Coccidioidal Meningitis

Clinical Presentation and Management in the Fluconazole Era

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Abstract: Despite the advent of new antifungal agents, coccidioidal meningitis (CM) remains a difficult-to-treat condition with significant morbidity and mortality. In this study we directly compare the clinical presentation and management of patients with *Coccidioides immitis* meningitis in the azole era (after 1980) to that of a cohort of patients from the pre-azole era. We reviewed 30 CM cases seen at 3 Los Angeles hospitals between the years 1993 to 2008 ("2008 cohort") and compared them to 31 patients ("1980 cohort") described by Bouza et al in a previous study. The demographics and clinical presentation of patients in the 2008 cohort were similar to those of the 1980 cohort except for a higher incidence of Hispanic patients (2008: 53% vs. 1980: 6%) and a greater percentage of patients with underlying, predisposing clinical conditions (2008: 66% vs. 1980: 32%). Ten patients in the 2008 cohort had human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), a condition not reported in the earlier study. Laboratory findings were similar between the 2 groups except for a lower incidence of peripheral leukocytosis and eosinophilia in the 2008 group.

There were marked differences in drug treatment between the 2 eras. In the 2008 cohort, 29 patients received fluconazole therapy: 13 were treated with fluconazole monotherapy, and 16 received a combination of fluconazole and intravenous amphotericin B. Although almost all patients (29/31) in the 1980 cohort received intrathecal amphotericin B, only 3 patients in the 2008 study received amphotericin B via this route. With respect to complications of CM, a similar percentage of patients in each cohort developed complications such as stroke and hydrocephalus. The 2008 cohort (40%) had similar mortality compared to patients in the 1980 study (39%); survivors in both groups experienced significant impairment of activities of daily living. Although recommended as first-line therapy for CM, azole-based therapies are not curative and do not necessarily prevent complications associated with the disease.

CM remains a serious illness with a high rate of morbidity and mortality. Immunocompromised individuals, especially those with HIV/AIDS, are at special risk for CM and represent a greater share of the overall population with this condition. Despite the clear advantages of azole treatment in CM, new therapeutic approaches are needed to provide definitive cure and to reduce the need for long-term suppressive therapy.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, AmB D = amphotericin B desoxycholate, CF = complement fixation, CM = coccidioidal meningitis, CSF = cerebrospinal fluid, CT = computerized tomography, ELISA = enzyme-linked immunoserologic assay, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, IRB = institutional review board, LAmB = liposomal amphotericin B, MRI = magnetic resonance imaging, po = orally, VP = ventriculoperitoneal.

INTRODUCTION

Despite the advent of new antifungal agents, coccidioidal meningitis (CM) remains a difficult-to-treat condition with significant morbidity and mortality. Up until the 1980s, intrathecal amphotericin B was the mainstay of treatment for this condition.[32] Although the drug offered the first effective therapy for the condition, administration of amphotericin B via the intrathecal route is difficult and is associated with significant toxicity.[30] The advent of azole agents in the early 1980s offered the hope that a new class of antifungal drugs would prove more effective and less toxic than previous drug regimens. Subsequent studies established the utility of fluconazole in the management of CM,[25] and the drug has now become the accepted first-line agent in the treatment of the condition.[24,30,67] In addition to fluconazole, other azoles such as itraconazole and voriconazole appear to have activity in CM and have been used to treat this condition.[17,49,63] Unfortunately, a major drawback of azole therapy is the need to continue treatment indefinitely—in patients with clinically proven CM, suspension of therapy is usually associated with relapse of the condition, sometimes with serious complications.[21]

We conducted the current study to compare the present management of CM with management of the condition in the pre-fluconazole era (before 1990). Our study is a retrospective analysis of a recent cohort of 30 patients in Los Angeles compared to a similar cohort of patients from the pre-azole era, described by Bouza and colleagues in 1981.[8]

History

Coccidioidomycosis was first described by the Argentinian physician Alejandro Posadas in 1892.[47] The initial case was a soldier who presented with progressive, destructive verrucous lesions of the face. A skin biopsy demonstrated a spherical, nonmotile organism with a highly refractile double wall. Despite the presence of the "parasite" on biopsy, Posadas (and his mentor Wernicke) did not believe this was the cause of the condition, and thought the patient actually had mycoses fungoides. Four years later, Rixford and Gilchrist described a similar condition in 2 patients residing in the San Joaquin Valley of central California.[52] Again, an organism was present on skin biopsy; however, these investigators believed the condition was caused by an underlying parasitic infection. The parasite resembled protozoa

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from the genus *Coccidia* and, upon the suggestion of the noted parasitologist G. W. Stiles, they named the organism *Coccidioides immitis*. The appellation "immitis" means "severe" and refers to the severe, progressive clinical course observed in the affected patients.

The next major advance in understanding the disease occurred in 1900 when William Ophüls, a professor of pathology at Cooper Medical College (which became Stanford Medical School in 1921), identified the fungal nature of the organism and succeeded in transmitting it to mice.[20] He later described the clinical spectrum of the disease in a case series that documents CM in a patient who died from disseminated coccidioidomycosis.[43] This is presumably the first described case of CM. Over the next several decades, clinicians and researchers delineated the clinical presentation and course of CM in a series of papers. In 1924 Morris reported the first case of CM as the sole site of extrapulmonary dissemination.[40] In 1936, Abbott and Cutler[1] reviewed 14 cases and described the typical cerebrospinal fluid (CSF) findings in the condition. A subsequent pathological report demonstrated the prime role of meningeal involvement with coccidioidal central nervous system infection.[18]

Early therapies for CM were ineffective, and patients almost always died within a few years of diagnosis. The Veterans Affairs (VA)-Armed Forces Cooperative Study of Coccidioidomycosis tracked over 700 patients with coccidioidomycosis during a period (1955–1958) before the advent of effective antifungal therapies. Vincent et al[65] reviewed these data and identified 21 patients who developed CM while under observation; 17 of these individuals died within 31 months of symptom onset. There were a few patients with more prolonged survival (55–146 mo); however, lacking effective antifungal therapy, CM was almost always a serious illness with a high mortality—there was significant neurologic disability, and most patients died within 2 years of diagnosis.

The outlook for coccidioidomycosis began to change with the introduction of amphotericin B in 1957. This drug is a lipophilic molecule that exerts its action by binding to ergosterols in the fungal cell; the subsequent altered membrane permeability and intracellular potassium loss leads to decreased cell viability. Parenteral amphotericin B was the first effective drug treatment for coccidioidomycosis, and quickly became the treatment of choice for severe and disseminated coccidioidomycosis. Unfortunately, parenteral amphotericin B had poor CSF penetration and was largely ineffective in treatment of CM. In the early 1960s, William Winn (and other investigators) pioneered the use of intrathecal amphotericin B for management of CM.[22,69] Although there was still a significant morbidity and mortality associated with the condition, intrathecal amphotericin B became the mainstay of management for CM until the advent of the azole therapies in the 1980s.[8]

Miconazole, a substituted imidazole, was the first azole used to treat coccidioidomycosis.[61] Imidazoles and related agents (triazoles) bind to fungal cytochrome P-450 enzymes and inhibit C-14α demethylation of lanosterol, a key step in production of ergosterol, an important component of the fungal cell membrane. Miconazole is fungistatic against *C immitis* and requires parenteral administration. Although the drug had some degree of CSF penetration, patients with CM often required intrathecal therapy for a clinical response. Early studies of miconazole (often in patients who had failed or had difficulty tolerating amphotericin B) provided mixed results. The high rates of relapse, due to its lack of fungicidal activity and the necessity for parenteral administration, made it an impractical agent for long-term therapy. Ketoconazole, a close relative of miconazole, was introduced in 1976 and was subsequently used to treat CM.[16] While ketoconazole had activity against *C immitis*, its poor CSF penetration and high rate of nausea/vomiting (associated with higher dosing) made it an ineffective agent for long-term therapy.

In 1990, Tucker et al[63] reported the first use of a triazole-itraconazole in the treatment of CM. Compared to the imidazoles, triazoles generally have more favorable pharmacokinetics including improved absorption, greater tissue penetration, and less inhibition of the human cytochrome P450 system. Although itraconazole had some demonstrable clinical benefit, its variable oral absorption and poor CSF penetration limited its use as a first-line agent for CM. In 1990, the triazole fluconazole was introduced in the United States. Compared to previous agents it has almost complete oral absorption, good CSF penetration, and excellent in vitro activity against *C immitis*. Similar to other members of the azole family, it is fungistatic to *C immitis* at clinically achievable concentrations. Animal studies in the late 1980s demonstrated potential efficacy of fluconazole in murine CM.[27,57] Subsequent case reports and studies outlined the use of fluconazole in humans with CM.[14,64] A report of 18 patients by Tucker et al[64] delineated the pharmacokinetics of fluconazole and reported a clinical response in 15 of the patients treated with the drug. The drug was well tolerated when given in doses ranging from 50 to 400 mg/day. The investigators commented on relapse of CM (when the drug was discontinued) and suggested that the higher doses might be useful in nonresponding patients. In 1993, the results of a National Institute of Allergy and Infectious Diseases (NIAID)-Mycoses Study Group trial further supported the use of fluconazole in the treatment of CM.[25] In this study, 50 patients with CM were treated with fluconazole at a dose of 400 mg per day for up to 4 years; 37 of 47 patients who could be evaluated (79%) responded to therapy, regardless of previous treatment with other antifungal agents (amphotericin B). Although discontinuance of fluconazole was associated with clinical relapse, this study further established the prominent role of fluconazole in the modern era of CM management. Published reports[34] of excellent in vitro activity of voriconazole against *C immitis* led to subsequent use of the drug in patients with CM.[17]

PATIENTS AND METHODS

Patient Selection

We retrospectively reviewed the medical records of all patients with a diagnosis of CM at 3 Los Angeles-area hospitals (VA West Los Angeles Hospital, Olive View Medical Center, and Cedars Sinai Medical Center) from the years 1993 to 2008. Institutional review board approval for chart review was obtained. CM was defined by a) positive CSF cultures or detection of complement-fixing antibody to *Coccidioides* antigen in the CSF in the presence of other CSF abnormalities typical of CM, or b) illness plus CSF abnormalities compatible with chronic meningitis and either detection of serum complement-fixing type antibodies or isolation of *Coccidioides* species from an extraneural site.[24] CSF abnormalities compatible with meningitis included CSF pleocytosis (CSF cell count >4 cells/mm^3), elevated total protein, and/or decreased CSF glucose (hypoglycorrhachia) according to laboratory standards at each facility. Lumbar arachnoiditis was defined as nerve root/back pain with evidence of lumbar nerve root enhancement on gadolinium-enhanced lumbosacral magnetic resonance imaging (MRI).

Conduct of Study

We obtained baseline information for patients at time of initial presentation with CM at the aforementioned hospitals.

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We reviewed patient admission data, hospital course, treatment, and follow-up. The majority of patients were followed for over 2 years. We compiled data regarding patient age, predisposing risk factors, initial presentation symptoms and signs, evidence of neurologic deficits, general serum and CSF laboratory parameters, serum and CSF serologies, imaging procedures, evidence of dissemination, dissemination interval, therapy received, neurosurgical interventions, and response to therapy including the ability to perform activities of daily living. Response to therapy was determined by clinical improvement including improved function/symptoms, CSF parameters, and decrease in CSF coccidioidal titer. We compared the data for this group ("2008 cohort") to data for a group of 31 patients with CM treated between 1964 and 1976 in the pre-fluconazole era described in a retrospective study by Bouza et al ("1980 cohort").[8]

Data Analysis

Patient clinical presentation and predisposing conditions in the present cohort (2008 cohort) were compared with those in the 1980 cohort. We compared the diagnostic modalities (for example, serology, CSF analysis, radiographic procedures) between the 2 groups when appropriate. Patient response to therapy in the 2008 cohort and subgroups was compared with that in the 1980 cohort. Special attention was placed on whether patients received azole alone or azole therapy in some combination with amphotericin. In addition, the need for VP shunt or Ommaya reservoir was contrasted with the need in the 1980 cohort. We also compared CM morbidity (for example, activities of daily living; employment status) and mortality among cases in the 2 cohorts.

RESULTS

We compared 30 patients with CM from 1993 to 2008 (2008 cohort) to 31 cases from the pre-1980 period (1980 cohort) (Tables 1–4). More extensive information on the current cohort (2008), including clinical presentation, laboratory studies, radiologic procedures, therapy and outcome is presented in Tables 5–12. Instructive cases from the current study are presented in the Appendix at the end of the paper. Similar data from the 1980 cohort can be obtained from the original paper by Bouza et al.[8]

Background Information

The age of our patients varied from 27 to 72 years (mean age, 42.9 yr). Men outnumbered women (24 male patients [80%]; 6 females [20%]). Sixteen (53%) patients were Hispanic, 8 (27%) were white, 4 (13%) were black, and 2 (7%) were Asian. All patients had lived in California for at least 2 months, and many came from endemic areas within the state. In the 1980 cohort, 19 (61%) patients were white, 10 (32%) were black, and only 2 (6%) patients were Hispanic.

Predisposing Factors and Underlying Disease

Of the 30 patients in the present cohort, 20 (66%) had predisposing conditions, including human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) (10 patients; 33%), diabetes mellitus (4 patients; 13%), alcohol abuse (3 patients; 10%) and pregnancy (1 patient; 3%). If Asian/black/Hispanic race were also considered as risk factors, then 97% (29/30) of the patients in the 2008 cohort would be considered to have at least 1 predisposing factor. In the 1980 cohort, 32% of patients (10/31) had predisposing factors; of these individuals, 8 (26%) had a recent history of alcohol abuse and 3 (10%) had underlying diabetes mellitus.

TABLE 1. Demographics and Clinical Presentation of Patients With Coccidioidal Meningitis: 2008 vs. 1980 Cohort*

	2008	1980
	No. of Pts (%)	No. of Pts (%)
No. of patients	30	31
Age in yr: mean (range)	42.9 (27–72)	41.3 (18–65)
Sex		
Male	25† (83)	27 (87)
Female	5 (17)	4 (13)
Race		
Asian	2 (7)	
Black	4 (13)	10 (32)
Hispanic	16 (53)	2 (6)
White	8 (27)	19 (61)
Predisposing factors‡	20/30 (66)	10/31 (32)
None	10	22
Alcohol abuse	3	8
Diabetes	4	3
Corticosteroids		2
Postpartum	1	1
Carcinoma		1
Pulmonary tuberculosis		2
Status posttransplant		1
HIV/AIDS	10	
Hypertension	3	
CM as initial manifestation	18/30 (60)	20/31 (65)
Extra-CNS before CM	12/30 (40)	10/31 (35)
Interval (initial Sx to CNS Sx)§	6.9 mo	17/24 <3 mo
Extra-CNS involvement		
Lung	17/30 (57)	15/31 (48)
Skin	3/30 (10)	13/31 (42)
Bones	2/30 (7)	8/30 (26)
Prostate	1/30 (3)	1/30 (3)
Clinical Sx/signs		
Headache	23/30 (77)	23/31 (79)
Nausea/vomiting	17/27 (63)	15/31 (48)
Fever (on admission)	20/30 (66)	24/31 (77)
Mental changes	22/30 (73)	14/31 (45)
Visual Sx	9/30 (30)	10/31 (32)
Papilledema	1/9 (11)	5/31 (16)
Weight loss	13/23 (56)	18/31 (58)
Focal neurologic signs	7/30 (23)	5/31 (16)
None	17 (57)	26 (84)
Focal	7 (23)	5 (16)
Non-focal (Generalized weakness)	4 (13)	
NA	2 (7)	
Meningeal irritation	11/28 (39)	10/31 (32)
Lumbar arachnoiditis	3/30 (10)	11/31 (35)

Abbreviations: CNS = central nervous system, NA = not available, Sx = symptoms.

*The 2008 cohort refers to a collection of 31 patients seen between 1993 and 2008; the 1980 cohort refers to the retrospective analysis of 31 patients seen between 1964 and 1976.[8]

†For purposes of tabulation, the female transsexual patient was reported as a male.

‡In 2008 cohort, the following conditions were seen in 1 patient each: seizure disorder (preexisting), idiopathic pulmonary fibrosis, intravenous drug user, asthma, hepatitis.

§For 2008 cohort, information available in 12 patients; 1 outlier (Pt #28: 15 yr) excluded.

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TABLE 2. Laboratory Data of Patients With CM: 2008 vs. 1980 Cohort

	2008	1980
	No. of Pts (%)	No. of Pts (%)
Leukocytosis (WBC >10,000 cells/mm^3)	1/30 (3)	10/27 (37)
Peripheral eosinophil count ≥350 cells/mm^3*	5/28 (18)	13/27 (48)
Abnormal hemoglobin/hematocrit	12/30 (40)	NA
Low serum Na+ (<135 mEq/dL)	18/30 (60)	NA
CSF		
OP ≥250 mm H_2O	10/12 (83)	7/23 (30)
WBC (>4 cells)	25/28 (89)	23/30 (77)
Lymphocyte predominance (>50% lymphocytes)	18/27 (67)	20/22 (91)
Low CSF glucose (≤40 mEq/dL)	19/27 (70)	17/28 (61)
Increased TP (≥45 mg/dL)†	23/27 (85)	22/29 (76)
+CSF culture	9/28 (32)	8/29 (28)
Spherules on wet mount	None	2/29 (7)
Serology		
+ Serum ELISA IgG	25/27 (93)	NA
+ Serum ELISA IgM	15/27 (56)	NA
+ Serum CF titer ≥1:2	22/23 (96)	25/30 (83)
+ Serum CF titer ≥1:16	20/23 (87)	
+ CSF ELISA IgG	15/21 (71)	NA
+ CSF ELISA IgM	8/22 (36)	NA
CSF CF	18 (60)	30 (97)
Positive	10 (59)	25 (83)
Negative	7 (41)	5 (17)
ACNS‡	1 (3)	
Not done	11 (37)	
Negative CSF CF titer	7/17‡ (40)	5/30 (17)

Abbreviations: ACNS = anticomplementary nonspecific CF titer, OP = opening pressure, TP = total protein, WBC = white blood cells.

