Therapy of Cryptococcal Meningitis in non–HIV-infected Patients

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Cryptococcus neoformans is the most common cause of fungal meningitis in HIV and non–HIV-infected patients. The organism has a worldwide distribution, with cases typically occurring among patients with well-recognized specific underlying disorders associated with dysfunction of cell-mediated immunity. While the therapy for disease was studied extensively in the 1970s and the 1980s among non–HIV-infected individuals, most of the recently published data have concerned therapy for central nervous system cryptococcosis in HIV-infected patients. As a result, the current approach to therapy for central nervous system cryptococcosis in the non–HIV-infected patient represents a hybrid of the established "gold standard," which includes at least 6 weeks of combination therapy with amphotericin B and 5-flucytosine, and the more contemporary regimen, which consists of 2 weeks of induction therapy with an amphotericin B-containing regimen followed by fluconazole. Clearly, well-designed prospective studies are needed to define the best approach to therapy in these patients, but until then, we must rely on the results of the existing clinical trials and carefully interpret the results of the available retrospective data. At present, amphotericin B (deoxycholate or lipid-associated) is recommended as initial therapy for all non–HIV-infected patients with proven or suspected cryptococcal meningitis. Fluconazole plays an important role in consolidation therapy and among selected patients who require long-term chronic suppression. The potential role of the newer triazoles (voriconazole and posaconazole) is undetermined.

Introduction

Cryptococcus neoformans is a ubiquitous pathogenic encapsulated yeast that causes human disease, ranging from asymptomatic pulmonary colonization to life-threatening meningitis and overwhelming cryptococcemia [1–4]. While disease may occur in normal hosts, the majority of patients have significant, usually advanced, underlying disorders of immune function [4,5]. Prior to the HIV epidemic, most patients with cryptococcosis had identifiable underlying disorders such as glucocorticosteroid treatment, solid organ transplantation, hematologic malignancies, sarcoidosis or other disorders associated with a cell-mediated immune dysfunction [6–8]. However, in the pre-AIDS era, up to 40% of patients with cryptococcosis had no underlying disorder associated with immune dysfunction, although selected defects in lymphocyte responsiveness to *C. neoformans* and other subtle abnormalities have been offered to explain disease occurrence in otherwise normal hosts [9–12].

Meningitis is one of the most common manifestations of infection with *C. neoformans*, and this organism remains the most common fungal pathogen involving the central nervous system (CNS). Even though CNS cryptococcosis is a relatively rare disease in HIV-negative patients, it is one of the best studied of the invasive fungal infections, ranking only behind infections caused by *Candida* species in terms of numbers of patients enrolled in well-controlled clinical trials [7,8,13,14]. Despite the significant number of antifungal compounds developed over the past decade, the relative difficulty in accruing non–HIV-infected patients with cryptococcal meningitis into randomized clinical trials has translated into very slowly changing therapeutic recommendations for this potentially devastating disease.

The standard therapy for cryptococcal meningitis for many years until the mid-1970s was amphotericin B alone. The classic study by Bennett *et al*. [7] established the superior efficacy of combination therapy with amphotericin B and 5-flucytosine for 6 weeks compared with amphotericin B alone for 10 weeks in patients with this disorder. Subsequent studies determined that selected groups of patients could be successfully managed with "short course" combination therapy for 4 weeks, although this approach did not apply to all patients [8]. In recent years, fluconazole, a triazole with excellent in vitro and in vivo activity against *C. neoformans*, has become widely used for the treatment of cryptococcosis since it was approved by the US Food and Drug Administration in 1990 [15]. All subsequent large prospective clinical studies establishing the importance of fluconazole in the management of cryptococcosis have been conducted among HIV-infected patients [13,14]. Similar studies have not been performed in HIV-negative patients, and therefore many of the recommendations and current approaches to management of cryptococcosis in

HIV-negative patients are derived from experience in the HIV-positive population.

Clinical Studies in the Pretriazole Era

Prior to the availability of amphotericin B, cryptococcal meningitis was considered to be uniformly fatal. When amphotericin B deoxycholate became available in the late 1950s, it became the drug of choice for cryptococcal meningitis with success rates of up to 60%. However, successful therapy was often limited by severe nephrotoxicity, electrolyte abnormalities, and infusion-related adverse events.

