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Diagnosis and Management of Central Nervous System Histoplasmosis

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Two cases of *Histoplasma* meningitis are presented, illustrating the difficulty in diagnosis and treatment. The first case occurred in a patient with acquired immunodeficiency syndrome as a relapse of disseminated histoplasmosis and resolved after prolonged treatment and ongoing antiretroviral therapy. The second case occured in a cardiac allograft recipient as meningitis and focal brain lesions that responded to liposomal amphotericin B, but the patient died shortly after therapy was completed. Unfortunately, there are no prospective studies addressing the diagnosis and management of patients with histoplasmosis of the central nervous system from which to provide evidence-based guidelines for care. In the absence of such data, an approach will be presented on the basis of our experience and opinions.

CNS involvement is clinically recognized in 5%–10% of cases of progressive disseminated histoplasmosis (PDH) [1]. Clinical syndromes include subacute or chronic meningitis, focal brain or spinal cord lesions, stroke syndromes, and encephalitis. CNS involvement may be a manifestation of widely disseminated disease or an isolated illness, occurring as the initial manifestation of PDH or relapse at a "privileged" body site poorly penetrated by antifungal therapy. Often, the diagnosis is not suspected, leading to chronic, untreated infection and, in some cases, to placement of ventricular shunt for normal-pressure hydrocephalus.

The diagnosis should be suspected in patients with chronic meningitis or parenchymal lesions for which results of tests for other causes are negative, particularly if the patient has been to areas where histoplasmosis is endemic. Once diagnosis is suspected, a panel of tests is needed to achieve the highest sensitivity for diagnosis. The optimal management is uncertain, but, given the high rates of failure of initial therapy (~20%) and relapse in the next few years (~40%) [1], an aggressive approach is recommended. Two cases will be reviewed to illustrate some of the difficulties in diagnosis and management of CNS histoplasmosis.

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CASE REPORTS

Case 1. The first patient was a 29-year-old Guatemalan woman with advanced AIDS complicated by multiple prior opportunistic infections who presented with PDH in October 1998, when her CD4 cell count was 2 cells/mm^3. Her condition responded to treatment with amphotericin B for 2 weeks followed by itraconazole treatment, 200 mg twice daily. Treatment with abacavir and efavirenz, 2 new antiretroviral agents to which she had not already failed to respond or become intolerant, was also started. Thereafter, her HIV-1 viral load was undetectable (<400 copies/mL). The itraconazole blood concentration in May 1999 was 2.16 μg/mL, which is consistent with therapeutic blood levels reported for this dosage [2]. In June 1999, histoplasmosis relapsed as meningitis, at a CD4 cell count of 66 cells/mm^3. The patient was fully adherent to antiretroviral and itraconazole therapy, but itraconazole concentrations were not determined at the time of relapse. The diagnosis was made on the basis of a *Histoplasma* antigen elevation in CSF of 4.6 ELISA units (EU), as well as symptoms and CSF profile, which unequivocally improved with amphotericin B therapy. The *Histoplasma* antigen was also present in serum, at 2.1 EU. Tests for antibodies to *Histoplasma capsulatum* were not performed, and fungal cultures of CSF were negative. The patient received 35 mg/kg once daily of amphotericin B over the next few months, after which the CSF was normal and *Histoplasma* antigen was not detected. Treatment with amphotericin B was then switched to treatment with fluconazole, 800 mg/day by mouth. In October 2001, her CD4

cell count was 419 cells/mm^3 and CSF was normal, so fluconazole treatment was discontinued. She remains healthy as of December 2004, with a CD4 cell count of 559 cells/mm^3 and a viral load of <50 copies/mL.

This case illustrates 4 features of diagnosis and management of CNS histoplasmosis: PDH relapsed as meningitis after successful treatment of PDH not involving the CNS; diagnosis was made on the basis of antigen detection; cure was achieved with amphotericin B followed by high-dose fluconazole treatment; and antifungal maintenance therapy was successfully withdrawn after immune reconstitution in response to antiretroviral therapy, as emphasized in another report [3].