*Maximum counts/percentage of eosinophilia in an individual patient: 2008: 783 cells/mm^3; 16%; 1980: 14,840 cells/mm^3; 53%.

†CSF total protein: 2008: mean = 155.7 mg/dL (8–453 mg/dL) excluding single pt with 4932 mg/dL; 1980: mean = 165.5 mg/dL (15–545 mg/dL).

‡One patient with ACNS CF titer.

History of Non-Meningeal Coccidioidomycosis

Background information on both patient cohorts is summarized in Table 1. Meningitis was part of the initial manifestation of disease in 60% (18/30) of patients in the current cohort and in 65% of patients in the 1980 cohort. Diagnosis of extra-CNS coccidioidomycosis before the clinical presentation of meningitis was similar in both groups (2008: 40%; 1980: 35%). With regard to extra-CNS disease, rates of lung involvement (2008: 57%; 1980: 48%) were similar in both groups; however, the 2008 cohort had lower rates of both skin disease (10% vs. 42%) and bone involvement (7% vs. 27%) compared to the 1980 cohort, respectively. For the 2008 cohort, pathological evidence of involvement outside the central nervous system is tabulated in Table 8 and discussed in the pathology section.

Interval Between First Symptom (or Exposure) and Meningitis

In the current study, the interval between the first symptom suggestive of any form of coccidioidomycosis and the first clinical sign of meningeal involvement could be estimated in 12 patients. The mean interval was 6.9 months with a maximum of 19 months (Patient 21). This compares with the 1980 cohort where the interval was less than 3 months in 17 of 24 patients.

Clinical Data

Headache

Headache is a common presenting clinical symptom of CM and is often described as "bilateral, intense and throbbing."[8] In the 2008 cohort, 77% (23/30) of patients had an initial presentation with headache; this was similar to the 1980 cohort, where the symptom was recorded in 74% (23/31) of patients. With respect to other signs of intracranial hypertension, 55% (15/27) of patients in the 2008 cohort presented with nausea and vomiting on admission, a figure that was comparable to the 1980 cohort (48%: 15/31 patients). Only 1 patient (Patient 19) in the current study had documentation of the triad of intracranial hypertension (headache, vomiting, and papilledema). Meningismus was equally common on physical examination in both groups (2008: 39%; 1980: 32%).

TABLE 3. Radiology in Patients With CM: 2008 vs. 1980 Cohort

	2008	1980
	No. of Pts (%)	No. of Pts (%)
Chest radiograph		
Normal	9/30 (30)	8/30 (27)
Abnormal	19/28 (68)	22/30 (73)
Diffuse bilateral infiltrates	9 (30)	4 (13)
Mediastinal/hilar nodes	8 (27)	5 (17)
Cavity*		4 (13)
Miliary nodules	11 (37)	3 (10)
Focal pneumonitis	7 (23)	14 (47)
Pleural effusion		3 (10)
Cardiomegaly		1 (3)
CT head	29/30 (97)	6 (19)
Normal	8 (28)	1 (17)
Abnormal	21 (70)	5 (83)
Intraventricular hemorrhage		1 (17)
Infarct	9 (30)	
Hydrocephalus	10 (33)	5 (83)
Basilar meningitis	5 (17)	
Atrophy	3 (10)	
Herniation	1 (3)	
Not done	1 (3)	25 (81)
MRI head	20/30 (66)	NA
Normal	1 (5)	
Abnormal	19/20 (95)	
Infarcts	4 (20)	
Hydrocephalus	6 (30)	
Basilar meningitis	9 (45)	
Atrophy	2 (10)	
Herniation		
Not done	10 (33)	
Other studies		
EEG		
Abnormal†	2/2 (100)	9/15 (60)

Abbreviations: EEG = electroencephalogram.

*1980: Two patients with concomitant pulmonary tuberculosis.

†Abnormal EEG: 2008: 1 diffuse slowing; 1980: 1 focal.

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TABLE 4. Treatment and Outcome in Patients With CM: 2008 vs. 1980 Cohort

	2008	1980
	No. of Pts (%)	No. of Pts (%)
Antifungal therapy		
Fluconazole monotherapy	13 (43)	N/A
Fluconazole + IV amphotericin B*	16 (53)	N/A
IV Amphotericin B alone	1 (3)	
IV Amphotericin B + IT amphotericin B		29/31 (94)
IV Amphotericin B (lipid product)	9 (30)	
IT amphotericin B‡	3 (10)	29/31 (94)
Itraconazole	1 (3)	N/A
Voriconazole	6 (20)	N/A
Neurosurgical procedures		
Intraventricular reservoir	2/30 (7)	15/31†
Ventriculostomy		
VP shunt	9/30 (30)	9/31 (29)
Shunt complications	2/7 (29)	4/9 (44)
Follow-up		
Survival		
Alive	17 (57)	19 (62)
Dead	12 (40)	12 (39)
Lost to follow-up	1 (3)	?
Activities of daily living (ADL)§		
ADL able	14/17 (82)	11 (35)
ADL unable	3/17 (18)	?
Working	2 (7)	10 (32)
Uncertain	1 (3)	

Abbreviations: ADL = activities of daily living, IV = intravenous, IT = intrathecal, N/A: not applicable, ? = unknown.

*Includes amphotericin B deoxycholate or lipid amphotericin B preparation.

†1980 study: total 27 reservoirs; 2/15 patients free of complications.

‡ Route of IT amphotericin B administration: 2008 study: lumbar: 1; reservoir: 2; 1980 study: cisternal: 11; lumbar: 17; reservoir: 21; VP shunt: 5; lumbar hyperbaric: 4; lateral cervical: 2; ventriculo-jugular: 3. (Some patients had IT amphotericin B administration by more than 1 route).

§Refers to survivors at last known follow-up.

Neurologic Complications

In the 2008 cohort, 73% (22/30) of patients presented with mental status changes (for example, lethargy, obtundation/confusion, dizziness, bizarre behavior, and disorientation) compared to 45% (14/31) in the 1980 cohort (see Table 1). Neurologic signs and symptoms were common in our patient cohort; 24 of 30 (80%) patients presented with focal (7/30) or nonfocal (17/30) neurologic findings; these abnormalities included generalized weakness, ataxia, diplopia, focal weakness, and confusion (see Table 5). Patients 8 (facial weakness), 13 (pupillary dilatation) and 27 (diplopia) had evidence of cranial nerve dysfunction. Focal findings in the 1980 study were seen in 16% of patients (5/31). Hydrocephalus (based on computerized tomography [CT] scan or MRI) was seen in 12 of 30 (40%) patients in the 2008 cohort; only 6 cases underwent CT scanning in the 1980 study, and 5 patients (5/31; 16%) had documented hydrocephalus. Lumbar arachnoiditis ultimately developed in 10% of patients (3/30) in the 2008 cohort compared to 35% (11/31) of individuals in the 1980 study.

Constitutional Signs and Symptoms

Constitutional symptoms such as fever (2008: 66%; 1980: 77%) and weight loss (2008: 56%; 1980: 53%) were similar in both groups.

Other Physical Findings

At clinical presentation, coccidioidal skin lesions were noted in 3 patients (10%) in the 2008 cohort compared to 13 patients (42%) in the 1980 cohort.

Laboratory Data

A comparison of admission laboratory data between the 2008 and 1980 cohort is presented in Table 2, and detailed laboratory data (serum and CSF) from the 2008 cohort are outlined in Table 6. In the present cohort, the peripheral white cell count (leukocyte count ≥10,000 cells/mm^3) was elevated in only 1 of 30 patients (3%) compared to 10 of 27 cases (37%) from the 1980 cohort. Peripheral eosinophilia (for example, eosinophil count ≥350 cells/mm^3) was less common in the current patient population (5/28; 18%) compared to the 1980 cohort (13/27; 48%). Significant anemia (hemoglobin <12.0 g/dL) was equally common in both studies (2008: 40%; 1980: 38%).

Serum Serology

The serum enzyme-linked immunoserologic assay (ELISA) test was not available in the 1970s at the time of the initial study, but was used for patients in the current protocol. In the present study, ELISA IgG was positive in 93% of patients (25/27) at some time during their clinical illness, and the ELISA IgM was positive in 56% (15/27). In 1 patient (Patient 30) both titers were negative early in the disease but subsequently turned positive. In the present cohort, the serum coccidioidal complement fixation (CF) test was elevated in 22 of 28 patients (range, 1:4 to 1:512); most of these patients (20/23; 87%) had titers of 1:16 or greater.

Cerebrospinal Fluid

More detailed data on CSF findings at clinical presentation from the 2008 study are presented in Table 6. In patients where an opening pressure was recorded, 9 of 11 cases (82%) had an opening pressure that was ≥250 mm H_2O. In the current study, other CSF parameters associated with CM include elevated CSF leukocyte count (25/28; 89%), lymphocyte predominance (18/27; 67%), hypoglycorrhachia (19/27; 70%), and increased total protein (23/27; 85%). These parameters were similar to those seen in the 1980 cohort (see Table 2). In a subset analysis of the current cohort, there was a slight trend toward polymorphonuclear predominance in patients with HIV (4/10; 40%) compared with non-HIV patients (4/17; 24%). Approximately one-third of patients in both studies (2008: 32%; 1980: 28%) had a positive CSF culture for *C immitis* sometime during their clinical course.

CSF Serology

In the 2008 study, the CSF ELISA IgG was positive in 11 of 21 cases (52%); the CSF ELISA IgM was positive in 8 of 22 cases (36%). In the present cohort, the CSF coccidioidal CF test was positive in 10 of 17 patients (58%) compared to 25 of 30 patients (83%) in the 1980 study.

Other Laboratory and Clinical Studies

Although not recorded in the 1980 study, a significant percentage of patients in the current cohort had hyponatremia at the time of clinical presentation (18/30; 60%). This tended to be

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TABLE 5. Background Information on 30 Patients With CM: 2008 Cohort

Pt	Admission Date	Clinical Presentation	Predisposing or Underlying Condition	Physical Exam Findings	Coxy Dx Before Meningitis	Presumed Dissemination Interval	Clinical Course
1	8/29/01	72-yr-old white male with previous diagnosis of CM (1998) presented with 2 mo history of fever, headache, weight loss (20 lb) and periodic disorientation.	Mild renal insufficiency S/P AVR and pacemaker Diabetes mellitus Hypertension	Fever LE weakness Bilateral LE edema Disorientation	Yes	1 yr	Responded to fluconazole but died in 2006 from perforated duodenal ulcer, seemingly unrelated to CM.
2	11/8/93	27-yr-old white male with history of drug use and newly diagnosed HIV/AIDS presented with 3 mo history of fever, weight loss (25 lb.) and lethargy.	HIV/AIDS (CD4 = 109): Drug abuse: Meth, MJ	Fever/lethargy Dystonic tongue movements L supraclav (2.2 cm) node RLL crackles	No	NA	Developed severe headache 3 d after admission with abnormal LP (elevated OP). Pt became comatose despite IV Amb and died 1 mo after admission.
3	1/26/98	32-yr-old HIV+ AA transsexual female presented with 3 mo history of fever, headache and lethargy (history of LOC).	Previous AIDS/HIV (CD4 = 273; VL <400) on HAART(stavudine/ lamivudine nelfinavir)	Lethargy	No	NA	Patient died 5 d later of cerebral herniation.
4	5/20/02	32-yr-old HIV+ white male presented with 2 wk history of headache, N/V, and obtundation.	Previous AIDS/HIV (CD4 = 171) on HAART (abacavir/lamivudine/efavirenz) History of migraine	Obtundation Meningismus	No	NA	Had elevated CSF pressure and remained obtunded. Died 2 d later despite fluconazole.
5	3/22/02	40-yr-old HIV+ Hispanic male with 6 wk history of fever, weight loss (30 lb) and SOB (+ pneumonitis).	AIDS/HIV (new diagnosis) (CD4 = 162; VL 299K)	Fever Cachexia	Yes	6 wk	Diagnosis of coccidioidomycosis on lymph node biopsy.
6	4/8/96	33-yr-old HIV+ Hispanic male with 1 wk history of fever, lethargy, and N/V.	AIDS/HIV (previous diagnosis) (CD4 = 17)	Fever Lethargy	No	NA	Treated with fluconazole and improved; discharged from hospital and lost to follow-up.
7	5/7/99	53-yr-old Hispanic male presented with fever, headache, weight loss (20 lb in 3 mo), altered mental status, and hydrocephalus.	History of ETOH abuse	Bizarre behavior	No	NA	Improved with shunt, fluconazole, and amphotericin B; long-term treatment with fluconazole.
8	11/17/98	42-yr-old AA male presented with 1.5 mo history of HA and altered mental status.	Preexisting seizure disorder + Hypertension	Bizarre behavior R sided weakness Urinary incontinence	No	NA	Deteriorated following fluconazole and IT amphotericin B. Later developed hydrocephalus but died despite shunting procedure.
9	1/3/02	54-yr-old AA male with previous diagnosis of pulmonary coxy presented with 3 mo history of headache, fever, and confusion after fluconazole noncompliance.	None	Fever Confusion Blurry vision R sided facial droop	Yes	1.5 yr	Subsequently developed hydrocephalus requiring shunt. Later treated with oral fluconazole but died from unclear reasons in 2005.
10	5/24/96	44-yr-old white male with diagnosis of coxy pneumonia presented several wk later with fever and "falling to R side."	History of IVDU; ETOH abuse Truck driver; Recent jail in San Joaquin Valley	Fever Falls to R side	Yes	4 wk	Patient with suspected CM but subsequently discontinued fluconazole several yr later with no apparent recurrence.
11	10/24/00	50-yr-old HIV+ white male presented with 3 mo history of headache and dizziness.	HIV/AIDS (CD4 = 24; VL 330K) Substance abuse (MJ; ETOH) +Truck driver	Fever Diplopia Ataxia Decreased touch in LE	No	NA	Treated successfully with IV amphotericin and fluconazole. Discharged to nursing home but later died from unclear cause.

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12	5/4/99	63-yr-old HIV+ Hispanic male with 4 d history of headache, dizziness and blurry vision.	HIV/AIDS	Blurry vision Abnormal gait	No	NA	Pt with HIV/AIDS was successfully treated with high-dose fluconazole but subsequently lost to follow-up.
13	7/29/00	39-yr-old Hispanic female with previous diagnosis of CM (1991) presented again in 2000 with fever, N/V, and altered mental status.	None	Fever Obtundation Bilateral + Babinski ↓ L pupil reaction	No	NA	Treated with IV fluconazole and amphotericin B; however, subsequently died following bout of ARDS and *C difficile* diarrhea.
14	9/6/00	68-yr-old white male with history of pulmonary fibrosis presented with 1 wk history of fever and rash. Found to have pulmonary infiltrates, erythema nodosum, and CM.	Idiopathic pulmonary fibrosis Chronic osteoarthritis S/P Billroth II pyloroplasty Coronary artery disease; hypertension; hyperlipidemia	Fever Lung: bibasilar rales Erythema nodosum	No	NA	Treated with fluconazole but died 6 wk later with progressive respiratory failure.
15	11/9/06	44-yr-old HIV+ Hispanic male with previous history of HIV/AIDS (off HAART x 2 yr) presented with 6 wk of fever, headache, skin lesions, and cough.	HIV/AIDS (CD4 = 98)	Fever with lethargy Meningismus + Skin lesions (facial nodules/pustules)	Yes	5 mo	Improved following fluconazole and amphotericin B; however, developed hydrocephalus requiring a VP shunt. Pt currently stable on HAART and oral fluconazole.
16	5/12/98	52-yr-old white male with 2 mo history of fever, headache associated with episode of transient loss of consciousness.	Factor V Leiden deficiency	Fever Confusion Meningismus	No	NA	Responded to fluconazole and currently stable on high-dose (1 g Qd) oral fluconazole.
17	7/6/05	52-yr-old Hispanic male with previous history of coxy pneumonia (1999) presented 6 yr later with 5 d history of headache and blurry vision.	None	Blurry vision	No	NA	Stable on high dose (1 g Qd) fluconazole.
18	6/19/06	37-yr-old Hispanic female presented with coxy pneumonia during pregnancy and subsequently developed headache, fever, and nausea/vomiting following delivery.	Pregnancy	Fever Meningismus Visual field deficit Bilateral UE weakness	Yes	1 yr	Treated with amphotericin B and fluconazole with subsequent relapses. Most recently, developed lumbosacral arachnoiditis and is currently stable on po voriconazole.
19	3/12/04	41-yr-old Hispanic male presented with 3 wk history of headache, N/V, and altered mental status (confusion).	None	Obtundation Meningismus Papilledema	No	NA	Treated with high-dose fluconazole (1600 mg Qd). Subsequently required VP shunt for hydrocephalus. Currently stable on fluconazole.
20	4/22/02	45-yr-old AA male presented with 3 wk history of fever, cough, headache, and weight loss (10–20 lb).	Diabetes mellitus × 2 yr	Fever + Skin lesion (L eyebrow, L ear) Lung: rales	No	3 wk	Died 1 wk after admission with ARDS and hypotension. Found to have CM on postmortem examination.
21	4/1/04	30-yr-old white female developed disseminated coxy (lung, bone) during third trimester of pregnancy. 19 mo later presented with recurrent fever and headache; CM was subsequently diagnosed.	Pregnancy	Fever Lethargy Meningismus	Yes	19 mo	Initially treated with LamB but had several relapses on azoles. Subsequently developed lumbosacral arachnoiditis. Currently stable on oral fluconazole and posaconazole.

