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Management of HIV-Associated Cryptococcal Meningitis

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Abstract

Purpose of Review Cryptococcal meningitis remains a significant cause of mortality among people living with HIV. This review summarizes current practices and recent advances in the management of cryptococcal meningitis.

Recent Findings Results from recent clinical trials have improved understanding of optimal induction therapy for cryptococcal meningitis, with the most recent data supporting the use of a single high dose of liposomal amphotericin B followed by two weeks of flucytosine and fluconazole. Studies have also demonstrated significantly reduced mortality with therapeutic lumbar punctures in patients with cryptococcal meningitis. Despite advances in management, long-term mortality remains high and may continue even after completion of antifungal therapy, emphasizing the importance of immune restoration in people living with HIV.

Summary Cryptococcal disease remains prevalent among people living with HIV, especially in resource-limited settings. Advances in treatment strategies, as well as increased accessibility to antifungal drugs, screening tests, and antiretroviral therapy, are critical for reducing morbidity and mortality from cryptococcal meningitis.

Keywords AIDS · Amphotericin B · Cryptococcal meningitis · Cryptococcus · Fluconazole · Flucytosine

Introduction

Cryptococcosis is a common opportunistic fungal infection caused by *Cryptococcus spp.,* encapsulated yeasts that are distributed globally. *C. neoformans* is a major cause of morbidity in people living with HIV (PLWH) and other immunocompromised populations and is estimated to cause 19% of all AIDS-related deaths [1•]. In total, an estimated 152,000 cases of and 112,000 deaths from cryptococcal meningitis occurred globally among PLWH with CD4 cell counts < 200 cells/mm^3 in 2020 [1•]. This review provides an update on advances in the management of cryptococcal meningitis, including recent data on induction regimens and the role of lumbar punctures for management of intracranial pressure (ICP).

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Mycology

C. neoformans is present throughout the world and is classically associated with bird droppings and soil. Exposure to *C. neoformans* appears to be ubiquitous as illustrated by high seroprevalence in study populations [2, 3]. Inhalation of yeast or spores may cause an initial colonization of the respiratory tract followed by dissemination to the cerebrospinal fluid (CSF) or skin. However, nosocomial transmission, vertical transmission, and donor-derived infection from transplant donors have been described [4–6]. On microscopy, *Cryptococcus* species can be visualized as spheric encapsulated cells with diameters ranging from 4–20 µm. The polysaccharide capsule is characteristically visualized with India ink stain as a "halo." *C. neoformans* can be grown on Sabouraud or other agars at 37 ˚C or lower. White, creamy colonies emerge usually within 72 h.

Risk Factors and Geographic Distribution

A major risk factor for cryptococcal meningitis is immunocompromised status and PLWH with CD4 cell counts < 200 cells/mm^3 constitute a major at-risk population. An

estimated 4.4% of this population have cryptococcal antigenemia and most of those cases have concurrent meningitis. 82,000 (54% of the global total) cryptococcal meningitis cases occurred in sub-Saharan Africa in 2020, with an additional 44,000 (29%) in South and Southeast Asia. With more widespread access to antiretroviral therapy (ART) and lower prevalence of advanced HIV disease, there were an estimated 2,000 cases across North America and Western Europe in 2020 [1•].

Clinical Manifestations

Cryptococcal meningitis may present with headaches, fever, and nausea/vomiting. However, these symptoms are not as common in advanced HIV in the presence of impaired immune and inflammatory responses. Mental status changes such as cognitive decline, personality changes, and difficulty with memory may occur. As a result of elevated ICP, papilledema or retinal hemorrhage may occur leading to possible visual disturbances including blindness. Seizures may also occur. Signs of cutaneous infection are common, especially among PLWH, and suggestive of disseminated disease. Cryptococcosis may also present as immune reconstitution inflammatory syndrome (IRIS) in PLWH following initiation of ART, in which symptoms may be similar to those of primary cryptococcal meningitis.