Two major randomized clinical trials addressing the treatment of cryptococcal meningitis were conducted in the late 1970s and mid-1980s, establishing the "gold standard" to which every subsequent regimen has been compared. The first of these randomized treatment trials involved 51 courses of therapy for cryptococcal meningitis in 50 patients, of whom 27 were treated with amphotericin B 0.4 mg/kg/d alone, and 24 with a combination of amphotericin B 0.3 mg/kg/d and 5-flucytosine 150 mg/kg/d [7]. Although the combination was given for only 6 weeks compared with 10 weeks for the amphotericin B alone regimen, significantly more patients were successfully treated (66% vs 41%), and there were fewer relapses (5% vs 18%) in the patients treated with combination therapy. In addition, there was more rapid sterilization of cerebrospinal fluid (CSF) and significantly less nephrotoxicity in the former group.

Based on the observations in this study, a second randomized, controlled, multicenter study was performed [8]. Overall, a total of 194 patients were enrolled into the study that compared combination therapy with amphotericin B plus 5-flucytosine given for either 4 or 6 weeks. Only 91 patients met criteria for randomization to either discontinuing therapy at 4 weeks or continuing therapy for 2 additional weeks. A significant number of transplant recipients (four of five patients) randomized to 4 weeks of therapy experienced relapse, and these patients were subsequently excluded from further randomization. The overall success rates in these two groups were similar, with successful outcomes in 75% and 85% of patients receiving 4 and 6 weeks of combination therapy, respectively.

Based on the observations from this study, including the identification of several prognostic factors influencing outcome, it was determined that among selected patients therapy could be safely discontinued at 4 weeks. This included patients who were not significantly immunocompromised, had no neurologic defects, had lower serum cryptococcal antigen titers, had more than 20 leukocytes/mm^3 in CSF, and who had demonstrated an excellent clinical and mycologic response at 4 weeks.

There were limitations to both of these two studies, but together they created the foundation upon which the approach to therapy for all patients with cryptococcal meningitis was subsequently based, and they continue to be the standard to which other therapies for non–HIV-infected patients with CNS cryptococcosis are compared.

Clinical Studies in the AIDS Era

The most recent clinical trials concerning the treatment of cryptococcal meningitis have been conducted mainly among HIV-infected patients. These studies coincided with the development and availability of the broad-spectrum antifungal triazoles (fluconazole and itraconazole), and much of the current approach to treatment of cryptococcal meningitis in non–HIV-infected patients is based on data that have been generated from these trials.

The first large randomized trial was published by Saag *et al.* [13] in 1992. In this study, 194 HIV-infected patients with CNS cryptococcosis were randomized to receive amphotericin B (at least 0.3 mg/kg/d) with or without 5-flucytosine compared with fluconazole (200 mg/d) alone as initial therapy for 10 weeks. Mycologic and clinical parameters were assessed at 2-week intervals throughout the study period. Fluconazole was better tolerated than amphotericin B, but there was a trend towards more rapid sterilization of CSF in the amphotericin B recipients. There was no statistically significant difference in overall success in either arm of the trial (amphotericin B = 40%, fluconazole = 34%). However, the higher early mortality (within the first 2 weeks) and less rapid sterilization of CSF noted among patients receiving fluconazole led to the practical conclusion that while fluconazole is an acceptable alternative for initial therapy, it should probably be reserved for patients who 1) are not critically ill, 2) have a normal mental status at presentation, 3) have no neurologic abnormalities, 4) have a lower fungal burden as determined by a negative CSF India ink, 5) have a CSF cryptococcal antigen less than 1:1024, and 5) have greater than 20 cells/mm^3 in CSF. The most important conclusion from the study was that selected patients with AIDS and cryptococcal meningitis could be successfully managed with either an initial 10-week course of amphotericin B (at least 0.3 mg/kg/d), with or without 5-flucytosine, or with fluconazole at a dose of 200 mg/d.

Based on the findings of this study, a second study was conducted in a similar group of HIV-infected patients with CNS cryptococcosis [14]. In this randomized, double-blinded study, 381 patients received amphotericin B 0.7 mg/kg/d for the first 2 weeks plus either 5-flucytosine 100 mg/kg/d (202 patients) or placebo (179 patients). Among patients who achieved a successful clinical response at 2 weeks, they were randomized again to receive either fluconazole 400 mg daily or itraconazole 400 mg daily for an additional 8 weeks. Parameters of success were based on negative CSF cultures at 2 and 10 weeks, or clinical stability at 2 weeks and asymptomatic status at 10 weeks. Following completion of this initial course of therapy, patients who had been successfully treated through the first 10 weeks of study were allowed to continue on either fluconazole or

itraconazole for an additional year to determine the efficacy of these agents in preventing relapse of cryptococcal infection.