(Continued on next page)

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TABLE 5. *(Continued)*

Pt	Admission Date	Clinical Presentation	Predisposing or Underlying Condition	Physical Exam Findings	Coxy Dx Before Meningitis	Presumed Dissemination Interval	Clinical Course
22	4/5/08	38-yr-old Hispanic male with diabetes mellitus presented with disseminated coxy (lung, skin) and treated with fluconazole. 8 mo later presented with fever, HA, weight loss (10 lb).	Diabetes	Fever Meningismus Blurry vision Multiple skin ulcerations Ataxia	Yes	8 mo	Symptoms resolved and patient currently stable on fluconazole.
23	1/4/01	42-yr-old AA male presented with altered mental status and pulmonary infiltrates. Diagnosed with "carcinomatous meningitis" but patient died shortly afterward and was found to have CM at postmortem examination.	None	Meningismus Confusion Bizarre behavior Anterograde amnesia LUE weakness	No	NA	Diagnosed with "carcinomatous meningitis" and started on corticosteroids and IT methotrexate. Subsequently died and was found to have CM.
24	1/25/07	22-yr-old Hispanic male with history of pulmonary coxy presented 9 mo later with HA, and confusion.	None	Meningismus Confusion/altered speech Generalized weakness	Yes	8 mo	Pt responded to voriconazole and currently remains stable on that drug.
25	4/13/07	44-yr-old Hispanic male with disseminated coxy (pneumonia, prostate) presented 2 yr later (after stopping fluconazole) with 1–2 mo headache, weight loss (50 lb), seizures, and altered mental status.	Diabetes mellitus	Fever Somnolence Confusion Generalized weakness Unable to walk L ankle skin lesion	Yes	5 mo	Subsequently developed hydrocephalus and required VP shunt. Pt has severe neurologic impairments but then stable on oral voriconazole.
26	6/28/04	25-yr-old Hispanic female presented with 1–2 wk history of fever, headache, nausea/vomiting, photophobia, and weight loss (8 lb).	None	Fever Meningismus Blurry vision Photophobia	No	NA	Treated with IV fluconazole following diagnosis of CM. Pt had recurrence but is currently stable on voriconazole.
27	9/7/07	37-yr-old HIV+ Hispanic male with history of coxy pneumonia presented with headache, altered mental status, and cough.	HIV/AIDS; (CD4 = 182) Primary syphilis	Drowsiness Diplopia	No	NA	Patient subsequently presented with aseptic meningitis and diagnosis of CM. Patient treated with IV fluconazole and successfully transitioned to oral fluconazole.
28	9/29/06	33-yr-old HIV+ Hispanic male with remote history of pulmonary coxy (1994) presented with fever, headache, nausea/vomiting, and dizziness.	HIV/AIDS (CD4 = 34) Coxy pneumonia (1994)	Fever RLE weakness	Yes	15 yr	Subsequently readmitted with seizure and clinical relapse; Ommaya reservoir placed and pt received IT amphotericin B. Pt developed lumbosacral arachnoiditis. Most recently treated with high-dose (1200 mg Qd) oral fluconazole.

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29	7/1/06	36-yr-old Hispanic male with pulmonary mass (+ *C immitis* spherules) presented with fever, headache, nausea/vomiting, and mild confusion.	Diabetes mellitus Hepatitis C	Fever Meningismus/confusion Generalized weakness Bilateral ↑ reflexes in LE (neg Babinski)	No	No	Diagnosed with CM and subsequently treated with po fluconazole. The patient remains stable on po fluconazole (400 mg po Qd).
30	6/6/96	49-yr-old Asian female presenting with fever, cough (pneumonia), headache, and confusion.	None	Fever Meningismus	No	NA	CM diagnosed 2 mo later when *C immitis* grew from CSF specimen. Patient initially responded to IV amphotericin B and po fluconazole; however, developed hydrocephalus and required VP shunt. Died 1 mo later from shunt malfunction and cerebral herniation.

Abbreviations: See previous tables. AA = African American, AVR = aortic valve replacement, CD4 = CD4 T-cell lymphocytes, coxy = Coccidioidomycosis, Dx = diagnosis, ETOH = ethanol, IVDU = intravenous drug use, L = left, LE = lower extremity, Meth = methamphetamine, MJ = marijuana, NA = not available, neg = negative, UE = upper extremity, R = right, S/P = status post.

a poor prognostic sign: 11 of these patients ultimately died. Liver chemistries were not reported in the 1980 cohort; however, approximately a third of the cases in the current study (30%) had abnormal liver function tests at clinical presentation. Unlike the 1980 cohort, the Coccidioidin skin test (1:100) was not performed in the 2008 study.

Radiologic Studies

Radiologic findings within the 2 cohorts are compared in Table 3, and data from the 2008 cohort are detailed in Table 7.

Chest Radiograph

In the 2008 cohort, chest radiographs were abnormal in 19 of 28 patients (68%), demonstrating findings that included diffuse bilateral infiltrates (30%), mediastinal adenopathy (27%), miliary nodules (37%), and focal pneumonitis (23%). In the 1980 cohort, 22 of 30 patients (73%) had abnormal chest radiographs, with a spectrum similar to the current study. Four patients in the 1980 cohort (compared to 2 patients in the 2008 cohort) had evidence of pulmonary cavities; 2 of these individuals had concurrent pulmonary tuberculosis, a finding not seen in the 2008 study.

Bone Involvement

Bone surveys were not routinely performed in the 2008 cohort; however, at least 1 patient (Patient 21) had a lytic lesion seen on a routine radiograph (see Table 7). In the 2008 cohort, bone scans were performed in 13 of 30 patients (43%); at least 2 patients (Patients 22, 25) showed areas of multiple uptake consistent with osteomyelitis, however, the remainder (11 patients) demonstrated nonspecific uptake that did not appear clinically significant. In the 1980 cohort, bone surveys were more commonly done, with 8 of 17 patients (47%) having signs of "osteomyelitis" including focal lytic lesions and vertebral involvement (4 patients).

Neuroradiology

CT brain scans have become an important tool in the diagnosis and management of CM. In the 2008 cohort, 21 of 29 patients (72%) had an abnormal CT brain scan that included findings of basilar meningitis (17%), cerebral infarct (31%), and hydrocephalus (34%). CT was an emerging technology at the time of the 1980 study, and only 6 patients underwent a CT brain scan; 1 of these patients had an intraventricular hemorrhage, and all 6 eventually were found to have hydrocephalus. Other radiologic studies performed in the 1980 cohort, including cerebral angiogram, pneumoencephalography, radionuclide brain scan, were not performed in any of the patients from the 2008 cohort.

MRI scanning was not available for the 1980 cohort but was used extensively (20/30 patients; 66%) in the 2008 cohort. Of patients who underwent an MRI brain scan, only 1 of 20 had a "normal" MRI; abnormal findings in the remainder of individuals included basilar meningitis (31%), hydrocephalus (30%), and cerebral infarct (20%). MRI of the lumbar spine was helpful in delineating the presence of spinal coccidioidomycosis; 3 patients (Patients 18, 21, 28) in the current study developed persistent back pain and were found to have cauda equina arachnoiditis on lumbosacral MRI.

Meningeal Biopsy

In the 1980 cohort it was noted that 2 patients had meningeal biopsies done at time of exploratory craniotomy to rule out tumor. Although meningeal involvement was discovered postmortem in 2 patients (Patients 20, 23), none of the patients in

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TABLE 6. Laboratory Data for 30 Patients With CM: 2008 Cohort

Pt	WBC ($\times 10^3$/uL)	Absolute Eosinophil Count (cells/uL)	Hb/Hct	Serum Na (mEq/dL)	Serum ELISA (IgM/IgG)	Serum CF Titer	LP OP/CP (mm H_2O)	CSF WBC (cells/mm^3) Diff (%)
1	10.9	109	13.9/41	131	Neg/Pos	1:4, then1:64	NR	ND
2	3.9	ND	9.3/27.5	126	Pos/Pos	1:128	300	1 (100P)
3	7	0	10.7/32	129	ND	ND	NR	128 (7L; 91P; 2M)
4	10.3	0	11.9/34.1	126	Neg/Neg	ND	500	793 (18L; 79P)
5	7.7	462	5.9/17.5	142	Neg/Pos	1:256	NR	4 (100L)
6	5.3	0	11.0/34	127	ND	ND	NR	145 (47L; 49P)
7	6.5	390	13.2/38.3	132	Pos/Pos	1:512 (5/20)	NR	33 (78L; 4P; 18M)
8	7.1	213	14.6/42.5	133	Neg/Pos	1:32 (10/28/98)	420	944 (54L; 43P)
9	5.4	162	12.9/39.2	125	Neg/Pos	1:128	NR	290 (52L; 6P; 5 M; 37 U)
10	10.6	191	16.4/48.4	139	Pos/Pos	1:8	NR	7 (98L; 2M)
11	7.2	65	12.1/33.7	130	Neg/Pos	1:4	350	374 (40L; 59P; 1 M)
12	5.8	116	13.6/40.6	135	Neg/Pos	ND	NR	1100 (83 L; 15P;2M)
13	9.5	0	7.6/25	134	Pos/Pos	Neg	NR	7 (65L; 35M)
14	9	270	10.5/32	132	Pos/Pos	1:16	NR	63 (100 L)
15	4.7	423	9.9/28.1	126	Pos/Pos	1:16	NR	40 (83L; 13E; 4M)
16	9	126	15.7/46.4	140	Neg/Pos	1:256	NR	271 (84L; 14P; 1E)
17	4.4	62	15.3/49.8	144	Neg/Pos	1:258 (10/14/04)	NR	270 (91L; 3P; 6M)
18	7.9	47	11.1/33.1	140	Pos/Pos	1:32	NR	186 (42L; 57P; 1M)
19	8.3	91	13.4/37.7	126	Pos/Pos	1:64	NR	840 Diff NA
20	14.9	298	14.3/42.7	117	Pos/Pos	1:16	NR	ND
21	10	20	14.5/41.4	135	Neg/Pos	1:32	280	144 (35L; 57P; 1E; 7M)
22	10.4	333	14.6/43.5	125	Pos/Pos	1:32	290	378 (21L; 60P; 15M)
23	5	ND	13/40	136	ND	ND	150	460 (92L; 8P)
24	12	120	15.21/46	140	Pos/Pos	1:512	NR	569 (98L; 1P; 1E)
25	6.4	403	13.4/38.7	134	Neg/Pos	ACNS	NR	4 (97L; 3P)
26	6.2	744	12.9/40	145	Pos/Pos	1:16	200	700 (92L; 8M)
27	8.7	783	11.1/31.6	132	Pos/Pos	>1:512	NR	8 (95L; 5M)
28	4.2	168	12.5/36.7	146	Neg/Pos	1:32	220	240 (61L; 1P; 3E; 34M)
29	8.9	71	13.5/39.8	130	Pos/Pos	1:16	NR	47 (90L;4P; 3M)
30	11.9	0	44/14.7	130	Neg/Neg (Later +/+)	<1:2	380	580 (65L; 10P; 16E; 9M)

Abbreviations: See previous tables. BAL = bronchoalveolar lavage, CP = closing pressure, CRAG = cryptococcal antigen, E = eosinphils, Hb/Hct = hemoglobin/hematocrit, IDCF = immunodiffusion complement fixation, Glu = glucose; L = lymphocytes, M = monocytes, NA = not available, ND = not done, NR = not recorded, OP = opening pressure, P = polymorphonuclear leukocytes, Pos = positive, RBC = red blood cells, TP = total protein, U = unidentified, probably plasma cells.

the 2008 cohort had a diagnosis of CM made by premorbid meningeal biopsy.

Pathology

We compared extra-CNS coccidioidal involvement in the 2008 cohort with that in the 1980 cohort (Table 8). In both groups, the respiratory tract was the most common site for involvement (2008: 17 patients; 1980: 15 patients). Skin involvement was the next most frequent extra-CNS site, although it was more common in the 1980 cohort (13 patients) than in the 2008 cohort (5 patients). In the current study, 7 patients had either biopsy or zautopsy specimens sent for pathological examination, including lung biopsy (2 patients), skin (3 patients), lymph node (2 patients), and prostate (1 patient). Autopsies were performed in 3 patients in the 2008 cohort, and all demonstrated multiple organ involvement. All autopsy patients (Patients 4, 20, 23) had meningeal involvement; Patient 23 had parenchymal involvement of the lumbar spinal cord in addition to meningeal findings.

Treatment

Antifungal therapy in the 2008 cohort is compared to that in the 1980 cohort in Table 4; more detailed information about the 2008 cohort is outlined in Table 9. In the 2008 cohort, a total of 29 patients received fluconazole therapy; 10 of these patients were treated with fluconazole monotherapy, and 16 patients received a combination of fluconazole and intravenous amphotericin B. Of the patients receiving combination azole/amphotericin B therapy, 8 patients (Patients 5, 7, 10, 11, 13, 15, 20, 21) had polyene and azole therapy started concurrently or within several days of each other. In this group, various forms of amphotericin B were used, including 6 patients (Patients 2, 8, 10,

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RBC	CSF Glu (mg/dL)	Serum Glu (mg/dL)	CSF TP (mg/dL)	CSF Culture	CSF ELISA IgM/IgG	CSF CF Titer	Other Laboratory Findings
ND	ND	ND	ND	ND	ND	ND	+ Serum IDCF Blood culture + *C immitis* BAL + *C immitis*
0	54	NA	27	Neg	ND	ND	None
15	29	185	198	Pos	Neg/Pos	NA	Autopsy: see Table 8
28	31	114	94	Pos	Neg/Neg	ND	Autopsy: see Table 8
4	60	109	40	Neg	Neg/Pos	<1:1	None
90	18	NA	213	Pos	ND	ND	None
2	57	NA	107	Neg	Pos/Pos	1:64	None
1	9	110	142	Neg	Pos/Pos	1:16	None
10,000	37	116	297	Neg	Pos/Pos	1:16	None
14	65	116	54	Neg	Neg/Neg	Neg	Sputum culture: + *C immitis*
0	24	125	231	Neg	Pos/Pos	(1:1)	+ Urine Histo Ag CSF CRAG 1:4 (Neg serum CRAG)
43	17	NA	220	Pos	Neg/Pos	ND	BAL (4/08): + *C immitis*
1	1	89	8	Pos	Neg/Neg	<1:1	None
2	60	104	35	Neg	Neg/Neg	ND	Sputum culture: + *C immitis* L arm skin bx: consistent with e. nodosum
0	29	78	49	Neg	ND	<1	None
22	18	NA	79	Neg	NA	1:16	None
5	<32	149	286	Neg	Neg/Pos	1:32	None
1	19	114	257	Neg	Pos/Pos	1:32	None
NA	NA	NA	NA	NA	NA	NA	None
ND	ND		ND	ND	ND	ND	Sputum: + *C immitis*
4	24	112	104	Neg	Neg/Pos	1:04	Bone Bx: illiac L tibia: *C immitis*
27	43	296	149	Nos	Neg/Pos	ND	None
0	35	102	453	Neg; repeat Pos	ND	ND	None
0	0	89	4932	Neg	Pos/Pos	1:128	None
3	64	131	98	Neg	Neg/Pos	Neg	None
0	<32	89	242	Neg	Pos/Pos	1:8	None
20	49	117	57	Neg	Neg/Neg	<1:2	RPR 1:512
1	32	96	190	Neg	Neg/Pos	ND	None
812	30	99	158	Neg	Pos/Pos	ACNS	None
9	37	NA	261	Initial: Neg Later: Pos	Neg/Neg (later +/+)	Initial: Neg Later: 1:4 from VP shunt	None

11, 13, 15) who received amphotericin B desoxycholate (AmB D) alone, 4 patients (Patients 5, 18, 20, 21) who received liposomal amphotericin B (LAmB), and 1 patient (Patient 7) who received either drug (AmB D or LAmB) at separate times. One patient (Patient 2) received parenteral AmB D therapy alone without any additional azole or intrathecal amphotericin B. A comparison of the maximum dose of fluconazole with patient mortality is outlined in Table 10.

In those receiving intravenous amphotericin B, the number of cycles varied from 1 to 3 with a mean of 1.36 cycles per patient. The total dosage of amphotericin product administered was able to be calculated in 10 patients; the range was 345 mg to 6000 mg, with 4 patients receiving ≥4 g of intravenous polyene therapy (note: these high dosages were associated with lipid forms of amphotericin). With regard to drug toxicities, the average drop in hematocrit per cycle in patients receiving polyene therapy was 9.52 percentage points. Some patients actually had an increase in hematocrit while on polyene therapy, but this may have been due to concurrent transfusions and/or overall improvement in clinical status with treatment. The average serum creatinine increase per cycle was 1.35, although only 1 patient developed serious nephrotoxicity (Patient 20: creatinine increase of 4.1 mg/dL).