Case 2. The second patient was a 73-year-old white man who underwent cardiac transplantation 11 years earlier and presented with a history of a few weeks of confusion, lethargy, and weakness and 1 week of fever. His medications included prednisone, cyclosporine, and mycophenolate. Initially, he was alert, and findings of a neurological examination were normal, but, within a few hours, he exhibited aphasia with unintelligible speech. He was admitted to the hospital with suspected cerebrovascular insufficiency and was treated with heparin. MRI of the brain showed atrophic changes and widespread punctuate foci that enhanced with gadolinium throughout both parietal and occipital lobes, involving gray and white matter. A CSF sample obtained on the hospital day 5 revealed 36 leukocytes/mm^3, of which 86% were mononuclear; a glucose level of 53 mg/dL; and a protein level of 126 mg/dL. Liposomal amphotericin B treatment was started on the hospital day 8, when a urine sample was reported to be positive for *Histoplasma* antigen, at 1.78 EU. A brain lesion was biopsied that day, and the specimen later revealed organisms consistent with *H. capsulatum*. Subsequently, a CSF sample was reported to be positive for *Histoplasma* antigen, at 6.04 EU, whereas the results of tests for anti-*Histoplasma* antibodies were negative. However, a serum sample was negative for the antigen, at 0.45 EU. Titers of anti-*Histoplasma* complement-fixing antibodies in serum were 1:64 to the mycelial antigen and 1:16 to the yeast antigen, and *Histoplasma* M precipitin was identified by immunodiffusion. Results of fungal cultures of blood and CSF were negative, but brain tissue was not cultured. Treatment with immunosuppressive medications was continued, and liposomal amphotericin B, 5 mg/kg/day, was given for 35 days, for a total dose of 15 g, at which time the neurological and mental-status abnormalities had largely resolved. High-dose fluconazole therapy, 200 mg daily, was started on the basis of impaired renal function, but, 2 days later, confusion and lethargy recurred, and MRI of the brain showed large bilateral subdural fluid collections. Surgical therapy was not felt to be appropriate, and the patient died a few days later.

As does case 1, this case illustrates the useful role of antigen detection for diagnosis, since it was the basis for initiation of antifungal therapy. This case also shows the poor prognosis for patients with CNS histoplasmosis, since the patient died despite high-dose liposomal amphotericin B therapy.

DISCUSSION

Approach to diagnosis of meningitis. These cases provide insight into the approach to diagnosis of CNS histoplasmosis. Of note is that no single test exhibits high sensitivity, which supports the use of multiple tests. Also important is the possibility of false-positive results from non–culture-based tests, including the *Histoplasma* antigen assay [4]. The sensitivity and specificity of the commonly used diagnostic tests are summarized in table 1 [1, 5–11]. Although diagnosis may be simple for patients with widely disseminated PDH—since organisms may be identified in multiple organs—difficulty occurs for those with isolated CNS involvement. For such patients, positive results may only be found with testing of the CSF, meninges, or brain tissue. Several cases have been reported in which a single positive culture result was obtained from ⩾10 specimens that were submitted, and the positive result was from culture of 15–43 mL of CSF [1, 12]. Thus, at least 10 mL of CSF should be cultured, to increase the sensitivity for isolating small numbers of yeast organisms (table 2). Although PCR is suited for detection of low concentrations of yeast, its use in diagnosis of histoplasmosis remains uncertain, and there are no reports of using PCR for diagnosis of *Histoplasma* meningitis. Without validation of PCR by comparison with the standard methods, the accuracy of PCR findings remains unknown, and their significance for patient management remains uncertain; a positive result should not be assumed to support the diagnosis, or a negative result to exclude it.

The antigen test developed by one of us (L.J.W.) has been used for diagnosis in several reported cases of CNS histoplasmosis [12–16]. The antigen test assisted in the diagnosis of CNS histoplasmosis in both of the cases reported here. Also, both cases exhibited higher antigen values in the CSF sample than in serum or urine samples, consistent with antigen production in the CNS, rather than passive diffusion from the serum in the presence of a breakdown of the blood-brain barrier or contamination of the CSF with blood caused by a traumatic lumbar puncture.