Diagnosis

The workup for suspected HIV-associated cryptococcal meningitis should involve lumbar puncture. Opening pressure, CSF protein, CSF glucose, and cell count should be measured. Absence of CSF abnormalities should not rule out cryptococcal meningitis as they are not universally present, especially in PLWH with markedly suppressed immune responses. Cryptococcal antigen testing (CrAg) should be run on CSF and may also be positive in serum. Current CrAg lateral flow assays (LFAs) have been demonstrated to be over 98% sensitive and specific for cryptococcosis [7, 8]. Antigenemia is often present weeks before symptoms emerge [9] and serum CrAg titers greater than 1:8 suggest disseminated disease [10].

Screening and Prophylaxis

Screening for cryptococcal meningitis with CrAg LFAs in newly identified PLWH in high-incidence areas, with positive tests followed up with preemptive fluconazole therapy, is useful in preventing adverse events and death [11–13]. Studies of screening programs for PLWH in low-incidence areas and in those with CD4 > 200 cells/mm^3 are lacking. However, with widespread availability and low costs of CrAg LFAs, screening may prove to be cost-effective even with low identification rates of cryptococcal meningitis.

In settings with high incidence of cryptococcosis and limited access to CrAg LFAs for screening, the role of primary prophylaxis in PLWH remains under debate. A recent trial of a combination prophylaxis regimen including fluconazole 100 mg/day compared with trimethoprim-sulfamethoxazole alone for PLWH with CD4 < 100 cells/mm^3 in sub-Saharan Africa showed a significant benefit in preventing mortality and cryptococcosis [14]. However, daily fluconazole prophylaxis was determined to be cost-ineffective in an analysis in South Africa [15]. Prolonged prophylaxis may also contribute to widespread resistance to fluconazole, and in vitro studies of *Cryptococcus* resistance among CSF isolates have showed increases in the minimum inhibitory concentration throughout the 2000s and the 2010s [16–19]. With concerns about cost-effectiveness and antifungal resistance as well as the increasing availability of CrAg LFAs for screening, the utility of fluconazole prophylaxis is likely to decrease over time.

Prognostic Indicators

While CrAg titers are valuable tools in the diagnosis of cryptococcal meningitis, they do not correlate well with response to antifungal therapy; instead, clinical signs should guide treatment. However, quantitative CSF cultures have been shown to correlate with worse clinical outcomes in cryptococcal meningitis [20]. Increased CSF opening pressures and high CSF lactate levels are associated with poor outcomes, as are other clinical signs including presence of altered mental status, low body weight, anemia, and leukocytosis [20, 21•, 22]. Similarly, hyponatremia, high baseline serum C-reactive protein levels, and CMV viremia are associated with higher mortality in cryptococcal meningitis [23–25]. Notably, antifungal susceptibility testing of CSF *Cryptococcus* isolates has recently been shown to lack correlation with clinical outcomes, so such testing should not guide treatment choices [26]. Overall, a high index of suspicion for and prompt identification of cryptococcosis is critical, as longer duration of symptoms before initiation of treatment is associated with higher mortality [27].

Treatment

Cryptococcal meningitis in PLWH has a 90-day mortality of 13–19% in resource-rich settings and about 51% in resource-limited settings, reflecting the necessity of prompt initiation of treatment [28–30]. Management of cryptococcal

meningitis involves regular monitoring of ICP, induction/consolidation/maintenance therapy with antifungals, and initiation of ART in ART-naïve patients. The induction phase typically lasts two weeks or longer depending on clinical response, followed by a consolidation phase of at least 10 weeks and then a maintenance phase of variable length.

Until recently, the standard induction regimen recommended by the WHO for cryptococcal meningitis was amphotericin B deoxycholate 1 mg/kg/day and flucytosine 100 mg/kg/day daily for one week followed by one week of fluconazole 1200 mg/day. This regimen was established by the results of the phase 3 ACTA trial [31], in which it had the lowest 10-week mortality compared with two weeks of flucytosine and fluconazole, one week of amphotericin B and fluconazole, and two weeks of amphotericin B with either flucytosine/fluconazole. In 2022, the results of the phase 3 AMBITION trial [32••] demonstrated that a single 10 mg/kg dose of liposomal amphotericin B followed by flucytosine 100 mg/kg/day and fluconazole 1200 mg/day for 14 days was non-inferior to the WHO-recommended regimen. In addition, the single-dose regimen resulted in adverse events in 50% of participants, significantly lower than the 62% in the control arm. Rates of anemia, hypokalemia, and thrombophlebitis were all decreased in the single-dose group [32••]. Subsequently, the WHO modified their recommendations to the liposomal single-dose induction phase.