In the 1980 cohort, almost all patients (29/31; 94%) received a combination of intrathecal and intravenous amphotericin B. The total dosage of intravenous amphotericin ranged from 131 mg to 8658 mg (mean, 3595 mg); 11 patients received ≥4 g of intravenous amphotericin B. Although patients did experience a creatinine increase per drug cycle (mean, 0.9 mg/dL), only 1 patient suffered serious nephrotoxicity requiring removal of a renal allogeneic homograft. Fluconazole was unavailable during this period; however, 3 patients who failed amphotericin B therapy received intravenous miconazole but had no clinical improvement.

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TABLE 7. Radiographic and Special Procedures on 30 Patients With CM: 2008 Cohort

Pt	Chest Radiograph (Admission)	CT Chest (Admission)	Nuclear Medicine Scan	CT Brain	MRI Brain	Other Imaging/Procedures
1	Normal		ND	R basal ganglia lacunar infarcts	ND	
2	BL interstitial infiltrates BL hilar adenopathy		ND	Mild diffuse atrophy	Normal	None
3	Small R pneumomediastinum BL LL infiltrates		ND	Severe hydrocephalus (noncommunicating); R brain subcortical stroke; Cerebellar edema consistent with cerebellar herniation	ND	
4	BL retic-nodular infiltrates		ND	L temporal hypodensity	ND	None
5	Patchy LLL infiltrate	BL retic-nodular infiltrates Med.l/hilar lymphadenopathy	PET scan: multiple focal areas of intense activity in the mediastinum and retroperitoneum consistent with lymphomatous involvement	ND	ND	CT abdomen: moderately severe retroperitoneal and mesenteric adenopathy.
6	Increased L hilum marking		ND	Mild-moderate atrophy	Marked atrophy	None
7	Normal		ND	Hydrocephalus (noncommunicating)	Basilar meningitis: + hydrocephalus Follow-up (2 yr later) S/P shunt: Decreased ventricular size + basilar meningitis R cerebral cortical infarct (old)	None
8	Mediastinal widening with lymphadenopathy		ND	L brainstem infarct	Hydrocephalus; R subcortical infarct L internal capsule/thalamic infarcts	EEG: diffuse slowing
9	Scattered pulm nodules			Hydrocephalus	Basal meningitis Mild hydrocephalus	None
10	BL pneumonitis with scattered nodules		Bone scan: + activity on distal femur	Normal	ND	None
11	BL upper lobe infiltrates		Bone scan: mild nonspecific uptake in the right lung base, R 2nd cervical vertebra and L ankle	Normal	Basilar meningitis	Bronchoscopy: endobronchial right upper lobe biopsy; bronchial mucosa showing *C immitis*.
12	Cardiomegaly with CHF	BL military nodules	ND	Mild atrophy; + small lesion L post insula	Mild atrophy; + lesion in L post insula with edema; No mass effect	None
13	RUL consolidation		Gallium whole body scan: Increased activity in RLL lung	Hydrocephalus	ND	

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14	RUL infiltrate	BL infiltrates consistent with pulmonary fibrosis; LLL honeycombing; + pretracheal lymph nodes Small pericardial effusion	Normal	Mild ventricular prominence	Minimal diffuse atrophy	None
15	BL pulm nodules	BL pulmonary nodules Mediastinal lymphadenopathy + spleen enlargement	Bone scan: some irregularity along few ribs on the posterior right upper rib cage; nonspecific findings	Hydrocephalus; Basilar meningitis; L thalamus infarct	Hydrocephalus; Leptomeningeal enhancement	None
16	Normal		ND	Negative	Basilar meningitis	None
17	Normal		Bone scan: nonspecific area of increased tracer activity in the skull	Basilar meningitis	White matter lesions consistent with small vessel disease	None
18	Normal		Bone scan: mild increased uptake in lungs, compatible with inflammatory process	R cortical and thalamus infarcts	ND	MRI lumbar spine: + cauda equine arachnoiditis
19	Normal		ND	Moderate hydrocephalus; Basilar meningitis Follow-up scan (1 yr later): hydrocephalus improved S/P shunt	ND	None
20	BL retic-nodular (miliary) pattern		ND	Negative	ND	EEG Markedly abnormal due to extremely low amplitude
21	BL dense consolidation in both lungs		Bone scan: rim of increased activity in the left iliac wing	Basilar/leptomeningeal thickening, Cerebellar infarct	Basilar meningitis + infarct in pons	MRI lumbar spine: + L4/L5 and cauda equine arachnoiditis
22	LLL pleural density	Lingular/LLL consolidation	Bone scan: increased uptake in left calvarium, 2nd and 4th ribs, R knee joint and right ankle involving the talus	Normal	ND	None
23	Normal		ND	Mild communicating hydrocephalus, small subarachnoid hemorrhage	Basal ganglia infarcts	None
24	RML/RLL pneumonia R pleural effusion	R lung nodular infiltrates; R pleural effusion; Mediastinal lymphadenopathy	ND	Hydrocephalus; Basilar meningitis	Basilar meningitis; Mild hydrocephalus	None
25	BL miliary pulm nodules	BL miliary pulm nodules; ↑ subcarinal lymph nodes; Small pericardial effusion	Bone scan: abnormal foci of intense activity at the R wrist, R elbow, R shoulder, L femur, R tibia, and L wrist	Mild hydrocephalus; Basilar meningitis; + catheter	Mild hydrocephalus; Right transfrontal ventricular catheter; Basilar meningitis	CT abdomen/pelvis: 2 low-density lesions in the prostate gland
26	Normal		Bone scan: normal	Mild hydrocephalus	Basilar meningitis	None
27	Normal	RUL mass with cavity; Prominent interstitial changes	ND	Increased density midbrain	Multiple small contrast-enhancing lesions throughout brain, midbrain, and cerebellum	None

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TABLE 7. *(Continued)*

Pt	Chest Radiograph (Admission)	CT Chest (Admission)	Nuclear Medicine Scan	CT Brain	MRI Brain	Other Imaging/Procedures
28	Normal		Bone scan: normal	Normal	Mild nodular dural thickening and enhancement in the parasellar region	MRI lumbar spine: L4-5 degenerative disc disease with mild to moderate disc bulge. Findings consistent with meningitis with enhancement of the lumbar roots and the cauda equina.
29	RLL infiltrate 1.4 cm pretracheal node	RLL mass (1.7 cm) with infiltrate	Bone scan: Focal increased tracer uptake seen in the right humeral head and right anterior superior iliac spine	Subacute infarct in left basal ganglia	L basal ganglia infarct	None
30	LUL infiltrate		ND	1st: Infarction of rostral brainstem 2nd: Massive infarction of brainstem and base of brain secondary to basilar artery occlusion	ND	None

Abbreviations: See previous tables. BL = bilateral, GB = gall bladder, LLL = left lower lobe, LUL = left upper lobe, PET = positron emission tomography, RLL = right lower lobe, RUL = right upper lobe.

Intrathecal Amphotericin B and Methods of Administration

Three patients in the 2008 cohort (Patients 8, 28, 30) received intrathecal therapy; however, only Patient 28 survived. Patient 8 received a cumulative dose of approximately 0.13 mg via the lumbar route for 8 days, but continued to do poorly and died following hospital discharge. Patient 28 received a total of 12.5 mg of amphotericin B via an Ommaya reservoir over a course of 6 months; this appeared to "stabilize" the patient, who was subsequently switched back to an azole regimen. Patient 30 had a ventricular catheter with external drainage and received intrathecal amphotericin B for approximately 19 days; she did poorly and ultimately died from presumed cerebral herniation. In the 1980 cohort, almost all patients (29/31; 94%) received intrathecal amphotericin B at some point during their treatment regimen (see Table 4). These injections occurred via a number of routes including cisternal (11 patients), lumbar (17 patients), and CSF reservoir (21 patients). In the 1980 study, 10 of the individuals who received the intralumbar injections subsequently developed lumbar arachnoiditis.

Use of Intracranial Devices (Reservoirs)

Only 2 of 30 patients in the 2008 cohort (Patients 23, 28) had an Ommaya reservoir placed for intrathecal chemotherapy; Patient 28 had a bacterial infection of the reservoir and required shunt replacement (Table 10). Patient 23 had placement of an Ommaya reservoir for intrathecal chemotherapy but did not receive amphotericin B via this route; he subsequently developed hydrocephalus and required a ventriculoperitoneal (VP) shunt. These findings contrast with the 1980 cohort, in which 15 of 31 patients (48%) had a total of 27 intraventricular reservoirs implanted for administration of intrathecal amphotericin B. Many of these patients suffered significant complications associated with this procedure including intraventricular hemorrhage (1 patient), bacterial infection (9/15; 60%), and obstruction requiring shunt removal or surgical revision (6/15; 40%).

Shunting Procedures

The results and subsequent course of CSF shunting procedures performed in 9 patients from the 2008 cohort are summarized in Table 11. The need for shunt placement in the 2008 study (9/30 patients; 33%) was similar to that in the 1980 cohort (9/31 patients; 31%). Five of the 9 patients in the current study had documented shunt complications including shunt infection (Patients 13, 25) and obstruction (Patients 13, 15, 30), and 1 patient who suffered an inguinal hernia believed secondary to VP shunt placement (Patient 9). As in the 1980 cohort, there was no evidence of intraperitoneal dissemination of coccidioidomycosis associated with the use of VP or ventriculo-jugular shunts. Three of the 8 HIV/AIDS patients (Patients 3, 15, 28) required a shunt or Ommaya reservoir.

Survival and Follow-Up Data

Follow-up data for the 2008 cohort are presented in Table 4 and Table 12; 12 of the 30 patients died, for an overall mortality of 40%. Follow-up time varied from less than 1 week to 9 years and 7 months. Almost all of the patients who died from complications suffered from a rapidly progressive course—initial survival time following diagnosis of CM varied from 2 days (postadmission) to 6 weeks. Of the 12 individuals who died, 1 patient (Patient 1) died from a seemingly unrelated cause (perforated duodenal ulcer), and another patient with HIV/AIDS (Patient 11) died from unclear causes. Four of the 12 patients who died had underlying HIV/AIDS. In the 1980 cohort, 12 of 31 patients (39%) died during the course of the study.

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TABLE 8. Places of Coccidioidal Involvement Other Than Meninges: 2008 vs. 1980 Cohort

	2008 Cohort			1980 Cohort		
		Diagnosis			Diagnosis	
Site	No. of Patients	Clinical	Autopsy*	No. of Patients	Clinical	Autopsy
Respiratory tract	17	17	2	15	14	3
Skin and subcutaneous tissue	3	3	0	13	13	0
Bone	2	2	0	8	5	3
Lymph nodes	4	1	3	8	5	3
Liver	0	0	0	6	5	1
Urine	0	0	0	6	6	0
Bone marrow	0	0	0	4	4	0
Spleen	2	0	2	4	1	3
Kidney	2	0	2	3	0	3
Peritoneum	0	0	0	2	2	0
Myocardium	1	0	1	2	0	2
Endocardium	0	0	0	1	0	1
Pericardium	0	0	0	1	1	0
Testes	0	0	0	1	1	0
Blood	0	0	0	1	1	0
Retroperitoneum (abscess)	0	0	0	1	1	0
Adrenal gland	1	0	1	1	0	1
Thyroid	0	0	0	1	0	1
Brain parenchyma	0	0	0	1	0	1
Esophagus	0	0	0	1	0	1
Pancreas	1	0	1	0	0	0
Spinal cord	1	0	1	0	0	0
Prostate	1	1	0	1	0	1
Multiple organs	6	3	3			

*Detailed autopsy information: 2008 cohort.

Pt. #4, 5/23/02: No gross meningitis; miliary pulmonary nodules with necrotic mass LLL; diffuse alveolar damage with bilateral pleural effusions; + *C immitis* culture from lung tissue.

Pt. #20, 5/03/02: Disseminated coccidioidomycosis involving lung, heart, lymph nodes, spleen, adrenal, pancreas, and kidney. Brain: mild chronic inflammation of meninges; no organisms identified.

Pt. #23, 1/01: Disseminated coccidioidomycosis with involvement of lung and lymph nodes. Pathology demonstrated caseating granulomas, spherules, multinucleated giant cells. Brain showed dilated ventricles with edematous choroid plexus. Lumbar spinal cord: edematous with *C immitis* organisms noted throughout. Cause of death: disseminated coccidioidomycosis with brain edema. No evidence of lymphoma.

Among living patients in the 1980 cohort, follow-up varied from 3 years to 16 years.

With respect to the 2008 study, 14 of the 17 survivors (82%) were able to perform activities of daily living. Although 2 of these individuals subsequently found work, the remaining patients did not appear to be employed. Three patients who had initially responded to treatment died from unrelated causes. As of their last follow-up visit, all survivors continued to receive therapy, except for 1 individual (Patient 10) who self-discontinued therapy after 1 year. In the 1980 cohort, specific follow-up is less certain; however, 11 patients appeared to be able to do activities of daily living and 10 patients were able to return to some type of employment.

DISCUSSION

In the current study we reviewed the clinical and therapeutic features of 30 patients with CM seen from November 1993 to April 2008 (the 2008 cohort) and compared this information with similar data from the pre-fluconazole era as represented by the 1981 study[8] in the journal *Medicine* (referred to here as the 1980 cohort). Review of the similarities and differences between these 2 cohorts demonstrates the changes in clinical presentation and management of this condition over the past 30 years.

Demographics and Risk Factors

In comparison to the 1980 cohort (see Table 1), a larger percentage of patients in the 2008 cohort had an underlying, predisposing medical condition. The presence of HIV/AIDS is a well-known risk factor for disseminated coccidioidomycosis—this was not present in the pre-1980 era but was found in 10 of 30 patients in the current study. Another difference was the much larger percentage of Hispanic patients (53%) in the 2008 cohort compared with the 1980 cohort (6%). Although there may be an increased risk of disseminated disease in this group, the larger percentage of cases in our series more likely reflects changing population demographics in Southern California—a large Hispanic influx has added to the labor pool, especially in outdoor trades (such as construction, landscaping) that place a patient at greater risk for acquiring coccidioidomycosis. CM is more common in male patients—in the current cohort, there was a 5:1 male to female ratio, a finding comparable to the 6:1 ratio seen in the 1980 cohort. As with the 1980 cohort, two-thirds of patients presented with meningitis as an initial or primary manifestation of

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TABLE 9. Treatment of CM in 30 Patients: 2008 Cohort

Pt	Azole	Total Time on Azole (Approx.)	Maximum Daily Azole Dose (mg)	Azole Toxicity	Amphotericin	Maximum Creatinine Increase/Cycle (mg/dL)	Comments
1	Fluconazole	5 yr	800	NR	None		
2	None	None	NA	NR	Amphotericin B*: Cum. dose: 710 mg Time on polyene: 18 d	NR	No evidence of toxicity.
3	Fluconazole	7 d	1000	NR	None	NR	
4	Fluconazole	3 wk	400	NR	None	NR	
5	Fluconazole	6.5 yr	800	NR	LAmB: Cum. dose: 6000 mg Time on polyene: 19 d	1.2	Developed allergic reaction (hives) and renal insufficiency on ABLC and then switched to liposomal AmB (AmBS).
6	Fluconazole	Uncertain	200	NR	None		
7	Fluconazole	9 yr	800	NR	AmB and LAmB: Cum. dose: 5701 mg Time on polyene: 8 mo	1.1	Developed cerebral salt wasting (5/99) and treated with demeclocycline. Pt also had alopecia, probably medication related.
8	Fluconazole	10 mo	800	NR	AmB: Cum. dose: 2000 mg Time on polyene: 35 d IT AmB (lumbar route) Cum. dose: 13 mg Time on IT AmB: 8 d	NR	
9	Fluconazole	3 yr	1200	NR	None received		
10	Fluconazole	2 yr	800	NR	AmB: Cum. dose: 2000 mg Time on polyene: 75 d	1.2	Pt took azole for 2 yr, then stopped without recurrence of symptoms.
11	Fluconazole Itraconazole	6 mo	1000 (Flu) 600 (Itra)	NR	AmB: Max dose 50 mg Cum. dose: 1000 mg	0.4	Pt did well on azole but died from unknown causes in 2001.
12	Fluconazole	1 mo	600	NR	None received		HIV pt on azole; LTFU after 1 mo.
13	Fluconazole	<1 mo (may have had previous Rx)	800	NR	AmB: Cum. dose: 345 mg Time on polyene: 9 d	0	Pt admitted with PMH of CM (+ VP shunt). Restarted (?) on azole but died within 1 mo following increasing lethargy.
14	Fluconazole	6 wk	400	NR	None		Pt transferred to Arizona; died after 6 wk of azole Rx.

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15	Fluconazole	2 yr	800	NR	AmB: Cum. dose: 350 mg LAmB (ABLC): Cum. dose: 1200 mg	0.8	Creatinine increased to 1.6 while on AmBD. Creatinine subsequently returned to normal upon completion of amphotericin B treatment.
16	Fluconazole	10 yr	1600	NR	None	NR	Pt currently on 1000 mg fluconazole Qd; symptoms return and titers rise when dose decreased below this level.
17	Fluconazole	9 yr	1000	NR	None	NR	Pt diagnosed at different facility and presented to Olive View Medical Center in 2005 with relapse secondary to self-decrease in dose.
18	Fluconazole Voriconazole	2.5 yr (Flu) 2 yr (Vor)	800 (Flu) 400 (Vor)	Ventricular tachycardia (Flu) Photosensitivity (Vor)	LAmB (AmBS): Cum. dose: 9600 mg Time on polyene: 36 d	0.7	Mild renal toxicity included potassium wasting. Pt subsequently developed ventricular tachycardia (torsades de pointe) 2–3 wk later while taking high-dose fluconazole. Patient also developed lumbosacral arachnoiditis while on azole. Switched to voriconazole in 3/08 and remains on this medication at the present.
19	Fluconazole	4.5 yr	1600	NR	None		
20	Fluconazole	1 wk	400	NR	LAmB (ABLC): 350 mg IV Qd (4/24/–4/30/02)	4.1	Pt had widely disseminated coccidioidomycosis and died after 1 wk of azole and amphotericin B treatment. Renal insufficiency (creatinine >5 mg/dL) likely multifactorial and related to severe sepsis syndrome.
21	Fluconazole Voriconazole Posaconazole	4 yr	800 (Flu) 600 (Vor) 800 (Pos)	Photosensitivity (Vor)	LAmB (5 courses): Cum. dose: 30,550 mg Time on polyene: 140 d	.2	Pt with poor compliance resulting in relapse requiring short admissions for retreatment with IV LAmB and fluconazole. Developed lumbosacral arachnoiditis. Trial of voriconazole but difficulty tolerating due to GI distress and photosensitivity. Pt currently on combination of fluconazole + posaconazole.