In earlier reports, the sensitivity of antigen detection was 38% in all patients [1, 9] and 67% in those with AIDS [10], but it may be higher for the assay being used currently. As evidence of the improvement in sensitivity of the antigen assay, 6 of 18 urine specimens that yielded false-negative results with the assay used in earlier reports yielded positive results with the assay we used. The sensitivity of the 2 assays for CSF has not been reported (L.J.W., unpublished data). Cross-reactions occur in blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection [17], and false-positive results may be caused by interfering

Table 1. Summary of the reported sensitivity and specificity of tests for diagnosis of *Histoplasma* meningitis.

	Sensitivity		Specificity	
Test	Proportion (%) of case patients[a]	Reference	Proportion of control subjects[b]	Reference
CSF culture	4/15 (27)	[1], Ind.	(100)	[5]
	26/40 (65)	[1], Lit.		
Meningeal or brain culture	1/2 (50)	[1], Ind.	(100)	[5]
	11/14 (79)	[1], Lit.		
Blood culture	7/13 (54)	[1]	…	
Bone marrow culture	4/12 (33)	[1]	…	
Culture at any site	13/17 (76)	[1]	…	
CSF antibody	8/10 (80)	[1]	30/36 (83)[c]	[6]
	8/9 (89)	[6]		
Serum antibody	12/13 (92)	[1]	342/357 (96)[d]	[7]
			74/90 (82)[d]	[8]
CSF antigen	6/15 (38)		27/28 (96)	[9]
	6/9 (67)	[1, 10], AIDS sub.		
Urine antigen	10/14 (71)	[1]	95/96 (99)	[11]
Serum antigen	6/16 (38)	[1]	(~98)[e]	[4]

NOTE. Whereas isolation of the organism from culture is generally specific, barring a specimen mix-up or incorrect identification of the fungus as *Histoplasma capsulatum,* isolation from a non-CNS site is not specific for CNS involvement. However, a positive culture result for a sample from a non-CNS site would provide strong evidence that histoplasmosis was the cause for the CNS disease, if other causes were excluded. AIDS sub., results from a subset of patients with AIDS; Ind., Indiana series; Lit., literature series.

[a] No. of case patients with a positive test result/total no. of case patients (%).

[b] No. of control subjects with a negative test result/total no. of control subjects (%).

[c] Cross-reactions noted in CSF of 5 (28%) of 18 patients with cryptococcal meningitis [6].

[d] Complement-fixation antibody titers of ⩾1:8 in healthy controls without fungal infection [7] or with other fungal diseases [8].

[e] Although rare, false-positive results occur more frequently in testing of serum because of the presence of interfering substances, such as rheumatoid factor, heterophil antibodies, and anti-rabbit antibodies [4].

substances, as was reported recently for antigenemia [4]. Interfering substances may include human anti-rabbit antibodies, rheumatoid factor, or heterophil antibodies.

Serologic tests for anti-*Histoplasma* antibodies in the CSF are also helpful, having positive results in up to 80% of cases [1, 18]. Of note is that positive complement-fixing antibody titers in the CSF may be at low dilutions, and titration must begin with undiluted CSF. However, the antibody response may be impaired in immunosuppressed individuals—for example, in patients with PDH, anti-*Histoplasma* antibodies were present in serum in samples from 67% of patients with AIDS, 80% of those with other immunosuppressive disorders, and 86% of those without underlying immunosuppression [5, 19]. It is conceivable that immunosuppression could result in lower sensitivity of CSF serologic tests as well. Serologic tests also may have false-positive results due to cross-reactions caused by infection with other fungi, including *Cryptococcus neoformans* [6]. Results of the complement-fixation test were positive at titers of ⩾1:8 for serum samples from ~4% of individuals without fungal infection [7] and 18% of those with other mycoses [8], whereas the immunodiffusion test was positive less frequently in 0.5%–5% of patients. Though false-positive antibody test results usually are at low titers of 1:8 or 1:16, true-positive and false-positive results overlap.

Testing of non-CNS specimens may also be useful, especially for patients with widely disseminated PDH. These tests include biopsy of other sites of suspected involvement, for histopathologic examination and culture; serologic testing of serum for anti-*Histoplasma* antibodies; and antigen testing of blood and urine. In patients without clinical findings of disseminated disease involving sites other than the CNS, results of tests for antigen and cultures of specimens from such sites would be expected to be negative. However, studies have not been reported that compare these parameters in cases in which the CNS is involved with and without involvement of other sites. Evidence for involvement of non-CNS sites would include laboratory findings indicating bone marrow or liver involvement, hepatosplenomegaly, lymphadenopathy, skin or mucous membrane lesions, or less-common findings suggestive of involvement of other tissues.