The analysis of these studies was conducted in three parts: the first 2 weeks of therapy, the subsequent or azole arm of initial therapy (2 through 10 weeks), and chronic maintenance therapy. There were no significant differences in outcome following analysis of the first component, with success rates of 60% and 51%, respectively, for combination and monotherapy in the first 2 weeks. However, there was a trend towards more rapid mycologic improvement and better overall clinical outcome in the combination amphotericin B plus 5-flucytosine arm. Similar success rates were also seen in both arms of the second phase of the study, with 68% and 70%, respectively, of fluconazole and itraconazole recipients responding by 10 weeks. In the chronic maintenance phase of the study, however, fluconazole 200 mg/d demonstrated vastly superior efficacy in preventing relapsing cryptococcosis when compared with itraconazole 200 mg/d [16••]. In addition, among patients who received amphotericin plus 5-flucytosine initially, relapse rates were lower than among patients who received amphotericin B alone after successful completion of the first 10 weeks of therapy.

Recent Studies in Non–HIV-infected Patients

There has been only one prospective treatment trial for cryptococcosis among non–HIV-infected patients in the 1990s [17]. This multicenter, open label, randomized trial compared amphotericin B deoxycholate 0.7 mg/kg/d plus 5-flucytosine 100 mg/kg/d for 2 weeks of induction therapy, followed by high-dose fluconazole (800 mg) for 10 weeks (total therapy 12 weeks), with an all-oral regimen of fluconazole 800 mg daily plus 5-flucytosine 100 mg/kg/d for 6 weeks, followed by fluconazole alone for 6 weeks. This study enrolled 16 patients, of whom 12 were evaluable. The study closed prematurely as a result of slow patient accrual, but it provided some important insights into the management of HIV-negative patients in the era of effective azole therapy. Specifically, six (86%) of seven patients in the amphotericin B-containing arm who were followed for 1 year post-therapy were cured. By comparison, only one (20%) of five patients in the all-oral regimen were cured, while four (80%) of five of these patients died during therapy, including two with overwhelming cryptococcosis. Perhaps the most important observation of this study was the observation of the excess early mortality among patients receiving an all-oral regimen, further emphasizing the importance of amphotericin B in the initial management of this disease in gravely ill individuals.

Two recently published retrospective trials have examined the treatment of CNS cryptococcosis in the non–HIV-infected patient. The first study was conducted by Dromer *et al.* [18] and reviewed 83 cases in France, including 60 patients with CNS involvement. Among these patients, 35 and 25 subjects received initial therapy with amphotericin B and fluconazole, respectively. This trend reflected a more aggressive therapeutic approach among patients with CNS disease, while the majority (15 of 23) of patients with extraneural disease received fluconazole as initial therapy. Patients with CNS cryptococcosis demonstrated similar outcomes regardless of initial therapy. Specifically, 74% and 68% of amphotericin B and fluconazole recipients, respectively, were successfully treated. Initial therapy was not significantly related to survival. Factors impacting survival included significant underlying disease, altered mental status, age greater than 60 years, and the presence of disseminated disease. The authors concluded that the management of CNS cryptococcosis in the non–HIV-infected patient must be approached thoughtfully, emphasizing the importance of early aggressive initial management with antifungal therapy.

In a more recent retrospective study, Pappas *et al.* [19••] report a series of 306 non–HIV-infected patients with cryptococcosis, among whom 157 patients had CNS disease. The demographics of this group demonstrated that 25% of patients had no obvious underlying disorder. The remainder of the patients were divided into groups of underlying diseases including transplantation, organ failure syndrome, chronic glucorticosteroids, hematologic malignancies, and other disorders. These patients were treated between 1990 and 1996, a time during which fluconazole was generally available. All but three patients with CNS disease received antifungal therapy. Despite the availability of fluconazole during this time, about 90% of patients received an amphotericin B-containing regimen as initial therapy. The median duration of therapy with amphotericin was 27 days in this population, and about two thirds also received flucytosine for a median time of 31 days. The total amount of amphotericin B given as antifungal therapy was approximately 800 mg, and the total daily dose of flucytosine was approximately 100 mg/kg. Fluconazole was given as initial therapy at doses of 400 to 800 mg in only a few patients; however, fluconazole was given in two thirds of patients following a successful induction regimen containing amphotericin B. These patients received fluconazole at a median dose of 400 mg for a median duration of 10 weeks. Other initial regimens were uncommon and could not be adequately assessed.