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TABLE 9. *(Continued)*

Pt	Azole	Total Time on Azole (Approx.)	Maximum Daily Azole Dose (mg)	Azole Toxicity	Amphotericin	Maximum Creatinine Increase/Cycle (mg/dL)	Comments
22	Fluconazole	7 mo	800	NR	None received	NR	
23	Fluconazole	3 d	400	NR	None received	NR	Pt initially misdiagnosed with carcinomatous meningitis. Subsequently found to have *C immitis* but died after 3 d of azole therapy.
24	Fluconazole Voriconazole	8 mo (Flu) 2.5 yr (Vor)	400 (Flu) 400 (Vor)	Photosensitivity (Vor)	AmB: Cum. dose: 180 mg Time on polyene: 3 d	NR	Pt has remained on voriconazole (200 mg po BID) from 9/07 to present despite presence of photosensitivity.
25	Fluconazole Voriconazole	3 yr (Flu) 1 yr (Vor)	800 (Flu) 400 (Vor)	NR	AmB: Cum. dose: 180 mg LAmB: 3 cycles from 2005–2007; cum. doses not available	0.4	
26	Fluconazole Voriconazole	4.5 yr	800 (Flu) 400 (Vor)	NR	LAmB: Cum. dose: 1050 mg Time on polyene: 30 d	0	Pt switched to po voriconazole (200 mg BID) after relapse on fluconazole (800 mg Qd)
27	Fluconazole	1.5 yr	800	NR	AmB: Cum. dose: 630 mg Time on polyene: 14 d	0	
28	Voriconazole Fluconazole	10 mo (Vor) 2 yr (Flu)	800 (Vor) 1600 (Flu)	NR	AmB: Cum. dose: 560 mg Time on polyene: 1 wk LAmB (ABLC): Cum. dose: 10,350 mg Time on polyene (total): 23 d IT AmB (Ommaya reservoir): Cum. dose: 12.5 mg Time on IT Ampho: 6 mo	1.2	Pt initially received combination of amphotericin B + voriconazole. Subsequently required course of IT amphotericin B. Received voriconazole (400 mg BID) from 9/28/06 to 7/31/07 and then switched to fluconazole (max dose 800 mg BID) with later decrease in dose to 1000 mg Qd (present).
29	Fluconazole	3 yr	400	NR	None received	NR	
30	Fluconazole	5 wk	1000	NR	AmB: Cum. dose: 870 mg Time on polyene: 60 d IT AmB (ventricular catheter) 9/1/96–9/19/96 (cum. dose unavailable)	NR	Therapy delayed for 2 mo. Pt initially responded to azoles but developed hydrocephalus requiring VP shunt. Subsequently had shunt complications (obstruction) and later died from brainstem infarct due to poorly controlled meningitis.

Abbreviations: See previous tables. ABLC = amphotericin B lipid complex, AmBS = ambisome, cum. = cumulative, Flu = fluconazole, LTFU = lost to follow-up, NA = not available, NR = none reported, Pos = posaconazole, Vor = voriconazole.

*"Amphotericin B" is amphotericin B desoxycholate unless otherwise specified.

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TABLE 10. Maximum Daily Dose of Fluconazole and Associated Mortality: 2008 Cohort

Maximum Daily Dose (mg)	No. of Patients	Alive	Dead
0	1	0	1
200	1	1	0
400	6	2	4
600	1	1	0
800	12	9	3
1000	4	1	3
1200	2	1	1
1400	0	0	0
1600	3	3	0
Total	30	18	12

disseminated coccidioidomycosis; in both groups, extra-CNS coccidioidomycosis was diagnosed before CM in approximately one-third of patients.

Clinical Presentation

The clinical presentation of the 2 groups was quite similar (see Table 1). Headache remained the most common presenting symptom (approximately 80% of patients) and signs of increased intracranial pressure (for example, nausea/vomiting) were seen in about 50% of patients. In our experience, headache is almost a universal complaint in CM; failure to report this may be seen when other symptoms (for example, altered mental status, confusion, stupor) alter the reliability of the patient history. Bedside findings consistent with meningitis (for example, meningeal irritation) were found in about a third of patients in both cohorts; however, the diagnosis remains heavily dependent on CSF examination, and absence of meningeal signs does not exclude underlying CM. In the 1980 cohort, there was chart documentation of funduscopic examination in all 31 patients, and approximately 16% of patients had papilledema. In the 2008 cohort, only 9 patients had a recorded funduscopic examination (1 patient with papilledema), a practice that likely reflects a greater reliance on CT scanning (rather than physical examination) for evaluation of the complications associated with CM.

Complications

Stroke remains an important complication of CM and may develop in apparently stable patients who appear to be improving clinically.[66] Evidence from pathological studies suggests that extensive meningeal involvement, especially at the base of the brain, results in localized vasculitis, endarteritis obliterans, and vascular obstruction.[39,66] These processes lead to brain parenchymal infarction with attendant neurologic findings such as hemiparesis, cranial nerve abnormalities, and altered consciousness. Coccidioidomycosis-induced vasculitis may be present in up to 40% of cases and, when present, is associated with a high mortality. Approximately one-third of patients in the 2008 cohort developed a stroke or had evidence of infarct on CT or MRI scanning (see Tables 2 and 3). As in the 1980 cohort, these patients had a myriad of focal neurologic signs including cranial nerve palsies, extremity weakness, and abnormal neurologic signs (for example, positive Babinski sign). Although the numbers were small, the presence of a focal stroke did not portend excess mortality when compared to other patients in the cohort. Optimal management of stroke or vasculitis in CM remains unclear—in addition to antifungal therapy, some authorities recommend a trial of corticosteroids (oral dexamethasone 20 mg po daily × 7 d with subsequent taper) in those with new-onset stroke or severe meningeal inflammation.[30]

Hydrocephalus is a serious complication of CM and remains responsible for significant morbidity and mortality in the

TABLE 11. Neurosurgical Procedures in Patients With CM: 2008 Cohort

Pt	Procedure/Date	Complications	Comment
3	1/27/98: Ventriculostomy for hydrocephalus	None	No improvement, died shortly thereafter
7	5/99: VP shunt	None	Marked improvement in mental status following shunt placement
8	11/25/98: VP shunt for increased ICP	None	Minimal improvement
9	1/18/02: VP shunt	Inguinal hernia	Marked improvement after shunt placement
13	1991: VP shunt	Shunt malfunction with hydrocephalus and infection with coagulase-negative staphylococci	Patient minimally improved after shunt placement in 1991. Since 1991, pt lived in convalescent hospital and was unable to do ADLs. Died in 2000
15	6/07: VP shunt 4/08: VP shunt revision 5/08: VP shunt replacement	4/08: Shunt obstruction 5/08: Recurrent obstruction	Marked improvement after shunt revisions
19	3/04: VP shunt	Unknown	
23	1/01: Ommaya reservoir 1/01: VP shunt	None	
25	8/07: VP shunt	Shunt infection	Improved after antimicrobial therapy
28	9/07: Ommaya reservoir 3/08: Ommaya reservoir replacement	Ommaya reservoir infection 2/08	
30	7/15/96: Ventriculostomy for hydrocephalus 8/01/96: VP shunt 8/06/96: VP shunt revision due to trapped L ventricle 8/18/96: Emergency surgery for blocked L ventricle shunt	8/18/96: Blocked L ventricular catheter	

Abbreviations: See previous tables. ICP = intracranial pressure.

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TABLE 12. Follow-Up Information on 30 Patients With CM: 2008 Cohort

Pt	Outcome	Admission Date	Date of Last Follow-Up	Follow-Up Time	Symptoms/Comments	Activities of Daily Living	Treatment at Time of Follow-Up
1	Dead	8/29/01	6/28/05	3 yr 10 mo	Symptoms improved but pt died from unrelated cause (perforated peptic ulcer).	Able	Fluconazole 400 mg Qd
2	Dead	11/8/93	12/2/93	1 mo	Pt died on 12/2/93 after 1 mo hosp and ~750 mg AmB. Had advanced HIV with poorly controlled disseminated coccidioidomycosis. Pt developed coma during the last few d of hospitalization.	Unable	AmB IV
3	Dead	1/26/98	2/1/98	2 wk	Pt died on 2/1/98 secondary to cerebral herniation with terminal extubation.	Unable	NA
4	Dead*	5/20/02	5/22/02	<1 wk	Pt died on 5/22/02 secondary to cerebral herniation.	Unable	NA
5	Alive	3/22/02	1/29/10	7 yr 10 mo	Pt currently on HAART and doing well with no obvious cognitive deficits.	Able	Fluconazole 200 mg Qd
6	Alive	4/8/1996	4/18/96	1 wk	Pt with advanced AIDS (CD4 = 17) improved, discharged from hospital but LTFU.	?	LTFU
7	Alive	5/7/99	6/1/07	8 yr 1 mo	Pt with recurrent bouts of headache requiring AmB and fluconazole. Last seen with high-dose fluconazole; difficulty with ADLs.	Unable	Fluconazole 600 mg Qd
8	Dead	11/17/98	10/30/99	11 mo	Pt with history of infarct, hydrocephalus, and VP shunt. Was discharged to nursing home on 10/05/99 with altered mental status (unresponsive to pain, commands; pupils slow reaction to light) on po fluconazole (800 mg Qd). Patient subsequently died in nursing home.	Unable	NA
9	Dead	1/3/02	6/12/04	2 yr 5 mo	Pt was stable on po fluconazole (800 mg Qd) following discharge and appeared stable at clinic visits. Died at different hospital in 2005 from unknown cause; not clear if related to CM.	Able	NA
10	Alive	5/24/96	6/24/98	2 yr 1 mo	Pt with suspected CM but off medications. Followed up at VA clinic but no clinical evidence of CM reactivation.	Able	None
11	Dead	10/24/00	3/13/01	5 mo	AIDS pt with CM diagnosed in 10/00. Treated for hip fracture in 11/15/00 with subsequent discharge to nursing home. In 3/15/00 was doing well with no headache, mild short-term memory loss; ambulates with cane. Patient later died of unclear cause.	Able	3/15/00 Pt was receiving: fluconazole (800 mg Qd) + itraconazole (200 mg TID) + HAART (ZDV/3TC/Nel) Medications at death unknown.
12	Alive	5/4/99	4/07/03	4 yr	Pt dx with AIDS; started on fluconazole (600 mg Qd) and HAART (stavudine/lamivudine). No recent contact since 4/07/03.	Able	LTFU

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13	Dead	1/1/91	7/29/00	9 yr 7 mo	Pt with history of CM diagnosed in 1991; s/p hydrocephalus and treated with VP shunt. Readmitted 7/27/00 and subsequently developed pseudomembranous colitis with respiratory failure. Became lethargic (but arousable), nonverbal, and died after transfer to general medical ward.	Able	NA
14	Dead	9/6/01	10/1/01	1.5 mo	Pt left hospital on 9/17/01 (10 d admx) on po fluconazole. Readmitted 3 d later to Arizona hospital with increased shortness of breath and progressive respiratory distress. Treated with IV AmB but died 6 weeks later.	Unable	NA
15	Alive	11/9/06	2/16/10	3 yr 3 mo	AIDS pt with hydrocephalus, s/p shunt. Requires full time care and is not able to do ADLs. Able to converse but is confused periodically.	Unable	Fluconazole 800 mg Qd HAART
16	Alive	5/12/98	7/27/06	8 yr 3 mo	Pt doing well and living on his own. Is currently retired but able to exercise. Symptoms return when dose is reduced to fluconazole 800 mg Qd.	Able	Fluconzole 1000 mg Qd Unable to decrease dose to 800 mg (light-headed)
17	Alive	7/6/05	7/28/08	3 yr 2 mo	Pt reportedly doing well, living on his own and working.	Able	Fluconazole 600 mg Qam; 400 mg Qpm
18	Alive	6/19/06	5/1/08	1 yr 11 mo	Pt with relapses requiring hospital admission (with short course IV AmB); has developed caudal aquina arachnoiditis.	Able	Voriconazole 200 mg BID
19	Alive by report	3/12/04	7/01/08	4 yr 3 mo	Transferred to different hospital after noncompliance with fluconazole meds and developed hydrocephalus requiring shunt placement; follow-up CT in 2005 demonstrated improvement. Pt not seen in ID clinic again after 2005 but is alive and working according to family.	?	Taking fluconazole but uncertain dose
20	Dead*	4/22/02	4/30/02	1 wk	Pt died from overwhelming CM after short hospitalization.	Unable	NA
21	Alive	4/1/04	6/26/08	4 yr 3 mo	Pt with recurrent symptoms requiring intermittent hospitalizations. Difficulty taking voriconazole (photosensitivity; disease relapse) and subsequently switched to fluconazole and posaconazole.	Able	Fluconazole 400 mg Qd + Posaconazole (400 BID)
22	Alive	4/5/08	4/14/08	<2 wk	Symptoms resolved including resolving cutaneous lesions; well controlled on fluconazole.	Able	Fluconazole 800 mg Qd
23	Dead*	1/4/01	1/24/01	<3 wk	Pt died from CM after 3 wk hospitalization.	Unable	NA
24	Alive	1/25/07	4/24/08	1 yr 3 mo	Pt working and doing well (asymptomatic) on medications. Has photosensitivity rash secondary to voriconazole with sun exposure.	Able	Voriconazole 200 mg BID
25	Alive	4/13/07	4/16/08	1 yr	Lives at skilled nursing facility, minimally active and requires almost total care.	Unable	Voriconazole 200 mg BID
26	Alive	6/28/04	5/15/08	3 yr 11 mo	Symptoms resolved, pt doing well, able to do ADLs and work, maintained on voriconazole 200 mg po bid. Had relapse after D/C of voriconazole but now doing well on medication.	Able	Voriconazole 200 mg BID

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TABLE 12. *(Continued)*

Pt	Outcome	Admission Date	Date of Last Follow-Up	Follow-Up Time	Symptoms/Comments	Activities of Daily Living	Treatment at Time of Follow-Up
27	Alive	9/7/07	5/24/09	1 yr 8 mo	AIDS pt had recurrence of CM after noncompliance with fluconazole and was successfully retreated with AmB and IV fluconazole. Has had ongoing difficulties with substance abuse and has experienced subsequent CM relapses. Currently requires significant family assistance.	Able	Fluconazole 800 mg Qd
28	Alive	9/29/06	1/08/10	3 yr 3 mo	AIDS pt had recurrence which required Ommaya reservoir and IT AmB. Subsequently maintained on high-dose fluconazole (1 g BID). Has subsequently developed seizure disorder (now taking anti-seizure medications) requiring several hospital admissions.	Able	Fluconazole 1200 mg Qd
29	Alive	7/1/06	8/5/08	2 yr 1 mo	Pt on fluconazole (400 mg Qd) and well controlled with no further symptoms. Still works as manager of small trucking company but has limited activity.	Able	Fluconazole 400 mg Qd
30	Dead	6/6/96	9/19/96	3 mo	Patient died 9/19/1996 secondary to brainstem herniation.	Unable	NA

Abbreviations: See previous tables. HAART = highly active antiretroviral therapy, NA = not applicable, ND = not done, Nel = nelfinavir, ZDV = zidovudine, 3TC = lamivudine.
*These patients underwent autopsy.

condition. In the initial study of fluconazole, 25% of the 50 patients with CM developed hydrocephalus.[25] As with stroke, hydrocephalus appears related to the extensive arachnoidal fibrosis associated with meningeal inflammation. Patients may present with communicating or noncommunicating hydrocephalus depending on the level of obstruction.[53] Despite widespread use of azole therapy, hydrocephalus was seen in almost a third of the patients in the current study. Although CT documentation was less common in the 1980 study, the equivalent need for VP shunting (9 patients in each cohort) suggests that the incidence of hydrocephalus was similar between the 2 groups. Hydrocephalus may develop rather suddenly in patients with CM and should be considered in any patient who experiences worsening headache or sudden neurologic deterioration. In this situation, the clinician should arrange for immediate CT scanning and should obtain neurosurgical consultation if hydrocephalus is present.