Since antigen detection and serologic testing are indirect, non–culture-based methods, the possibility of a cross-reaction or false-positive result must be recognized, which emphasizes the need to obtain supportive laboratory results, to carefully correlate the results with the clinical and epidemiological fea-

Table 2. Recommendations for evaluation of suspected *Histoplasma* meningitis.

Specimen type, class of case, recommended test or procedure
CSF; all cases, repeat at least once, and preferably twice, if there is no diagnosis
Culture of a large-volume sample (>10 mL)
Histoplasma antigen testing
Anti-*Histoplasma* antibody testing by complement fixation, beginning with undiluted CSF
Blood; all cases
Fungal culture, 3 sets
Histoplasma antigen testing, to assist in determination if CSF antigen positivity may have been caused by contamination of the CSF with blood
Anti-*Histoplasma* antibody testing
Urine; all cases
Histoplasma antigen testing
Biopsy of non-CNS site, if there is a clinical or laboratory finding indicating involvement at the site
Histopathologic examination for fungi
Fungal culture
Cisternal or ventricular fluid, if the diagnosis is uncertain after the performance of the evaluations above
Histopathologic examination for fungi
Fungal culture
Histoplasma antigen
Anti-*Histoplasma* antibody
Brain or meninges, if the diagnosis is uncertain after the performance of the evaluations above
Histopathologic examination for fungi
Fungal culture

tures, and to evaluate the response to antifungal therapy. Furthermore, repeat testing is recommended to verify the initial result, to increase the reliability of the indirect tests.

If the initial evaluation fails to yield a diagnosis, the diagnostic workup should be repeated at least once, including culture of at least 10 mL of CSF. If the results remain nondiagnostic, more invasive methods may be justified. Cisternal or ventricular fluid analysis [12, 20, 21] or biopsy of brain lesions or involved meninges have been helpful in such cases [1]. For severely ill patients, biopsy may be preferred over additional CSF evaluation, to obtain definitive results more quickly, at which time a large volume of CSF should be obtained. Empiric antifungal therapy may be appropriate while awaiting results of the biopsy. If empiric therapy is instituted without biopsy, a large volume of CSF should be obtained for culture before therapy is initiated.

Treatment of meningitis. The optimal treatment for CNS histoplasmosis in unknown. Unfortunately, prospective studies from which an evidence-based approach can be formulated have not been conducted yet. The guidelines provided here are our opinions and are based on our experience and on the literature illustrating the poor outcome of CNS histoplasmosis [1]. Liposomal amphotericin B achieves higher concentrations in brain tissue than does the standard deoxycholate formulation and was a more effective treatment of PDH in patients with AIDS [22]. Also, reduced nephrotoxicity allows more-aggressive dosing.

The role of the triazoles is also unclear. Fluconazole achieves high concentrations in the CSF and has been used successfully for treatment of *Histoplasma* meningitis (table 3) [12, 20, 27, 29, 31], but there also have been failures [23, 28]. Itraconazole does not penetrate the CSF, but was effective in an experimental model of *Histoplasma* meningitis [32]. There are also reports of success [14, 21, 23, 25, 26] and failure [2, 24] in using itraconazole for treatment of *Histoplasma* meningitis in patients. A summary of outcomes of triazole therapy for CNS histoplasmoma is shown in table 4.

The role of combination treatment with amphotericin B and itraconazole or fluconazole was studied in a murine model. Fluconazole antagonized amphotericin B, whereas no adverse interaction occurred with itraconazole [32]. The question of whether the addition of itraconazole could improve the clinical outcome of treatment with amphotericin B was not thoroughly investigated, however, which precludes recommendation of combination treatment.

