting symptom was headache (83%), followed by change in mentation (53%). Fever was not reported at presentation in 50% of the patients. The median duration of symptoms was 3 weeks (IQR, 1–6 weeks). Concomitant involvement of lungs was noted in 41%, followed by cutaneous (5%) and osseous (1.5%) lesions. Workup for other sites of dissemination was done by the managing team only for patients presenting with symptoms and signs of extrapulmonary dissemination. Two patients in this dataset had concurrent bone disease involving spine and ankle. They were diagnosed by magnetic resonance imaging and confirmed by pathology. Seven patients had skin and/or soft tissue involvement diagnosed by biopsy and/or cultures. In 38 patients, data regarding the duration between the first diagnosis of coccidioidomycosis and the development of meningitis were available. In these patients, meningitis symptoms developed at a median of 5 weeks after the initial diagnosis (IQR, 2–24 weeks).

Table 1. Characteristics of Patients With Coccidioidal Meningitis (N = 133)

Characteristic	No. (%)
Demographics	
Age, y, median (IQR)	44.0 (31–55)
Sex, male	114 (80)
Race, White	96 (72)
Ethnicity, Hispanic	71 (53)
Medical conditions	
Diabetes mellitus	34 (25)
HIV	11 (8)
Other immunosuppressive conditions	5 (3)
Occupational exposure	55 (41)
Clinical features	
Headache	111 (85)
Encephalopathy	71 (55)
Fevers	64 (50)
Ataxia	32 (26)
Vision change	31 (25)
Weight loss	32 (26)
Fatigue	55 (44)
Laboratory findings	
CSF opening pressure, cm H_2O, median (IQR)	22 (15–34) (n = 80)
CSF WBC count, cells/μL, median (IQR)	246.5 (113–527)
CSF lymphocytic pleocytosis present	118 (91)
CSF protein, g/dL, median (IQR)	217.5 (128–361)
CSF glucose, g/dL, median (IQR)	29 (19–47)
CSF culture yield of *Coccidioides*	22 (17)
CSF PCR positive for *Coccidioides*	50 (37)
CSF *Coccidioides* serology positive (IgG)	118 (86)
Serum *Coccidioides* serology positive (IgG)	123 (92)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IQR, interquartile range; PCR, polymerase chain reaction; WBC, white blood cell.

Laboratory and Imaging Findings

The median CSF opening pressure was 22.0 cm of H_2O (IQR, 15–34 cm of H_2O). Lymphocytic pleocytosis was noted in 91% of the patients, but CSF eosinophilia was noted in

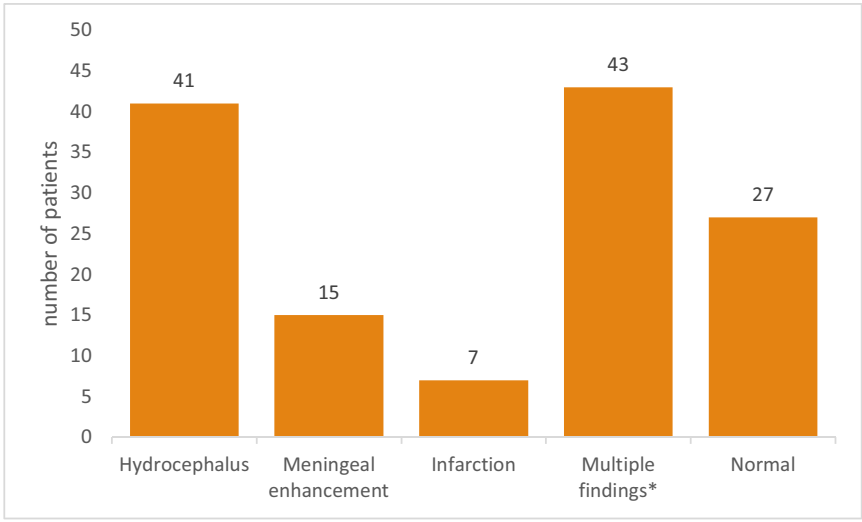


Figure 1. Brain imaging findings in patients with coccidioidal meningitis (N = 133). *Combination of hydrocephalus and meningeal enhancement.

only 24%. The median CSF glucose level was 29 g/dL (IQR, 19–47 g/dL). CSF protein levels were elevated at a median of 217 g/dL (IQR, 128–361 g/dL). *Coccidioides* was recovered from CSF cultures in only 16% of patients. Ninety-six patients had *C immitis* PCR performed on CSF and 50 of these patients tested positive. CSF *Coccidioides* immunoglobulin G (IgG) was detected in 86% of patients and serum *Coccidioides* IgG was detected in 94%. Most patients had initial CSF complement fixation titers ranging from 1:4 to 1:16 and serum complement fixation titers ranging from 1:16 to 1:64. Brain imaging revealed hydrocephalus in 31% patients, with another 32% showing multiple findings, including hydrocephalus and meningeal enhancement (Figure 1).