Importantly, the trial was conducted in resource-limited settings across multiple countries in sub-Saharan Africa. Its results may therefore not be directly applicable to resource-rich settings, where complications of amphotericin B-associated toxicity can be more effectively managed and liposomal amphotericin B is more accessible. In such settings, the standard induction therapy for cryptococcal meningitis has been two weeks of high-dose amphotericin B plus flucytosine 100 mg/kg/day. This regimen has been demonstrated to be more effective than amphotericin B alone in multiple trials using amphotericin B deoxycholate since the late 1990s [33, 34]. Since then, use of liposomal amphotericin B 3–4 mg/kg/day has replaced deoxycholate due to its safer adverse event profile. While two weeks of liposomal amphotericin B alone has been demonstrated to have no significant difference in mortality and lower rates of nephrotoxicity, hypokalemia, and anemia compared with deoxycholate alone [35], no clinical trials have specifically evaluated two weeks of liposomal amphotericin B with flucytosine for the treatment of cryptococcal meningitis. Therefore, further studies may be needed to determine whether the single high-dose regimen is the optimal induction therapy for PLWH with cryptococcal meningitis in resource-rich settings.

As liposomal amphotericin B has higher costs compared with amphotericin B deoxycholate, it is less available in resource-limited settings. The efficacy and safety of the single-dose liposomal amphotericin B regimen from the AMBITION trial cannot be extrapolated to deoxycholate, and so one week of amphotericin B deoxycholate with flucytosine would be the recommended induction therapy if liposomal is unavailable or cost-prohibitive. Flucytosine is also often inaccessible in resource-limited settings due to its high cost, with fluconazole often being used instead. In combination with amphotericin B, flucytosine was shown to be superior to fluconazole in the treatment of cryptococcal meningitis in the ACTA trial [31], and similar mortality rates were seen in routine care settings with higher estimated cost-effectiveness compared with fluconazole-containing regimens [36, 37]. However, when flucytosine is unavailable, amphotericin B plus fluconazole 800 mg/day for induction results in better fungal clearance and survival compared with amphotericin B alone [34]. If amphotericin B is unavailable, flucytosine 100 mg/kg/day plus fluconazole 1200 mg/day has been associated with better outcomes and higher cost-effectiveness than fluconazole monotherapy in the treatment of cryptococcal meningitis [38, 39]. Flucytosine-fluconazole combination therapy has even shown to be noninferior to and more cost-effective than 2-week amphotericin B regimens [31, 40]. In situations where neither amphotericin B nor flucytosine are available, fluconazole 1200 mg/day results in faster fungal clearance than 800 mg/day dosing [41]. However, fluconazole monotherapy has a poor prognosis with mortality greater than 50% at 10 weeks and rising to over 75% by one year [42].

The consolidation phase typically used is fluconazole 800 mg/day for 8–10 weeks. While this has been demonstrated to be superior to itraconazole for cryptococcal meningitis, no recent trials have compared this regimen with other antifungal regimens [33]. Maintenance therapy then consists of fluconazole 200 mg/day [43]. This should be a minimum of one year for PLWH on ART with suppressed viral loads and CD4 counts > 200 cells/mm^3. Cessation of maintenance therapy in PLWH once CD4 counts reach 100 cells/mm^3 results in a very low incidence of cryptococcosis recurrence and so may be considered safe [44]. If fluconazole is not tolerated, itraconazole may be used, though it has been demonstrated to be less effective in preventing relapse of cryptococcosis [43, 45]. Other antifungal triazoles (voriconazole, posaconazole, and isavuconazole) have been used to treat cryptococcal meningitis in small studies [46–49]. They may be used for consolidation or maintenance therapy in patients with intolerance to or disease progression on fluconazole; however, evidence of their efficacy compared with fluconazole is lacking. As fluconazole is an inhibitor of CYP2C9 and CYP3A4, drug-drug interactions should be examined before its administration [50]. In AIDS patients who cannot achieve immune reconstitution, antifungal therapy may need to be lifelong.