Therapy should be aggressive and prolonged. Recommendations are summarized in table 5. Liposomal amphotericin B treatment is recommended at 3–5 mg/kg/day for a total dose of 100–150 mg/kg for 6–12 weeks. Then, treatment could be switched to high-dose fluconazole (600–800 mg daily, adjusted for renal function) or itraconazole (200 mg 2 or 3 times daily), to complete at least 1 year of therapy. In the presence of severe immunodeficiency that cannot be reversed, life-long maintenance therapy may be required. Until recently, maintenance therapy was the standard of care for patients with disseminated histoplasmosis who also had AIDS. Recent results of a treatment withdrawal study show that maintenance therapy can be stopped for patients who have achieved a good immune response, indicated by a CD4 cell count of >150 cells/mm^3 [37]. Of note is that the study excluded cases with CNS involvement. The first case in the present report illustrates sustained remission off antifungal therapy in a patient with AIDS who achieved a CD4 cell count of 559 cells/mm^3 in response to antiretroviral therapy [3], and experience with cryptococcal meningitis in patients with AIDS supports the safety of discontinuation of maintenance therapy for patients who have achieved immune reconstitution [38]. Patients with CNS histoplasmosis and AIDS or other immunosuppressive disorders that are felt to have achieved immune reconstitution, and in whom discontinuation of maintenance therapy is under consideration, should have received at least 1 year of antifungal therapy and should demonstrate clearance

Table 3. Reported outcomes of triazole therapy for *Histoplasma* meningitis: summary of individual case reports.

Triazole, reference	Underlying disease or condition	Type of therapy[a]	Triazole dosage	Treatment outcome; comment
Itraconazole				
[2]	AIDS	Primary	400 mg daily for 2 weeks	Failure; itraconazole concentration 1.8 μg/mL
[23]	AIDS	Primary	400 mg daily for 16 months	Success
[3] (PR case 1)	AIDS	Secondary (primary was AmB for 2 weeks)	400 mg daily for 5 months	Failure; lapse in adherence
[24]	AIDS	Secondary (primary was AmB 0.3 g total)	400 mg daily and AmB 40 mg weekly for 2 months	Failure
[25] (CPC)	AIDS	Secondary (primary was AmB 1 g total)	Unknown dosage for 6 months	Success
[14]	Renal TR	Secondary (primary was AmB, prolonged)	Unknown	Success
[26]	None	Secondary (primary was AmB 25 mg/kg total)	Unknown dosage for 3 years	Success
[21]	SLE	Secondary (primary was AmB 2.5 g total)	400 mg daily for 9 months	Success
Fluconazole				
[20]	None	Primary, combined with AmB for 2 weeks	200 mg daily for 1 year	Success; also shunt replaced
[27]	AIDS	Primary	800 mg daily for 8 months	Success
[23]	AIDS	Primary	400 mg daily for 3 months	Failure; death of patient
[3] (PR case 1)	AIDS	Secondary (primary was AmB 35 mg/kg total)	800 mg daily for 2 years	Success
[28]	AIDS	Secondary (primary was AmB 0.6 g total)	100 mg daily for 2 months	Failure
[28]	AIDS	Secondary (primary was AmB 1.0 g total)	50–100 mg daily for 1 month	Failure
[12]	None	Secondary (primary was AmB 2.5 g total)	600 mg daily for 1 year	Success; also shunt removed
[16]	None	Secondary (primary was AmB 2 g total)	400 mg daily for 6 months	Success
[13]	None	Secondary (primary was AmB for 75 days)	400 mg daily for 1 year	Success
[29]	None	Salvage (previously failed AmB 1.5 g and 0.8 g total)	200 mg daily for 5 months	Success; also shunt removed
Voriconazole				
[30][b]	None	Salvage (failure of AmB, L-AmB, itraconazole, fluconazole)	Unknown	Failure
Posaconazole				
[30][b]	None	Salvage (failure of voriconazole)	800 mg daily for unknown time	Success

NOTE. AmB, amphotericin B; CPC, clinical pathology conference; L-Amb, liposomal amphotericin B; PR, present report; SLE, systemic lupus erythematosus; TR, transplantation.

[a] Primary therapy indicates initial treatment; secondary indicates continued treatment followed by initial response to another antifungal agent, usually amphotericin B; and salvage indicates treatment after failure of other regimens.

[b] Same case.

of CNS lesions by neuroimaging procedures, normalization of CSF abnormalities, and undetectable levels of *Histoplasma* antigen in all fluids in which it was previously detected, including CSF.