There was a clear difference in the incidence of lumbar arachnoiditis between the 2 cohorts (2008: 10%; 1980: 35%) (see Table 1). The increased incidence in the 1980 cohort may be due to the more common use of intralumbar amphotericin B during that period[8]—in that study, the majority of patients received intrathecal amphotericin via the lumbar route (see Table 4). Nevertheless, even without a history of intralumbar therapy, lumbosacral myelopathy/arachnoiditis may appear as a complication of CM—although they had not received intralumbar amphotericin B, 3 patients in the current study developed this problem (documented via clinical history and MRI scan). Optimal management of this complication remains unclear. In an earlier report, a case of coccidioidal spinal arachnoiditis was managed with a combination of VP shunting (the patient had concomitant hydrocephalus) and a course of intensive antifungal therapy (intravenous amphotericin B and oral ketoconazole).[70] Similarly, 2 of our patients appeared to improve after a repeat course of intravenous LAmB (1 wk) followed by azole therapy. Aside from the decreased incidence of lumbar arachnoiditis, the current widespread use of azole therapy has not altered the incidence of serious complications, such as stroke and hydrocephalus, in patients with CM.

Laboratory Findings

Table 2 outlines some of the differences and similarities in laboratory studies between the 2 groups. In the 2008 cohort, leukocytosis was actually uncommon compared to the 1980 cohort (2008: 3%; 1980: 37%). The cause of this difference is unclear; however, impaired leukocyte response is recognized in HIV/AIDS patients, and patients in this subset had a lower leukocyte count compared to non-HIV patients (2008 HIV patients: mean, 6480 cells/mm^3; 2008 non-HIV patients: mean, 8710 cells/mm^3). In endemic regions, the presence of eosinophilia is a clinical clue to active infection with *C immitis*. Although eosinophilia was seen in the 2008 cohort, there was a lower incidence compared to the 1980 cohort (eosinophil count $\geq$350 cells/mm^3; 2008: 18%; 1980: 48%). Upon further analysis, the presence of HIV/AIDS did not appear to have a significant effect on this parameter—absolute eosinophil counts were slightly higher in HIV patients compared to non-HIV patients (mean eosinophil counts: HIV patients, 224 cells/mm^3 vs. non-HIV patients, 197 cells/mm^3). A notable finding in the 2008 cohort, not reported in the 1980 cohort, is the incidence of hyponatremia (serum Na <135 mEq/L) at the time of clinical presentation. This was seen in 60% of patients and was often a poor prognostic factor: 11 of the 18 patients with this finding subsequently died.

CSF findings were generally similar between the 2 studies and reflected the typical presentation for fungal meningitis—over

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half of the patients in each group had a lymphocyte predominance or evidence of low CSF glucose. While almost all patients with CM have CSF pleocytosis, a "normal" CSF does not exclude the diagnosis—in the 1980 cohort, up to 5 patients had initially normal studies yet eventually developed CM or had concurrent positive cultures. Overall, about one-third of patients in each group eventually had a CSF culture positive for *C immitis*. This finding demonstrates the difficulty in culturing the organism from CSF and reemphasizes the importance of not excluding the diagnosis based on a "negative" spinal fluid culture. Although we were unable to assess the amount of spinal fluid collected, culture yields are likely to be higher when a large volume (for example, 8–10 cc of CSF) is sent to the laboratory.

Serology

A major difference between the current study and the 1980 protocol is the present availability of the ELISA IgG/IgM test for both serum and CSF. In the current study (see Table 2), the serum ELISA IgG was positive in almost all patients (25/27; 93%) at some time during their illness and was positive in the CSF in 75% of cases (15/21 patients). ELISA IgM, a marker of acute infection, was found to be less reliable; at clinical presentation, the serum ELISA IgM was positive in only 55% (15/27) of patients and was present in only 35% (8/22) CSF samples. An important caveat for serologic diagnostics is the timing of the studies. In a patient with "early" disease (<4–6 wk), serologic testing may well be negative, a finding that could lead to premature exclusion of the diagnosis. In the current study, this was seen in Patient 30: despite a compatible clinical presentation, this individual had a significant delay in receiving effective therapy, in part related to the initial negative serologies and fungal cultures. Effective therapy was not started until almost 2 months after the onset of symptoms, when a repeat CSF fungal culture (obtained 1 month *after* initial presentation) turned positive. While *Coccidioides* serology can be quite helpful in confirming a suspected diagnosis of CM, a negative serology does not exclude the diagnosis and should not dissuade the clinician from initiating empiric therapy in the appropriate clinical setting.

Our experience with the serum CF test in the 2008 cohort demonstrated a relatively high sensitivity—titers were positive in 95% of patients (22/23) at some time during their clinical course, and almost all positive patients (20/23; 87%) had titers ≥1:16, a traditional marker of disseminated disease. In the current study, the CSF CF was not as sensitive—only 10 of 17 patients (59%) were positive in comparison to the 1980 cohort (83%). Again, serology can be helpful in confirming a diagnosis of CM, provided that enough time has elapsed for seroconversion to occur. Several studies have demonstrated impaired serologic response in immunocompromised patients, and clinicians must avoid being misled by negative serologic studies.[6,7]

Radiology

As noted in Table 3, the initial chest radiographic findings were similar between the 2 cohorts. An abnormal chest radiograph was found in about two-thirds of patients in each group (2008: 68%; 1980: 73%) with a myriad of findings including bilateral infiltrates, focal pneumonitis, pulmonary cavities, and mediastinal/hilar adenopathy. Findings suggestive of dissemination— diffuse bilateral infiltrates and miliary nodules—were more common in the current cohort, probably reflecting the high incidence of clinically apparent "disseminated" disease in patients with HIV/AIDS.

A major difference between the 2 studies is the ready availability of CT and MRI scanning in the current era, which have become indispensable tools in the diagnosis and management of CM-related complications. In the current study, 21 of 29 patients (72%) had an abnormal CT scan. Most patients in the 1980 cohort did not undergo CT scanning; however, scans were ultimately abnormal in all 6 patients who underwent the procedure. MRI scanning was not available for the 1980 cohort but was extensively used in the 2008 cohort. Although the numbers are relatively small, MRI scanning appeared to be more sensitive in detection of basilar meningitis compared to CT scanning (MRI: 9/20 [45%] vs. CT: 5/29 [17%]).

Previous investigators have attempted to use neuroimaging to predict patient outcome in CM.[4] In that study, the presence of basilar meningitis did not appear to influence outcome; however, development of hydrocephalus predicted a higher mortality, especially in HIV/AIDS patients. Our study had smaller numbers of patients but generally similar trends—mortality with basilar meningitis was 18% (2/11 patients) compared to 50% in those who developed hydrocephalus.

Patients with suspected CM should initially undergo a brain CT scan to rule out hydrocephalus or cerebral edema. If the initial scans are negative, most experts recommend obtaining an MRI scan (with gadolinium contrast reagent) to look for the presence of basilar meningitis, a finding suggestive of underlying mycobacterial or fungal meningitis. In patients with an established diagnosis of CM, a repeat head CT scan is generally adequate to screen for complications such as hydrocephalus or cerebral edema. Although a head CT scan (with contrast) may also detect stroke, our experience suggests that an MRI might be more sensitive in selected cases. Radiographic scanning is invaluable in the management of CM; a head CT scan should always be obtained in patients with suspected complications or significant signs of clinical deterioration.

Therapy

Antifungal Therapy: Azoles

The almost complete change to azole therapy from the previous standard of intrathecal amphotericin B (see Table 4) is the most obvious difference between the 1980 and 2008 cohorts. In the 2008 group, only 3 patients received intrathecal amphotericin (usually with concomitant azole therapy), and then only for relatively short periods of time. Approximately half (13 cases) of the patients in the 2008 cohort received an azole alone, while 16 patients received some combination of fluconazole plus parenteral amphotericin B. Since about 5 patients died in each of these 2 groups, it is difficult to say if there were any differences between the 2 approaches to therapy. The optimal starting dose of fluconazole for CM patients is unclear, with some data suggesting that a lower starting dose (400 mg) might be successful in some cases.[24,25,30] In the current study, about two-thirds of patients ultimately received high-dose (≥800 mg) fluconazole in accord with Infectious Diseases Society of America guidelines for treatment of CM[24] (see Table 10). While overall numbers are small, mortality was high (5/8 patients) in those receiving lower-dose (<800 mg) fluconazole, suggesting that early, high-dose (≥800 mg) fluconazole therapy is likely to have better outcomes in patients with CM. Following successful initial therapy with parenteral fluconazole, patients were converted to equivalent doses of oral azole and maintained under clinical control for considerable periods of time (Patient 16 has been on fluconazole for over 10 years). Azoles are not curative for CM, and almost all patients who stopped therapy suffered a clinical relapse that required retreatment. The only exception was Patient 10, where the diagnosis of CM must remain clinically suspect. Although he met study criteria for CM (for example, symptoms and minimally elevated

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CSF leukocyte count), other parameters (CSF glucose, total protein, CSF serology, and CSF cultures) were normal, raising questions about the true presence of CM in this case.

Six patients in the 2008 cohort received voriconazole, an agent with reported efficacy in patients with fluconazole failure.[17,49] This was clearly the situation in 1 of our cases (Patient 26; see Appendix) who responded to oral voriconazole (200 mg po twice daily) after experiencing 2 clinical relapses while receiving high-dose fluconazole (800 mg daily). Although voriconazole is an attractive agent for CM, there is less experience with it than with fluconazole, and its use is hampered by selected side effects such as photosensitivity and visual disturbances. Despite these concerns, a trial of voriconazole could be helpful in patients who appear to be failing high-dose fluconazole.

Drug interactions between voriconazole and antiretroviral agents are complex, which makes using voriconazole difficult in HIV/AIDS patients with CM.[71] Concomitant use of ritonavir both increases (early) and decreases (later) concentrations of voriconazole as the drug induces changes in P450 CYP-dependent levels.[35] Because of these interactions, voriconazole is generally contraindicated in patients receiving concomitant ritonavir or efavirenz.[13] Nevertheless, recent studies suggest that voriconazole can be given in patients receiving low-dose ritonavir (100 mg twice daily) provided that serum voriconazole levels are available to help guide voriconazole dosing.[41]

Posaconazole has excellent in vitro activity against *C immitis*; however, it has poor CSF penetration and it is not currently recommended for treatment of CM. Nevertheless, the drug has been successful in some patients with poorly controlled, nonmeningeal coccidioidomycosis[3,59] and has been used in other types of CNS fungal infection.[46] We used posaconazole in combination with fluconazole to help manage 1 case of lumbosacral coccidioidal arachnoiditis (Patient 21). Although this patient experienced some clinical improvement, the role of posaconazole is unclear, and we do not routinely recommend posaconazole for management of CM.

The occurrence of azole "failure" raises the question of preexisting or acquired fungal resistance to azole agents, similar to that seen with *Candida* species. There are few data supporting this in the coccidioidomycosis literature; however, a recent case raises the possibility of fluconazole resistance as a cause of treatment failure.[33] The patient had a history of chronic pulmonary disease and CM and was receiving long-term fluconazole (sometimes on an intermittent basis). He experienced a relapse of pulmonary symptoms with *C immitis* recovered again from pulmonary specimens. The patient clinically responded to intravenous LAmB and was subsequently maintained on weekly treatments with the drug. The *C immitis* isolate demonstrated decreased susceptibility to several azoles including fluconazole. This was an unusual case and its significance for management of CM remains unclear—although a "resistant" *C immitis* isolate was isolated from pleural fluid, the CSF examination (after LAmB) was within normal limits. Previous studies suggest that almost all isolates of *C immitis* are susceptible to fluconazole; most patients have a clinical response to treatment, and routine susceptibility testing is not necessary. Nevertheless, if *C immitis* is re-isolated in patients failing therapy, consider obtaining fungal susceptibilities to rule out the possibility of azole resistance.

Antifungal Therapy: Azole Toxicity

Previous studies of high-dose fluconazole demonstrate variable degrees of hepatotoxicity depending on the dose and clinical situation. In a study of high-dose fluconazole (800 mg daily) in patients with disseminated candidiasis,[51] 9% of individuals required discontinuation of fluconazole due to hepatitis. In addition, other studies suggest that fluconazole toxicity may be more common in patients in the intensive care unit,[26] or in patients with AIDS.[9] In the first major study of fluconazole in CM (dose of 400 mg daily), abnormal liver function abnormalities were seen in only 3 patients (out of 47), and there were no documented cases of serious hepatotoxicity.[25] Despite the high doses of fluconazole used, we found relatively little azole toxicity in the current study. Some patients had difficulty tolerating higher doses (for example, nausea/vomiting); however, none of our cases appeared to experience clinically significant hepatotoxicity. Despite these observations, hepatotoxicity remains a potentially serious side effect of azoles. When prescribing these agents, it is important to warn patients about relevant symptoms, and it is reasonable to check liver tests periodically to exclude subclinical hepatitis. Clinicians should exercise special caution when using high-dose azole therapy in patients with underlying hepatitis or in those receiving other hepatotoxic drugs.

In addition to hepatotoxicity, other serious side effects associated with high-dose fluconazole include ventricular arrhythmias and adrenal insufficiency. Ventricular tachycardia, especially torsades de pointes, is a rare but recognized complication of azole therapy.[38,62] One of the cases (Patient 18) in the 2008 cohort developed ventricular tachycardia (torsades de pointes) while receiving high-dose fluconazole (800 mg po daily). This episode occurred several weeks after the patient had received a course of intravenous amphotericin B; this treatment was associated with hypokalemia, and the patient had persistent hypomagnesemia at the time of the event. Following correction of the electrolyte disorder, the patient was able to tolerate azoles without evidence of subsequent arrhythmia. When prescribing high-dose fluconazole, be cautious in patients with preexisting QT prolongation, with underlying electrolyte abnormalities (for example, hypokalemia, hypomagnesemia), or in those receiving drugs known to be associated with QT prolongation.

Adrenal insufficiency is an uncommon, but well-described, side effect of high-dose azole therapy.[54] Since fluconazole does not appear to impair mineralocorticoid production, traditional electrolyte abnormalities associated with adrenal insufficiency (for example, hyperkalemia, hyponatremia) are generally not present. We did not see evidence of overt cortisol deficiency in any of the patients in the current study; however, another of our coccidioidomycosis cases—a patient receiving treatment for vertebral coccidioidomycosis—developed adrenal insufficiency while receiving high-dose (800 mg/d) fluconazole. Consider the possibility of adrenal insufficiency in fluconazole-treated patients who develop unexplained fatigue, malaise, or hypotension. In this situation, order additional studies to rule out adrenal insufficiency (for example, cortisol levels; ACTH stimulation test) and consider administering empiric cortisol therapy until test results are available.

Photosensitivity drug eruption due to sun exposure is a significant side effect of voriconazole.[36] This condition is likely to be more common in desert regions where CM is endemic, and was seen in at least 3 of the 6 individuals treated with voriconazole in our study. Although individuals with severe photosensitivity may need to discontinue the drug, most patients have milder reactions and can minimize the condition by limiting sun exposure or using protective measures such as clothing and sunblock.

Antifungal Therapy: Intrathecal Amphotericin B

In the pre-azole era, intrathecal amphotericin B was the mainstay of therapy for CM. The relative convenience and tolerability of azole therapy has relegated intrathecal amphotericin to a more subsidiary role in the management of CM. In the current

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study, only 3 patients (10%) received intrathecal amphotericin B, compared to 94% of patients from the 1980 study. Despite these changes, there may still be benefits to intrathecal amphotericin B, especially in patients with a poor response to azoles. Shirvani et al[55] retrospectively reviewed 23 patients who were "non-responders" to fluconazole and found that a majority responded to a relatively brief course (<3 mo) of intrathecal amphotericin B. One potential advantage of intrathecal amphotericin B is the fact that some patients appear "cured" (or have long-term control) of CM following aggressive intrathecal therapy. In the 1980 study, 15 of the survivors were no longer receiving drug therapy at the time of follow-up. While a future relapse requiring additional therapy could not be ruled out, some individuals appeared to have prolonged periods of drug-free survival. Aside from 1 patient where the diagnosis of CM remains in doubt (Patient 10), none of the patients in the 2008 cohort was cured of their condition, and all required long-term azole therapy.

While our experience was limited, there are clearly situations where intrathecal amphotericin B might be appropriate, especially in patients who appear to be doing poorly on azole therapy. In the 2008 study, Patient 28 (HIV with CM) appeared to be failing azole/intravenous amphotericin B and seemed to benefit from a 6-month course of intrathecal amphotericin B (cumulative dose of 12.8 mg). There is some debate about the best route of administration—some investigators recommend intralumbar administration,[60] while others prefer the intracisternal approach.[30] Amphotericin B may also be administered directly into the cerebral ventricle via Ommaya reservoir or ventricular catheter. Some patients benefit from this approach; however, it may be less effective because the drug is not being delivered directly to the basilar cisterns where most disease resides. A recent paper described successful management of CM following continuous infusion amphotericin B therapy via a programmable implanted pump into the cisternal subarachnoid space.[5] Although intrathecal amphotericin B may be necessary in selected cases, it is not without toxicities—there are often significant side effects (such as nausea/vomiting, headache) as well as serious neurotoxicity (for example, arachnoiditis, paraparesis) associated with chemical meningitis. In the 1980 cohort, a far larger percentage of patients developed lumbar myelopathy/arachnoiditis, probably related to prolonged intralumbar administration of amphotericin B.