The approach to therapy among these patients was remarkably consistent in this review, and alternative regimens were distinctly uncommon. Overall successful response to therapy among patients with CNS cryptococcosis was 81%, with the best outcomes seen among patients with either no underlying disease or among transplant recipients.

The conclusions of the study included a strong endorsement for an amphotericin B-containing regimen as initial therapy, with the role of fluconazole probably limited to subsequent therapy after a significant clinical and mycologic response had been achieved. Early and aggressive therapy was emphasized in an effort to minimize mortality and serious neurologic sequelae.

Management of Increased Intracranial Pressure

One of the key issues surrounding the management of patients with cryptococcal meningitis is control of elevated intracranial pressure and/or hydrocephalus. Many of the devastating neurologic sequelae of CNS cryptococcosis such as blindness, deafness, and other cranial nerve abnormalities associated with cryptococcal meningitis are often related to poorly controlled intracranial pressure, rather than untreated or uncontrolled infection, although clearly these factors are inextricably linked.

Increased intracranial pressure is a common finding among patients with cryptococcal meningitis occurring in the majority of patients, whether HIV positive or negative. Data concerning the use of chronic measures, such as permanent shunting to reduce increased intracranial pressure, are difficult to assess, but most reports suggest that between 10% and 15% of non–HIV-infected individuals with CNS cryptococcosis will eventually require a permanent shunting procedure to reduce intracranial pressure. This is usually accomplished using a ventriculoperitoneal or ventriculoatrial shunt. The current understanding, based solely on anecdotal experience rather than controlled trials, suggests that the timing of placement of a permanent shunt should not be influenced by concern for risk of dissemination of cryptococcosis to non-CNS sites (either peritoneum or blood stream) [20•], nor is there good evidence to suggest that early placement of a shunt leads to persistence of infection or to ventricular infection of the shunt itself. Since there is little clinical evidence to support any of these concerns, once it is determined that a patient requires permanent ventricular shunting, it should be accomplished as soon as the procedure can be safely performed.

An important alternative in the management of increased intracranial pressure in patients with cryptococcal meningitis is the use of repeated lumbar punctures with removal of sufficient CSF to reduce the intracranial pressure to 200 mm of H_20 or less. The interval and frequency with which this procedure is performed is completely dependent on the clinical assessment and cooperation of the patient. Many patients have been managed with repeated lumbar punctures (up to 40), ultimately avoiding the need for placement of a ventricular shunt.

Medical therapy for mild to moderately elevated intracranial pressure (200–250 mm of H_20) is generally limited to oral acetazolamide, 250 mg four times daily, or intravenous mannitol. The specific role of these agents in overall management has not been prospectively evaluated, but anecdotal evidence suggests a benefit in selected patients. The use of dexamethasone to reduce elevated intracranial pressure is discouraged in patients with active CNS cryptococcosis.

Current Recommendations

The current recommendations for treatment of CNS cryptococcosis in the non–HIV-infected patient have been recently described [21•]. These recommendations reflect an integrated clinical analysis of the published data over the past two decades, including all prospective trials and the two large retrospective trials among non–HIV-infected patients described above. Based on these data, the current recommendations for treatment of this disorder among non–HIV-infected patients are described in Table 1. As described, there is emphasis on initial therapy with an amphotericin B-containing regimen (usually between 2 to 4 weeks) until disease is controlled, followed by fluconazole to complete at least 10 weeks of therapy, which depends on the clinical response and nature of the underlying disorder.

Chronic suppressive therapy with fluconazole at moderate doses (200–400 mg/d) may be warranted in selected patients with disorders associated with ongoing immunosuppression, but this must be determined on an individual basis. The role of the lipid formulations of amphotericin B is probably limited to patients with intolerance to amphotericin B deoxycholate, or patients with significant pre-existing renal dysfunction, because there are little data to suggest superiority of any of these agents over amphotericin B deoxycholate. A recently completed trial among over 200 HIV-positive patients with CNS cryptococcosis randomized to receive either liposomal amphotericin B or amphotericin B deoxycholate revealed decreased toxicity in the liposomal amphotericin B arm, but no clinical superiority of this agent [22].