Management Characteristics at Initial Diagnosis

Fluconazole was the initial antifungal used for management in 95% of the patients. Intrathecal amphotericin was used in 3 patients and intravenous amphotericin in 3 patients. The initial dose of fluconazole was between 800 and 1000 mg in >75% of patients (Table 2). There was 1 pregnant woman in this dataset, who was diagnosed in her third trimester in an outside facility and remained on fluconazole treatment. Surgical intervention was needed in 72%, such as ventriculoperitoneal shunt placement (90% of those needing a procedure) or external ventricular drain placement (6%).

Table 2. Management, Follow-up, and Outcomes of Coccidioidal Meningitis (n = 133)

Characteristic	No. (%)
Antifungal management	
Fluconazole initial therapy	124 (93)
Amphotericin B (intravenous or intrathecal)	6 (4)
Dose of fluconazole	
400 mg	10 (8.5)
600 mg	10 (8.5)
800 mg	58 (49)
1000 mg	32 (27)
1200 mg	9 (7.5)
Medication noncompliance	57 (43)
Provider-initiated change in regimen	30 (27)
Intracranial pressure management	
Ventriculoperitoneal shunt	80 (60)
Extraventricular drain placement	5 (3.8)
Ommaya reservoir	3 (2.3)
Shunt revision surgery	42 (52.5) (n = 80)
Follow-up	
Duration of follow-up, wk, median (IQR)	36 (8–72) (n = 75)
No. of visits, median (IQR)	7 (1–15) (n = 75)
Lost to follow-up	78 (58)
Outcomes	
Shunt failure	42 (52.5) (n = 80)
Serological failure	45 (33.8)
Rehospitalizations due to CM	78 (58.6)
Death	29 (21.8)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CM, coccidioidal meningitis; IQR, interquartile range.

Follow-up and Outcomes

The median duration of follow-up for those who did follow-up was 36 months (IQR, 8–72 months), with a median of 7 documented outpatient visits (IQR, 1–15). Sixty-two percent of patients were lost to follow-up as outpatients at some point during their care.

Nonadherence to antifungal therapy was noted in 43% of patients overall during the course of follow-up. Provider-initiated change in antifungal therapy was noted in 27% of the patients. Reasons for change in antifungal therapy included uncontrolled symptoms (33%), medication adverse effects (23%), shunt failure (20%), and rising serum *Coccidioides* complement fixation titers (16%). Fluconazole was the agent stopped 90% of the time (n = 30), with voriconazole (66%) and posaconazole (8%) being the most common alternative agents selected. Common adverse effects of fluconazole were xerosis (16%), alopecia (3%), and liver enzyme elevation (10%).

Of the 80 patients who underwent VP shunt placement for management of intracranial pressure, shunt failure requiring revision surgery occurred in 42 (52.5%) patients overall during their course of follow-up. Multiple revisions were often needed ranging from 1 to 6 times (average, 2.6).

Rehospitalizations due to CM-related reasons were exceedingly high and occurred in 78 of 133 patients (59%), on average 3 times per patient during their entire course (range, 1–9). Multiple shunt revision surgeries were needed, ranging from 1 to 6 times (average, 2.6).

Complications noted from CM included hydrocephalus (63%), stroke (12%), paresis and back pain related to arachnoiditis (22%), and brain abscess (1.5%).

Twenty-three percent of patients (n = 29) died due to complications from CM, on average 22 months after the diagnosis of CM. Nine patients died within the same hospitalization after a new diagnosis of CM was made despite medical and/or surgical management (range, 3–40 days from presentation). The results of the unadjusted Cox regression models indicated that encephalopathy at presentation was associated with a significantly higher risk of death (hazard ratio [HR], 9.01; $P < .001$). The hazard ratio remained significant after controlling for covariates (HR, 8.85; $P = .006$). The presence of diabetes (HR, 2.74; $P = .009$) and HIV (HR, 3.72; $P = .009$) were also associated with higher mortality rate in the unadjusted models. The association was significant for HIV (HR, 9.42; $P = .014$) but not diabetes ($P = .162$) after controlling for the covariates. In terms of shunt failure, experience of headache was strongly associated with shunt failure in both unadjusted (odds ratio [OR], 10.40; $P = .031$) and adjusted models (OR, 14.17; $P = .036$). Presence of hydrocephalus and multiple findings with hydrocephalus and meningeal enhancement was associated with the increased risk of rehospitalization in both the unadjusted (hydrocephalus: OR, 6.33, $P < .001$; multiple: OR, 4.20, $P = .010$) and adjusted model (hydrocephalus: OR, 7.73, $P = .005$; multiple: OR, 8.39, $P = .008$). However, none of the factors were significantly associated with serological failure in the serum.

DISCUSSION

Despite several years of experience, multiple diagnostic tools, and antifungal options, the management of CM remains a challenge. Here, we describe a large cohort of 133 patients with CM in a large referral center in central California over a 10-year period between 2010 and 2020.