Measurement of blood concentrations of the triazole early in the course of therapy is recommended. This is especially important when using itraconazole, because of the extreme variability in blood concentrations observed for the same dosage of itraconazole [2]. With a dosage of 200 mg twice daily, blood concentrations should be at least 1 μg/mL; lower concentrations should prompt evaluation of adherence and potential drug interactions with medications that reduce the ab-

Table 4. Reported outcomes of triazole therapy for CNS histoplasmoma: summary of individual case reports.

Triazole, reference	Underlying disease or condition	Type of therapy[a]	Triazole dosage	Treatment outcome; comment
Itraconazole				
[33]	None	Primary	200 mg iv for unknown time	Failure; patient later responded to AmB 2.0 g followed by itraconazole 400 mg for 4 months
[34]	Diabetes	Primary	400 mg daily for 1 year	Success
[24][b]	AIDS	Secondary (primary was AmB 0.3 g total)	400 mg daily and AmB 40 mg for 2 months total	Failure
[33]	MDS	Secondary, ABLC for 6 days	Unknown dosage for 6 days	Patient died
[33]	AIDS	Secondary (primary was AmB 1.0 g total)	400 mg daily for 8 months, then 200 mg daily maintenance	Success
[35]	None	Secondary (primary was AmB 45 mg/kg total)	400 mg daily for unknown time	Success
Fluconazole				
[27]	AIDS	Primary	800 mg daily for unknown time	Success
[33]	None	Secondary (primary was AmB 2.0 g total)	400 mg daily for 6 months	Success
[16]	None	Secondary (primary was AmB 2.0 g total)	400 mg daily for 6 months	Success
[36]	None	Salvage (failed AmB and keto)	400 mg daily for 4 months	Success
Voriconazole				
[15]	None	Primary, with L-AmB and intrathecal AmB	400 mg daily for 3 months	Success; also abscess drained

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; keto, ketoconazole; L-AmB, liposomal amphotericin B; MDS, myelodysplastic syndrome.

[a] Primary therapy indicates initial treatment; secondary indicates continued treatment followed by initial response to another antifungal agent, usually amphotericin B; and salvage indicates treatment in cases failing other regimens.

[b] Same case from [24] listed in table 3.

sorption or enhance the metabolism of itraconazole. If no cause for the low concentration can be determined, and if a second measurement confirms the low result, then the treatment options would include the use of the solution formulation of itraconazole and an increase in the dosage to 200 mg 3 times daily. Ideally, concentrations should be measured at their nadir just before the next dosage of itraconazole, but the concentrations vary little over time because of the long serum half-life of itraconazole. Fluconazole concentrations are more predictable, and do not show much intersubject variability. Although the authors prefer to monitor fluconazole concentrations as well, this recommendation is not evidence based. Situations in which measurement of fluconazole concentration may be more important include the use of high-dosage fluconazole in patients with renal impairment and the evaluation of the cause of treatment failure or relapse. In adult patients receiving 800 mg/day of fluconazole, the expected blood concentration range is 40–100 μg/mL [39].

Hydrocephalus occasionally complicates *Histoplasma* meningitis. In such cases, neurosurgical evaluation is needed for consideration of the placement of a ventricular shunt. Optimally, shunt placement should be delayed until the patient has received at least 2 weeks of amphotericin B treatment, to reduce the likelihood of colonization of the newly placed shunt material. In other cases, the shunt may have been introduced before the meningitis was recognized, raising concern about the ability to cure the infection in the presence of infected foreign material. Patients with shunts should be observed closely for relapse, in which case shunt removal and replacement should be considered.

Follow-up of meningitis. Progression of illness during the first 2 weeks of therapy or lack of improvement in 1 month should prompt a reevaluation of the diagnosis, if not proven by culture, and a review of the adequacy of therapy, including the specific drug formulation and dosage and treatment adherence. Two cases have been reported that responded to courses of amphotericin B at a total dosage of 2.5–5 g, with resolution of clinical findings, but that demonstrated persistent CSF pleocytosis and positive cultures from 2 to 22 years later [40, 41], illustrating the need for follow-up CSF analysis and

Table 5. Recommended treatment for CNS histoplasmosis.