New antifungal agents such as voriconazole and posaconazole have not been adequately studied among patients with cryptococcosis to make recommendations concerning their potential role in the management of this disorder, though both compounds exhibit superior in vitro activity compared with currently available azoles. The echinocandins have poor in vitro activity against *C. neoformans*, and probably have little role in the treatment of infection caused by this organism.

Conclusions

Central nervous system cryptococcosis continues to be an important condition among non–HIV-infected patients, including patients with no significant discernable underlying disorder. The "gold standard" therapy for this disorder in non–HIV-infected patients is based on data that have been published over 20 years ago. Despite advances in the development of new antifungal agents, no large prospective trials have been conducted in this important group of patients, such that current management of these patients largely reflects the well-defined approach to this disease in HIV-infected patients, which has been based on well-controlled, prospective randomized trials. Therapy with amphotericin B, with or without 5-flucytosine, is important in the initial therapy of this disorder. Fluconazole has an important role as subsequent therapy and in selected patients with significant ongoing immunosuppression.

Table 1. Approaches to therapy for central nervous system cryptococcosis in HIV-negative patients

1. Amphotericin B 0.7–1.0 mg/kg/d plus 5-flucytosine 100 mg/kg/d for at least 14 days, then fluconazole 400 mg/d for a minimum of 10 weeks
2. Amphotericin B 0.7–1.0 mg/kg/d plus 5-flucytosine 100 mg/kg/d for 6–10 weeks*
3. Amphotericin B 0.7–1.0 mg/kg/d for 6–10 weeks
4. Lipid formulation of amphotericin B 3–6 mg/kg/d for 6–10 weeks†

*For 5-flucytosine use greater than 2 weeks, renal function should be monitored frequently and dose adjustment made via nomogram, or 5-flucytosine concentrations should be checked at least weekly (optimal levels 30–80 μg/mL) 2 hours following oral dosing.
†Not Food and Drug Administration approved for this use, but liposomal amphotericin B 3–5 mg/kg/d is probably the best choice based on recent experience in HIV-positive patients [22].

Because of the diverse nature and the relative rarity of these patients at any given medical center, it is unlikely that a prospective trial of CNS cryptococcosis in the non–HIV-infected patient will be conducted in the near future. Given these limitations, it is likely that future recommendations concerning therapy will continue to be based on published trials in patients with AIDS, retrospective reviews, and anecdotal data. Until we are able to devise alternative means of conducting clinical trials of efficacy requiring far fewer numbers of patients, we will be limited in our ability to perform adequately powered randomized controlled studies in a timely manner to address these and other important questions concerning the management of cryptococcosis.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This study evaluated patients receiving either fluconazole 200 mg/d or itraconazole 200 mg/d as chronic maintenance therapy among HIV patients who had responded to a 10-week induction course of therapy. It established that at the doses studied, fluconazole was clearly superior to itraconazole in preventing relapse, and established fluconazole as the drug of choice for chronic suppressive therapy.

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This is the largest of the retrospective studies evaluating the current management of cryptococcosis in non–HIV-infected patients. The review includes 157 patients with CNS cryptococcosis. In contrast to the paper by Dromer *et al.* [18], most patients in this study received amphotericin B plus 5-flucytosine for approximately 1 month, followed by fluconazole for approximately 10 weeks. Success rates were approximately 80% consistent with the previously published data.

20. • Park MK, Hospenthal DR, Bennett JE: **Treatment of hydrocephalus secondary to cryptococcal meningitis by use of shunting.** *Clin Infect Dis* 1999, **28:**629–633.

This is a retrospective review of 10 patients who underwent permanent ventricular shunting procedures for hydrocephalus associated with CNS cryptococcosis. The study suggested that there was no evidence of dissemination of infection, nor was there evidence to suggest persistent catheter-associated infection caused by *C. neoformans*.

21.• Saag MS, Graybill RJ, Larsen RA, *et al.*: **Practice guidelines for the management of cryptococcal disease.** *Clin Infect Dis* 2000, **30:**710–718.
These guidelines represent a consensus approach to the treatment of all forms of cryptococcosis based on published literature and the consensus opinion of the writing committee. It should be emphasized that these are guidelines, and that specific therapy must be individualized on a patient-by-patient basis.

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