There was a significant male preponderance in our study, with 80% of the affected population being male similar to prior studies, possibly related to their occupation [15, 16]. A substantial proportion of them were Hispanic and had occupational exposure to coccidioidal spores, with central California being home to a large population of immigrants and agricultural field workers. A case-control study in 2018 from neighboring Kern County identified subjective dust exposure and working with root and bulb vegetable crops as an increased risk for coccidioidomycosis among Hispanic farm workers [17]. Due to the retrospective nature of the study, further information regarding the type of occupation and exposure is not available in our current dataset. In our study, other than 25% of the study population with underlying diabetes and 8% with HIV or other immunocompromising condition, the remaining majority of the population did not have an underlying immunocompromising condition. A recent study by Hsu et al of 67 nonimmunocompromised patients from Arizona identified possible DECTIN-1 gene variants leading to reduced *Coccidioides* antigen sensing and cellular response leading to disseminated disease [18]. Whether similar genetic variants causing reduced cellular response and delayed antigen sensing are present in the Central Valley population needs to be studied.

Several management challenges were noted in this study group during the outpatient follow-up. Intrathecal amphotericin, which was previously the mainstay of treatment for CM prior to advent of azoles, was used only in 3 of our patients [19]. However, because azoles have been found to be efficacious in management, they have largely become the mainstay of therapy [11, 20, 21]. Recently, Gupta et al reported a significant rate of failure of fluconazole therapy in patients with CM [22]. Our study identified similar issues with treatment failure in addition to nonadherence to antifungal treatment. Medication nonadherence was noted in more than half of the patients. Provider-initiated changes in antifungal agents occurred in 30% (n = 30 for fluconazole) with documented reasons being uncontrolled symptoms, medication adverse effects, shunt failure, and rising serum *Coccidioides* complement fixation titers.

In addition, 62% of patients were lost to follow-up outpatient care at some point during the course of their management. Along with this, the rehospitalization rates due to CM-related complications were also exceedingly high at 59%, with most patients needing rehospitalization multiple times. The presence of hydrocephalus was associated with an increased risk of rehospitalization compared to those with normal images. Patients who underwent VP shunt placement for hydrocephalus required revision surgery, often multiple times (52%), likely contributing to the rehospitalization rates. While high rates of medication nonadherence was noted and may have contributed

to shunt failures, previous studies in patients with CM have shown high rates of shunt failure even with adequate medical management [7, 16, 23, 24]. Twenty-three percent of the patients died due to complications from CM, and we found that encephalopathy at presentation was associated with a significantly higher risk of death.

Our study has several limitations. Since the study was conducted at a tertiary referral hospital, the severity of the disease is likely to be greater than that seen in the general population. As this was a retrospective study, with patients lost to follow-up, essential information regarding the outcomes was missing.

Our study highlights the tragedy of this devastating lifelong infection in central California, home to a large agricultural population with elevated levels of poverty and low levels of health literacy who were exposed to this infection while trying to earn a livelihood. Despite advances in diagnostics, early recognition, and treatment options, even in the year 2023 CM remains a difficult condition to manage. One of the main challenges is that the mainstay antifungal agents, azoles, as a class are not curative. The need for lifelong antifungal therapy leads to further complications such as adverse effects, toxicities, and nonadherence. In addition, the failure of azole therapy identified in recent studies including ours is a concern. There is an urgent need for new efficacious antifungal agents that would be curative without the need for lifelong treatment. Olorofim, first of the new orotomide class of antifungals, has shown efficacy in experimental models of central nervous system coccidioidomycosis [25]. Further studies are needed to see if it would be curative for CM and obviate the need for lifelong or prolonged treatment. While new drugs and diagnostics are highly needed, until a curative agent is available, CM will need to be managed like other chronic health conditions and infections such as HIV. A current major challenge is that the most vulnerable group of patients (such as rural agricultural workers), often with the most serious forms of this infection, lack easy access to care, are nonadherent to treatment, and cannot continue lifesaving medications that are already available. Consequently, understanding the barriers to patient adherence to care and antifungal therapy and identifying the means to overcome such barriers are of paramount importance. Guided by implementation research tools such as the Consolidated Framework for Implementation Research, a well-established implementation science framework, systematic studies should be conducted to examine barriers to treatment adherence and follow-up and identify measures to overcome these barriers, at both the organizational and individual levels [26].

CONCLUSIONS

Coccidioidal meningitis, the most devastating form of disseminated coccidioidomycosis, remains a challenging condition to manage, with high morbidity and mortality. Data from our center show that patients with CM have many barriers to care, such as medication nonadherence and being lost to follow-up. Our study identified frequent challenges encountered in management of patients with CM, such as failure of antifungal therapy, high rates of rehospitalization, and the need for repeated shunt revision surgeries. Patients seen in our center reside in San Joaquin Valley, California, home to a large population of Spanish-speaking, Hispanic, rural agricultural field workers with elevated levels of poverty and low health literacy. The need for new antifungal drugs that are safe, efficacious, and curative for CM is imperative. In addition, studies should also focus on understanding the barriers to patient adherence to care and antifungal therapy and identifying means to overcome such barriers via patient-centered implementation research.

Notes

Patient consent. The patients' written consent has been waived as this is a retrospective chart analysis. The design of the work was approved by the CRMC institutional review board.

Potential conflicts of interest. G. S. is on the advisory board for Mycovia Pharmaceuticals and F2G. All other authors report no potential conflicts..

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