Type of infection	Primary therapy	Secondary therapy
Meningitis or focal lesions in immunosuppressed host or in the presence of PDH in non-CNS sites	Liposomal amphotericin B, 3–5 mg/kg, for a total dose of 100–150 mg/kg, for 6–12 weeks	Itraconazole, 200 mg b.i.d. or t.i.d., for 1 year, or fluconazole, 600–800 mg q.d., for 1 year
Focal lesions without complicating conditions	Amphotericin B, 0.7–1 mg/kg/day, or lipid formulation of amphotericin B, 3–5 mg/kg/day for 2–4 weeks	Itraconazole 200 mg b.i.d. or t.i.d. or fluconazole 600–800 mg q.d. for 6–12 months

NOTE. PDH, progressive disseminated histoplasmosis.

the possible need for long-term triazole treatment. Additional CSF analysis is recommended after the first month of therapy in all cases, and sooner if the patient's condition worsens during the first week of therapy or has not shown some improvement by the end of the second week of therapy. CSF analysis also should be repeated when amphotericin B is replaced with a triazole, if relapse is suspected, and after 1 year of therapy, when the decision must be made to stop or to continue therapy. Persistent pleocytosis or presence of *Histoplasma* antigen in the CSF after 1 year of therapy would support continued therapy until the CSF abnormalities have resolved and, possibly, long-term suppressive therapy.

Treatment of histoplasmoma. The response to therapy of focal brain or spinal cord lesions, so-called histoplasmomas, is variable. Such lesions may be isolated findings of disseminated histoplasmosis, may be associated with meningitis, or may complicate disseminated disease [1]. Although most cases have been treated with amphotericin B, success has been reported with itraconazole [34] or fluconazole [27] alone, as has been failure [33]. In patients who are not severely ill, who do not have meningitis or widespread dissemination, and who have no underlying immunosuppression, a brief course of amphotericin B followed by 1 year of a triazole may suffice. After 2–4 weeks of amphotericin B treatment, MRI of the brain should be repeated. If the patient's condition responded clinically and the lesions improved, as seen on MRI, then treatment with amphotericin B could be replaced with itraconazole, 200 mg 2 or 3 times daily, or fluconazole, 600–800 mg daily. Lesions may appear to worsen during the first month of eventually successful therapy, and this does not mandate a change in the regimen [1]. Also, worsening of CNS lesions may be a manifestation of immune reconstitution in patients with AIDS who initiate antiretroviral therapy (D. Bamberger and S. Norris, personal communication). However, clinical worsening or progressive expansion of or development of new lesions would support a decision to reassess the treatment strategy. For patients with concurrent meningitis, widespread disseminated disease, or underlying immunosuppression, treatment as described above for meningitis is recommended.

Although some patients have undergone excision of CNS lesions [1], the need for surgery in those cases was unclear. Most patients have multiple lesions, not all of which could be safely excised, and most lesions clear with antifungal therapy alone [1, 16, 26, 27, 34–36, 42, 43]. Surgical excision may have been necessary in a case of a spinal cord abscess [15], but we have treated a similar case of spinal cord histoplasmosis causing anesthesia in one leg that resolved with antifungal therapy and dexamethasone alone (L.J.W., unpublished data). Surgery is unnecessary and is not recommended in most cases, and the indications for surgery are unclear.

Salvage therapy for failure of other regimens. For patients whose condition fails to respond to therapy or who experience relapse after treatment is stopped, the first task should be to evaluate adequacy of the initial treatment. If the previous therapy did not follow the guidelines proposed in table 5, additional treatment in accordance with these guidelines should be considered. Direct injection of amphotericin B into the ventricles is poorly tolerated and marginally effective [1], and it is not recommended. For patients whose infection fails to respond to itraconazole or fluconazole treatment, a trial using the newer triazoles may be useful. Voriconazole is active in vitro [44] and penetrates the CSF well, but it failed to cure one case of refractory *Histoplasma* meningitis [30] (table 3). That patient had previously received fluconazole, raising the possibility that cross-resistance to voriconazole was the cause of treatment failure. Posaconazole does not penetrate the CSF but was curative in that case [30]. Long-term suppressive therapy may be needed for patients for whom appropriate therapy repeatedly fails.

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