Antifungal Therapy: Parenteral Amphotericin

Intravenous AmB D has poor CSF penetration and, by itself, has a limited role in CM management. Nevertheless, many patients with CM often receive concomitant parenteral amphotericin B as supplemental therapy, especially in those with severe, disseminated extrameningeal disease. This was true in the 1980 study—almost all patients who received intrathecal amphotericin B received a concomitant course of intravenous AmB D. In general, serious long-term nephrotoxicity was rare in this group—the average creatinine increase per cycle was 0.9 mg/dL, and only 1 patient (Patient 30) developed serious nephrotoxicity resulting in failure of a renal allogeneic homograft. In the 2008 study, the presence of serious nephrotoxicity was equally rare—the average increase in creatinine per cycle of parenteral amphotericin B was 0.85 mg/dL, and in almost all patients, the creatinine returned to normal following completion of the amphotericin B. The 1 patient who experienced significant renal failure on parenteral amphotericin B (2008 study: Patient 20; creatinine increase 4.1 mg/dL) died from overwhelming disseminated coccidioidomycosis; in this case, the renal failure was likely multifactorial and related to the hypotension associated with sepsis syndrome. The availability of less-nephrotoxic lipid preparations is likely to reduce further the risk of long-term nephrotoxicity: in the 2008 cohort there was a definite trend toward use of these products in patients that had any evidence of rising creatinine while receiving standard AmB D. An important point to remember is that lipid-based amphotericin B products, while less nephrotoxic, still have electrolyte loss associated with renal tubular toxicity. As described above, this became especially important in 1 patient (Patient 18) who developed fluconazole-induced ventricular tachycardia associated with electrolyte disorders (for example, hypokalemia, hypomagnesemia) related to a previous course of LAmB.

Recent studies examining lipid preparations of amphotericin B, such as LAmB, suggest that these preparations have better penetration of brain parenchyma and meningeal tissue, a feature that would predict improved outcomes in CM.[15] Indeed, in an experimental rabbit model of CM, LAmB alone was sometimes curative when used at higher than normal doses (7.5 mg/kg).[11] These results need to be interpreted with caution, because the animal model of CM may not completely mimic human CM. Such outcomes have not been duplicated in humans, and this therapy approach (high-dose LAmB alone) awaits further clinical trials. Nevertheless, many investigators see a benefit in combined therapy, and some form of amphotericin B is often given in combination with azole therapy, especially in patients with severe disease or clinical relapse. In the current study, about half of the patients received concomitant amphotericin B, either the standard agent (9 patients) or the less toxic lipid formulations (9 patients). Although outcomes in these cases were similar to those seen with azole-alone therapy, the numbers are too small to make any definitive conclusions.

Neurosurgical Procedures

Not surprisingly, the number of patients who underwent placement of an intraventricular reservoir for intrathecal amphotericin B was far less in the present study (2 patients; 7%) compared to the 1980 cohort (15/31 patients; 48%). In the 1980 group, this procedure was often problematic—13 of the 15 cases had complications requiring removal of the device, such as catheter obstruction or bacterial meningitis. While the need for intraventricular reservoirs has decreased, the widespread use of azole agents has not necessarily reduced the need for placement of VP shunts—almost a third of patients in the 2008 cohort required a VP shunt, a percentage similar to that reported in the 1980 cohort. Hydrocephalus remains a common complication of CM, and patients with severe recurrent headache should have a repeat CT scan to rule out the condition. Those with significant hydrocephalus may require a ventriculostomy or VP shunt and should be evaluated by a neurosurgeon.[53]

Outcomes

Despite the switch to more convenient azole therapies, CM remains a serious disease with a relatively high mortality. The mortality in the 2008 cohort (40%) was almost identical to that in the 1980 cohort (38%). Morbidity in both groups was also significant—only about 40% of individuals in each cohort were able to carry out activities of daily living. It is noteworthy that fewer patients in the present cohort (2008: 2 patients vs. 1980: 10 patients) were able to return to some type of employment. The presence of HIV/AIDS in the present cohort may also have influenced this observation—mortality was similar in this group (compared to other patients); however, none of these individuals was able to return to gainful employment. Although this may reflect other factors (for example, presence of underlying disease, availability of disability insurance), it raises questions

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about the durability of the azole response and reemphasizes the morbidity associated with this condition.

HIV/AIDS

A major difference between the 1980 cohort and the 2008 cohort is the advent of HIV/AIDS during the post-1980 period-almost a third of patients in the 2008 group had underlying HIV infection. In HIV patients, coccidioidomycosis is often a manifestation of significant immunosuppression—many patients have low CD4 T-cell counts (<250 cells/mm^3) with signs of associated disseminated, extrameningeal disease. Reported mortality of CM in HIV is high: of the 32 cases of CM reported in 3 studies of coccidioidomycosis-infected HIV patients, over two-thirds of the patients died.[23,25,56] Although some of these deaths were due to underlying HIV-associated conditions, complications of CM accounted for mortality in many of the individuals.[25]

The clinical presentation in the HIV/AIDS patients in the current study was varied and was similar to that seen in the non-HIV cohort (Table 13). Most individuals presented with findings of "typical" chronic meningitis—a several-week history of headache, often accompanied by fever and mental status changes. Some individuals (Patients 2, 3, 4) had a rapidly progressive downhill course leading to stupor/coma and death from suspected cerebral herniation. Other cases survived their initial hospitalization and were successfully started on antiretroviral therapy in addition to continued treatment for CM. When compared to the non-HIV patients, HIV-infected patients were more likely to have evidence of widespread disseminated coccidioidomycosis. Although 1 of our patients (Patient 28) presented with isolated CM, 9 of 10 patients had disseminated extrameningeal disease as evidenced by diffuse pulmonary infiltrates or miliary nodules. As with previous studies, CM was associated with more advanced HIV infection—at the time of clinical presentation, all our patients had CD4 T-lymphocyte counts less than 250 cells/mm^3. Compared to non-HIV patients, HIV-infected patients had a lower incidence of peripheral leukocytosis and a decreased percentage of CSF lymphocytosis. These findings likely reflect the impaired marrow response and T-cell lymphocytopenia seen in HIV. The CSF findings may have clinical import: in at least 1 of the cases in the 2008 cohort (Patient 3), the CSF polymorphonuclear leukocyte predominance led to an initial suspicion of bacterial meningitis. In coccidioidomycosis-endemic regions, consider the possibility of *C immitis* infection in HIV patients with suspected pyogenic meningitis.

Because the numbers in our study are relatively small, and previous studies were from the era before highly active antiretroviral therapy (HAART), it is difficult to compare the effects of antiretroviral therapy on clinical presentation and progression of CM. Recent studies suggest that the advent of HAART is likely to have a salutary effect on control of coccidioidomycosis—researchers from Arizona found a correlation between successful control of HIV infection (secondary to HAART) and decreased severity of coccidioidomycosis in HIV-infected individuals.[37] Although most HIV patients in the 2008 cohort had not received prior antiretroviral therapy, 2 individuals (Patients 3, 4) developed CM while receiving HAART. Both patients developed obtundation and died within a relatively short time. Patients diagnosed later in the study period seemed to have improved survival, perhaps as a consequence of earlier recognition of CM and more aggressive antiretroviral therapy. More recent cases (Patients 5, 15, 27, 28) were still alive several years after their diagnosis. Despite the apparent improved outcomes in our cohort, the morbidity of CM remained impressive. One individual (Patient 15) developed hydrocephalus and had several procedures including placement of bilateral VP shunts with subsequent revision; at 1 point he was hospitalized for almost a year because of complications related to CM and HIV/AIDS. Although at last follow-up he was clinically stable and able to perform activities of daily living, he had definite cognitive impairment and a possible seizure disorder, and was unable to work. Another patient (Patient 28) was stable on HAART and fluconazole but had recurrent seizures and cognitive impairment. A third patient (Patient 27) had a history of substance abuse (with sometimes poor medication compliance) and required significant family assistance. All 3 of these patients had several hospital admissions requiring re-treatment with intravenous amphotericin B and high-dose azoles. Reports from other AIDS clinicians mirror these observations—management of CM in HIV/AIDS remains difficult with a high incidence of treatment failure and relapse.[13]

In 2009, the federal government released updated guidelines on the prevention and management of opportunistic infections in HIV/AIDS patients, including those individuals at risk for coccidioidomycosis.[31] In coccidioidomycosis-endemic regions, the guidelines recommend primary antifungal prophylaxis (fluconazole or itraconazole) in individuals with a positive serologic test for *C immitis* (either IgG or IgM) and a CD4 count <250 cells/μL. HIV-infected patients with CM should have initial therapy with fluconazole at a standard dose of 400–800 mg per day. Considering the severity of the cases in the 2008 cohort, our experience suggests that a higher starting dose of fluconazole (for example, 800 mg daily) may be more appropriate. Because of the high incidence of extrameningeal dissemination, concomitant amphotericin B may well be appropriate, especially in moderately to severely ill individuals. Because of the potential for drug interactions, experts generally recommend against voriconazole use in patients receiving HIV protease inhibitor drugs and/or efavirenz.[13] Despite this warning, a 2009 paper suggested that dual administration of voriconazole and antiretroviral drugs (for example, efavirenz) may be successful if therapeutic drug monitoring is available.[12] Likewise, determination of drug levels permitted successful treatment of cryptococcal meningitis with voriconazole in an HIV patient receiving lopinavir/ritonavir.[41] For HIV patients, voriconazole therapy for fluconazole failures is a definite option; however, monitoring of voriconazole levels should be done in patients receiving selected antiretroviral agents. Although only minimal data are available, voriconazole does not appear to have significant interactions with nucleoside reverse transcriptase inhibitors or the integrase-inhibitor raltegravir.[71] Despite optimal azole dosing, treatment failure with azoles may occur, and some patients may require intrathecal amphotericin B. Our experience with intrathecal amphotericin B in HIV-CM coinfection (only 1 patient) suggests that a limited course (3–6 mo) of intrathecal amphotericin B may help stabilize a failing patient and permit subsequent control with an oral azole. Nevertheless, complications of CM (hydrocephalus, stroke) are common in HIV/AIDS patients, and the morbidity can be quite considerable. As with non-HIV patients, lifelong azole therapy is likely to be necessary for HIV patients with CM.

Based on these observations, a clinical picture of CM in patients with HIV/AIDS can be outlined. The presentation of CM in HIV/AIDS patients is similar to that seen in non-HIV infection. There is a spectrum from cases with a relatively acute presentation (with a relatively sudden onset with rapid progression to obtundation/coma) to cases resembling a more subacute, chronic meningitis. In HIV/AIDS, CM is usually seen in patients with more advanced immunologic impairment (CD4 T-cell counts <250 cells/mm^3), often reflected in a high incidence of extrameningeal dissemination as demonstrated by diffuse pulmonary infiltrates. Although serology may be negative in early disease, patients who survive usually develop positive confirmatory

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TABLE 13. CM in Patients With HIV/AIDS: 2008 Cohort

Pt	Admission Date	Clinical Summary	CD4 Cells at CM Dx (cells/mm^3)	CSF Findings	Cultures	Serology	Chest Radiograph	Therapy	HIV Treatment
2	11/8/93	27-yr-old male with history of drug use and newly diagnosed HIV/AIDS. Developed severe headache 3 d after admission with abnormal LP (elevated OP). Pt became comatose despite IV Amb and died 1 mo after admission.	109	1 WBC (100 P) Glu: 54 mg/dL TP: 27 mg/dL	CSF: Neg Blood: Pos	Serum ELISA IgG/M: Pos/Pos Serum CF: 1/128 CSF ELISA IgG/M: Pos/Pos CSF CF: ND	Diffuse pulm infiltrates	AmB	None
3	1/26/98	32-yr-old female (transsexual) with previous history of HIV/AIDS (on HAART) admitted twice over 3 mo with "aseptic" meningitis. Pt developed hydrocephalus requiring ventriculostomy and died shortly thereafter despite IV AmB and fluconazole.	273	128 WBC (91 P) Glu: 29 mg/dL TP: 198 mg/dL	CSF: Pos	Serum ELISA IgG/M: ND/ND Serum CF: ND CSF ELISA IgG/IgM: Pos/Neg CSF CF: ND	BL lower lobe infiltrates	Fluconazole Surgery: + ventriculostomy	*Stavudine Lamivudine Nelfinavir
4	5/20/02	32-yr-old male with history of HIV/AIDS (on HAART) presented with 2 wk history of headache. Presented with obtundation and died 2 d after admission despite fluconazole treatment.	171	793 WBC (79 P) Glu: 28 mg/dL TP: 94 mg/dL	CSF: Pos	Serum ELISA IgG/M: Neg/Neg Serum CF: ND CSF ELISA IgG/M: Neg/Neg CSF CF: ND	Diffuse pulm infiltrates	Fluconazole	*Abacavir Lamivudine Efavirenz
5	3/22/02	40-yr-old male with new diagnosis of HIV/AIDS and 6 wk history of weight loss and pneumonitis. Dx of coxy on lymph node biopsy treated with LAmB and fluconazole. Discharged to nursing home on po fluconazole.	162	5 WBC (Diff: NA) Glu: 60 mg/dL TP: 40 mg/dL	CSF: Neg LN: Pos	Serum ELISA IgG/M: Pos/Neg Serum CF: 1:256 CSF ELISA IgG/M: Pos/Neg CSF CF: <1:1	Diffuse reticular-nodular infiltrates; Bilat mediastinal adernopathy	Fluconazole LAmB	Unknown

(Continued on next page)

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TABLE 13. *(Continued)*

Pt	Admission Date	Clinical Summary	CD4 Cells at CM Dx (cells/mm^3)	CSF Findings	Cultures	Serology	Chest Radiograph	Therapy	HIV Treatment
6	4/8/96	33-yr-old male with previous history of HIV/AIDS with 1 wk history of fever, lethargy, and N/V. Treated with fluconazole and discharged to nursing home in 4/96; subsequently lost to follow-up (4/16/96).	17	145 WBC (49 P) Glu: 18 mg/dL TP: 213 mg/dL	CSF: Pos	Serum ELISA IgG/M: ND/ND Serum CF: ND CSF ELISA IgG/M: ND/ND CSF CF: ND	L hilar enlargement	Fluconazole LAmB	*Zidovudine Lamivudine
11	10/24/00	50-yr-old male with HIV/AIDS presented with 3 mo history of headache. Treated successfully with IV amphotericin and azoles. Died at later date (3/13/01) of unclear causes.	24	374 WBC (59 P) Glu: 24 mg/dL TP: 231 mg/dL	CSF: Neg TBBX: Pos	Serum ELISA IgG/M: Pos/Neg Serum CF: 1:4 CSF ELISA IgG/M: Pos/Pos CSF CF: 1:1	Diffuse pulm inflitrates	Fluconazole Itraconazole AmB	None
12	5/4/99	63-yr-old male with newly diagnosed HIV/AIDS presented with headache and aseptic meningitis. Initially treated for TB until CSF/BAL grew *C immitis*. Treated with fluconazole and discharged to nursing home. Pt last seen on 4/07/03 but current status is uncertain.	NA	1100 WBC (15 P) Glu: 17 mg/dL TP: 220 mg/dL	CSF: Pos BAL: Pos	Serum ELISA IgG/M: Pos/Neg Serum CF: ND CSF ELISA IgG/M: Pos/Neg CSF CF: ND	Diffuse pulm infiltrates (disseminated nodules)	Fluconazole	Unknown
15	11/9/06	44-yr-old male with previous hx of HIV/AIDS (off HAART × 2 yr) presented with 6 wk of fever, headache skin lesions and cough. Improved following fluconazole and AmB; however, subsequently developed hydrocephalus requiring a VP shunt. Pt last seen on 2/16/10; requiring assistance but stable on HAART and po fluconazole.	98	40 WBC (0 P 13 EOS) Glu: 29 mg/dL TP: 49 mg/dL	CSF: Neg	Serum ELISA IgG/M: Pos/Pos Serum CF: 1:16 CSF ELISA IgG/M: ND/ND CSF CF: < 1:1	BL pulm nodules + mediastina adenopathy	Fluconazole AmB LamB Surgery: + VP shunt for hydrocephalus	Abacavir Lamivudine Ritonavir Darunavir
27	7/9/07	37-yr-old male with HIV/AIDS with primary syphilis and coxy pneumonia. CM was diagnosed on subsequent admission with relapse of aseptic meningitis and + *C immitis* serology. Pt treated with IV fluconazole and successfully transitioned to po azole. Alive and last seen 5/24/09.	182	8 WBC (95 L) Glu: 49 mg/dL TP: 57 mg/dL	CSF: Neg	Serum ELISA IgG/M: Pos/Pos Serum CF: 1:512 CSF ELISA IgG/M: Neg/Neg CSF CF: < 1:2	RUL mass with cavity and associated nodules	Fluconazole AmB	Tenofovir Emtricitabine Lopinivir/ Ritonavir

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28	9/9/06	33-yr-old male with previous pulmonary coxy (1991) presented in 6/2006 with CM. Initially treated with voriconazole but relapsed in 7/07 with recurrent seizures. Had placement of Ommaya reservoir in 9/07 with subsequent IT AmB treatment. Pt last seen 1/08/10 and stable on fluconazole (1200 mg Qd) and HAART.	34	240 WBC (64 L; 34 M) Glu: 32 mg/dL TP: 190 mg/dL	CSF: Neg	Serum ELISA IgG/M: Pos/Pos Serum CF: 1:16 CSF ELISA IgG/M: Pos/Pos CSF CF: ACNS	Neg	Voriconazole Fluconazole AmB (2 cycles of AmB) IT AmB Surgery: Ommaya reservoir	Tenofovir Emtricitabine Lopinivir/ Ritonavir

Abbreviations: See previous tables. Dx = diagnosis, Diff = differential, Max = maximum, NA = not available, ND = not done, Pulm = pulmonary, Rit = ritonavir, RUL = right upper lobe, TBBX = transbronchial biopsy.

*Receiving antiretroviral therapy at time of CM diagnosis; 2 of these pts (Pt #3, #4) subsequently died, and 1 pt (Pt #6) was lost to follow-up. In the remaining pts, antiretroviral therapy represents treatment at last known follow-up.

serology (for example, positive ELISA IgG/IgM, CF) or grow *C immitis* from 1 or more sites. Therapy of CM in HIV-infected patients is similar to that of non-HIV cases. In those with mild to moderately severe disease, high-dose fluconazole (≥800 mg/d) is the appropriate initial therapy, with dose-escalation in those who do not respond to the initial regimen. In patients with more severe disease, especially those with evidence of extrameningeal dissemination, a course of parenteral amphotericin B may be appropriate. Voriconazole remains an option for individuals who fail fluconazole; however, because of drug interactions (CYP450), the use of long-term voriconazole may require therapeutic drug monitoring in those on selected HIV antiretroviral agents (for example, protease inhibitors, efavirenz). As with non-HIV cases, some patients fail high-dose azole therapy and require a course of intrathecal amphotericin B to stabilize the disease. Serious complications of CM are equally common in HIV patients, and some individuals will require a VP shunt to manage hydrocephalus. The morbidity and mortality of CM remains high in HIV-infected individuals, and their course is complicated by drug adherence difficulties in those requiring treatment for 2 serious medical conditions.

Study Limitations

Although the outcomes between the 2008 and 1980 cohorts seemed similar, these groups are not strictly comparable and there may be referral bias in the current group (2008 cohort). In the current study, there was a higher incidence of preexisting clinical disorders, a factor that could have skewed our cohort to more adverse outcomes. The study is also hampered by the varied treatment experiences at different sites—these patients were cared for by a large number of individuals with varying levels of experience with CM. Although treatment might not be as consistent as at a single referral center, our experience more likely represents the level of treatment available in the community setting. Widespread availability of oral azoles may also have influenced our referral patterns—we may have received more difficult, complicated cases while patients with "milder" disease remained in community settings. We cannot exclude this possibility; however, the experience in 1 of our hospitals (Olive View Medical Center), a community-based facility, suggests otherwise—our patient mix seems similar to that seen by other colleagues in our community. No matter what the venue of care, our experience confirms that CM remains a difficult-to-treat illness with a high rate of relapse and complications.

Therapy Recommendations

The treatment in the 2008 cohort generally followed recommendations outlined by the Infectious Diseases Society of America and experts in the field.[24,30] In patients with suspected CM, empiric therapy with fluconazole is appropriate pending the initial diagnostic studies. Although there is some disagreement about the optimal starting dose, we prefer a higher initial dose (800–1000 mg/d) when CM is suspected. Whatever the starting dose of fluconazole, dose escalation to higher levels (>1000 mg/d) is appropriate in those who appear to be failing initial therapy. Patients receiving high-dose fluconazole should be monitored for serious side effects such as hepatotoxicity and (rarely) ventricular arrhythmia and adrenal insufficiency. If patients continue to do poorly with a fluconazole regimen, some patients may benefit from a switch to voriconazole. Our experience emphasizes the importance of medication compliance—those who discontinued azole therapy almost always suffered from relapses with the attendant complications.

While the utility of concomitant parenteral amphotericin B therapy is uncertain, we often add this drug in critically ill

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patients or those who have evidence of widespread extrameningeal dissemination. Although the best amphotericin B formulation in this situation remains unclear, we generally prefer high-dose LAmB (5 mg/kg) because of a more favorable toxicity profile and the potential benefits of CNS penetration. For critically ill patients, or those who fail to respond to azole therapy, a trial of intrathecal amphotericin B may be indicated. While the best approach is unclear, treatment via the intracisternal or intralumbar route can be used as described in previously published protocols.[30,59] Intraventricular amphotericin B therapy (via an Ommaya reservoir) also appears beneficial; however, it may be less likely to deliver drug to the site of the infection (for example, basilar cisterns) and is hampered by complications associated with long-term catheter placement (such as bacterial meningitis, obstruction). When using intrathecal amphotericin, it is important to use AmB D, because lipid-associated products have not been approved for intrathecal administration. In general, except for the reservations concerning voriconazole in patients receiving selected antiretroviral agents, recommendations for therapy in HIV/AIDS patients are similar to those in non-HIV patients.

In addition to antifungal therapy, proper management of CM-associated complications remains critical. Individuals who develop worsening headache or altered mental status should have a repeat CT scan to rule out hydrocephalus. Patients with this complication may require a VP shunt and should be seen by a neurosurgeon as soon as possible. The management of complications associated with vasculitis such as stroke remains unclear. Although the long-term benefit is unclear, many practitioners recommend treatment with corticosteroids to ameliorate basilar and perivascular inflammation. An empiric trial of corticosteroids is especially appropriate in patients who suffer severe clinical deterioration or have evidence of life-threatening cerebral herniation.

Summary

To our knowledge, this is the first study comparing management of *Coccidioides* meningitis in the azole era (1993–2008) with a well-defined patient population from the pre-azole era (pre-1980). The clinical presentation of the 2 cohorts was quite similar except for a higher prevalence of Hispanic patients in the current group and the emergence of HIV/AIDS (30% of patients in the current study) as a significant underlying predisposing factor. The laboratory findings were also quite similar except for a lower incidence of peripheral leukocytosis and eosinophilia in the 2008 cohort. Since the advent of azoles, fluconazole and related agents have almost completely supplanted intrathecal amphotericin B in the management of CM. Although azoles have become the first-line therapy of CM, concomitant parenteral amphotericin B is often administered, especially in patients with severe clinical illness and widely disseminated disease. Because intrathecal amphotericin B was rarely used in the 2008 cohort, very few patients had placement of an Ommaya reservoir for intrathecal therapy. Despite the differences in therapy, there did not seem to be major changes in the complications associated with the condition: approximately one-third of patients in the 2008 cohort experienced a stroke or developed hydrocephalus requiring a VP shunt. Morbidity and mortality remain high—over a third of patients in the current cohort died as a consequence of CM, a mortality rate similar to that seen in the pre-azole era. Despite the convenience associated with fluconazole use, these agents are not curative and do not necessarily prevent the more serious complications associated with CM. New therapeutic approaches are required to provide definitive cure of CM without the need for long-term azole suppressive therapy.

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APPENDIX ILLUSTRATIVE CASES

Case 4: CM in a Patient With AIDS

A 32-year-old white man with a history of AIDS (on HAART: abacavir/lamivudine/efavirenz; CD4 = 171 cells/mm^3) presented to the emergency room on May 19, 2002, with a 2-week complaint of "migraine headache" and fever, accompanied by recent (5 d) history of nausea/vomiting, photophobia, and stiff neck. Following initial evaluation, the patient refused a lumbar puncture and signed out against medical advice. He returned 1 day later with "altered mental status" and underwent a repeat head CT scan—this now showed a focal hypodensity in left posterior temporal lobe without evidence of midline shift. A lumbar puncture demonstrated an opening pressure of 50 cm H_2O, a leukocyte count of 793 cells/mm^3 (79% polymorphonuclear leukocytes), total protein of 94 mg/dL, and glucose of 31 mg/dL. A chest radiograph showed bilateral interstitial infiltrates. The patient was started on ceftriaxone, ampicillin, vancomycin, and fluconazole (400 mg IV daily). On the second day of hospitalization, the patient rapidly decompensated, requiring intubation and pressor support. Considering the severity of the illness, the family decided "do not resuscitate" (DNR), and he died 3 days after admission with progressive hypothermia and an episode of ventricular arrhythmia.

All *Coccidioides* serology was negative; however, CSF, sputum, and lung cultures subsequently grew *C immitis*. The autopsy demonstrated a large inflammatory mass (6 cm) in the left lower lobe of the lung containing confluent necrotizing granulomas and spherules consistent with *C immitis*. The central nervous system showed granulomatous meningitis secondary to coccidioidomycosis, with associated cerebral edema and tonsillar herniation. The cause of death was determined to be disseminated coccidioidomycosis secondary to AIDS.

Comment: This case demonstrates several features of CM in HIV-infected individuals. In HIV patients with meningitis from coccidioidomycosis-endemic areas, the presence of diffuse pulmonary infiltrates or a miliary pattern on chest radiograph might be clues to the diagnosis of CM. The CSF results may mimic bacterial meningitis with an elevated leukocyte count with polymorphonuclear predominance. *Coccidioides* serologies may be negative, reflecting recent onset of symptoms (seroconversion may take 6–12 wk) or the failure to develop a serologic response in HIV/AIDS patients (up to 20% of patients). The role of HAART in preventing disseminated coccidioidomycosis is unclear—this patient developed CM despite excellent control of the HIV infection. Although he received antifungal therapy on the second emergency room visit (intravenous fluconazole), the poor outcome is not surprising considering the rapid progression of symptoms and the onset of severe brain edema. Although intrathecal or parenteral amphotericin may be helpful in seriously ill patients, it is unlikely that amphotericin would have changed the clinical course in this case. With the increasing number of HIV-infected patients in the American Southwest, disseminated coccidioidomycosis with CM is likely to be a continuing problem in this population.

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Case 21: Disseminated Coccidioidomycosis in Pregnancy With Subsequent CM

A 30-year-old white woman with a past medical history of asthma presented during her 26th week of pregnancy with fever, hip pain, and diffuse pulmonary infiltrates. She became progressively hypoxic and developed respiratory failure, requiring intubation and mechanical ventilation. Biopsy of a lytic hip lesion demonstrated *C immitis*; a serum *Coccidioides* CF titer was 1:32. Given her pregnant status, she was initially treated with intravenous amphotericin B rather than fluconazole. Her hospital course was complicated with multiorgan failure, fetal demise (requiring a dilatation and curettage) and renal failure (secondary to amphotericin B); however, she gradually recovered and was ultimately discharged from the hospital on voriconazole therapy. Her first lumbar puncture (after having already received several weeks of voriconazole) was negative and showed no evidence of CM. The patient's compliance with the voriconazole was poor, and 1 year later she was readmitted to the hospital with headache and CSF pleocytosis. CM was diagnosed, and she was re-treated with intravenous amphotericin B and fluconazole. After a second attempt to reintroduce voriconazole failed, the patient was eventually transitioned to oral fluconazole (800 mg po daily). More recently, she developed persistent back pain and was found to have lower lumbar arachnoiditis (L2, L4-L5 on MRI scan) with a normal neurologic examination. She received a brief (1 wk) course of LAmB and was discharged on a combination of oral fluconazole (400 mg po daily) and posaconazole (200 mg po twice daily). At last follow-up the patient was stable on this regimen with minimal back pain, and had no evidence of neurologic deterioration.

Comment: This case was originally reported in 2007 with an emphasis on the initial clinical presentation and associated fetal loss.[28] Our report outlines her subsequent course, including the development of CM approximately 1 year later. As predicted in the original report, her later course was marked by periodic relapses, often related to medication intolerance or poor compliance with an azole regimen. Although pregnancy does not appear to be a risk factor for primary coccidioidomycosis, pregnant patients with coccidioidomycosis have a higher rate of dissemination compared to "normal" hosts (10% vs. 1%).[10] In this situation, CM is the most common site of extrapulmonary dissemination and is especially likely during the third trimester. The increased risk for dissemination during the latter stages of pregnancy is probably related to the hormonal changes and increased immunosuppression (due to lower CD4 T-lymphocyte counts) seen during this period.[58] In a literature review of over 80 published cases of coccidioidomycosis in pregnancy, fetal or maternal demise was seen in up to 70% of patients; these figures are considerably better in the modern era, probably related to earlier diagnosis and more effective antifungal therapy.[19] CM treatment during pregnancy is problematic because of the known association of azole agents with teratogenicity. Although short course (<10 d), low-dose (<700 mg daily) fluconazole appears relatively safe in pregnant women,[42] prolonged use of high-dose fluconazole during pregnancy has been associated with Antley-Bixler syndrome, a cluster of fetal craniofacial and skeletal abnormalities linked to azoles.[50] The risk of azole therapy is especially high during the first trimester of pregnancy when the fetus has the greatest risk of developing the characteristic skeletal abnormalities. Although data are limited, some experts believe that azole therapy may be safe in late stages of pregnancy, when fetal skeletal development is less likely to be affected.[58] Several decades of experience with amphotericin B suggest that this drug is safe during pregnancy and can be given without concern for teratogenicity. During the first trimester, every effort should be made to avoid azole therapy and to use intrathecal or parenteral amphotericin B.[45]

Case 23: CM Masquerading as Carcinomatous Meningitis

The patient was a 42-year-old African American man without significant past medical history who presented to Olive View Medical Center with bizarre behavior and acute mental status changes. On brain MRI the patient had bilateral enhancement of the basal ganglia and sylvian fissures. A CT of the chest demonstrated "right middle lobe linear air space opacity with nodularity and possible cavity"; however, no biopsy was performed, and the cause of the lung lesion was unclear. CSF cytology revealed what appeared to be malignant cells, compatible with carcinomatous meningitis. Flow cytometry of CSF sent to an outside laboratory demonstrated LCA (leukocyte common antigen) positive/CD20 positive cells, a finding believed to be highly suggestive of B-cell lymphoma. Because of this finding, carcinomatous meningitis from unknown primary (most likely B-cell lymphoma) was diagnosed, and the patient was started on intrathecal methotrexate and corticosteroids. On this regimen, the patient failed to show improvement, and he was transferred to another hospital for placement of an Ommaya reservoir and chemotherapy infusion. His mental status continued to worsen, and he developed hydrocephalus requiring placement of a VP shunt. The patient died 2 days after surgery secondary to brainstem herniation. At autopsy, the patient was found to have disseminated coccidioidomycosis with CM; there was no evidence of CNS lymphoma.

Comment: This patient's clinical presentation demonstrates how CM can mimic other disease processes, including carcinomatous meningitis. The initial misdiagnosis was related to the negative CSF cultures and the failure to obtain serologies for *C immitis*. This was compounded by the abnormal CSF cytology and flow cytometry results suggesting the diagnosis of CNS lymphoma. The patient's clinical status was likely made worse by the subsequent chemotherapy (with corticosteroids) and failure to start empiric antifungal treatment. Only at postmortem was a there a clear diagnosis of CM leading to withdrawal of the CNS lymphoma diagnosis. Another patient (Patient 30) presented with a somewhat similar issue. Initial studies (bronchoalveolar lavage with sputum fungal culture, CSF fungal culture, CSF/blood serologies) were negative for coccidioidomycosis; however, a subsequent CSF cytology suggested the possibility of CNS lymphoma. There was a delay in antifungal therapy, and consideration was given to starting antineoplastic chemotherapy. The diagnosis of CM became apparent when an earlier CSF sample (taken 1 mo *after* the initial presentation) began to grow *C immitis*. Following the return of these culture results, the interpretation of the CSF cytology was revised to "benign, most likely inflammatory." In a patient with possible CM, great care must be exercised in CSF analysis: over-reliance on CSF cytology may lead to a false diagnosis of carcinomatous meningitis.

Case 26: CM Failing Fluconazole With Subsequent Response to Voriconazole Therapy

A 25-year-old previously healthy Hispanic woman presented to Olive View Medical Center with a several-week history of headache, nausea/vomiting, and fever. On examination she was confused and had nuchal rigidity. Chest radiograph and head CT were normal. Examination of the CSF showed an opening

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pressure of 200 mm H_20 with 700 leukocytes (92% lymphocytes), glucose of <32 mg/dL, and a total protein of 242 mg/dL. CSF cultures were negative but CM was confirmed by serology (serum/CSF ELISA +; serum CF 1:16; CSF CF 1:8). She improved on intravenous fluconazole and was discharged on oral fluconazole, 800 mg po daily. Despite stated adherence to this regimen, she returned with an episode of recurrent meningitis in October 2004, and was treated in-hospital with intravenous LAmB and oral voriconazole (200 mg po twice daily). She did well on oral voriconazole as an outpatient; however, she developed a possible photosensitivity reaction and was switched back to fluconazole (800 mg po daily). Despite adherence to this regimen, she returned 3 months later with recurrent meningitis. The patient again responded to intravenous amphotericin B and voriconazole and was discharged on oral voriconazole. At last follow-up she remained clinically stable on voriconazole (200 mg po twice daily) with normalization of her CSF parameters, except for a positive CSF ELISA (+IgG/+IgM).

Comment: This case is similar to several other reports in the literature and represents the potential benefit of voriconazole in patients who have failed or are intolerant of fluconazole therapy.[17,48,49] As alluded to earlier, the optimal dose of fluconazole in CM is unclear and is likely to vary from patient to patient. In addition to intolerance of the agent, failure of the drug may be secondary to subtherapeutic levels due to inadequate absorption or poor patient compliance. Although not assessed in this patient, serum fluconazole levels may be helpful if there is a question about drug absorption or medication adherence. Voriconazole is not approved for treatment of endemic mycoses; however, it has good in vitro activity against *C immitis*, and its pharmacokinetic profile (95% oral availability; low protein binding; good CSF/tissue penetration) suggests it would be a reasonable choice for treatment of this condition.[29] Voriconazole can be given initially via an intravenous route (6 m/kg for 2 doses, then 4 mg/kg IV Q12 hr) followed by oral therapy (200 mg po twice daily). Higher oral doses (300 mg po twice daily) can be used, but these may have a higher rate of side effects. Recent studies in patients with invasive mycoses suggest a wide range of voriconazole blood levels following standard dosing.[44] In selected cases, therapeutic drug monitoring (serum levels) may be helpful in documenting adequate serum levels (>1 μg/mL) or explaining side effects secondary to toxic levels (>5 μg/mL). In our experience, the photosensitivity reaction may be serious; however, in most cases symptoms can be ameliorated by using sunblock or protective clothing to reduce light exposure.

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