Increased ICP is a significant contributor to mortality and morbidity, including visual loss, in cryptococcal

meningitis [21•, 51]. This should be managed with serial lumbar punctures and other methods for CSF drainage (e.g., lumbar drain), which significantly reduce mortality during induction treatment [21•, 52, 53]. A recent study demonstrated that baseline opening ICPs greater than 35 cm H_2O were associated with higher fungal burden, lower Glasgow Coma Scale scores, and higher risks for seizures, as well as higher 30-day mortality. Furthermore, mortality was lower for all patients who received follow-up lumbar punctures within the first seven days after diagnosis, including those with normal baseline ICPs, compared with those receiving only one [54••]. Performing four or more lumbar punctures in the week after diagnosis of cryptococcal meningitis was associated with decreased mortality than three or fewer lumbar punctures in a setting where CSF manometry was not available [55]. In addition, prompt initiation of lumbar punctures is essential, as delay of initial lumbar puncture beyond one day has been associated with increased mortality [56]. Overall, evidence demonstrates a benefit for multiple therapeutic lumbar punctures in patients with cryptococcal meningitis irrespective of opening pressure.

Acetazolamide is not recommended for decreasing ICP as it has been associated with high risks for metabolic acidosis and other adverse events [57]. The addition of glucocorticoids to induction and consolidation treatment has been shown to lead to increased rates of disability and lower rates of fungal clearance compared with placebo, in addition to more frequent adverse events such as opportunistic infections, renal injury, and cardiac events [58]. Sertraline, which demonstrated activity against *Cryptococcus* in pre-clinical experiments, has been shown to be ineffective as an adjuvant in the treatment of cryptococcal meningitis [59, 60]. Tamoxifen has also shown anti-cryptococcal activity in vitro, yet failed to decrease yeast clearance compared with placebo in a clinical trial [61]. Interferon-gamma has demonstrated promise for use in cryptococcal meningitis as an adjuvant with standard therapy. A phase 2 trial showed that 100 µg or 200 µg of interferon-gamma administered thrice weekly for 10 weeks with amphotericin B induction therapy and fluconazole consolidation therapy increased rates of fungal clearance compared with placebo [62]. A subsequent randomized controlled trial showed that either two or six 100 µg doses of interferon-gamma during induction treatment significantly decreased time to fungal clearance compared with placebo, though there was no difference in mortality at two or 10 weeks [63].

While ART should be initiated as soon as possible in ART-naïve PLWH in the management of most opportunistic infections, cryptococcosis presents a risk for IRIS [64]. The rapid restoration of the immune system may lead to an overactive inflammatory response to an underlying cryptococcal infection, which may appear as a paradoxical worsening of the clinical course or recurrence of meningitis. In one study, 0/14 patients randomized to start ART 4–5 weeks after diagnosis of cryptococcal meningitis were found to have IRIS, compared with 7/13 of patients starting ART after one week [65]. Another randomized controlled trial showed significantly higher 26-week mortality with initiation of ART 1–2 weeks (45%) versus 5 weeks (30%) after diagnosis, with most excess deaths occurring during weeks 2–5 after early initiation [66]. Therefore, starting ART at least four weeks after diagnosis may be beneficial for preventing excess mortality from IRIS, though concerns over the risks of prolonged immunodeficiency remain.

IRIS is a clinical diagnosis, in which recurrent symptoms of meningitis follow initiation of ART, and should be suspected in the setting of culture-negative CSF, low or negative CSF CrAg, and after exclusion of other infectious causes. IRIS is associated with higher pre-ART serum CrAg values, as well as higher levels of serum inflammatory markers [67]. One study found higher 2-week mortality among PLWH with cryptococcal meningitis receiving ART for 14 days or fewer compared with those receiving ART for more than 14 days and ART-naïve patients, suggesting that initiation of ART may "unmask" cryptococcosis and lead to IRIS [68]. However, another study did not find any differences in 2- or 10-week mortality between durations of ART [69]. Given the lack of strong evidence either way and the ongoing risks of immunodeficiency, ART is typically continued upon diagnosis of IRIS, though no trials have specifically examined this practice [43]. Treatment strategies include lumbar punctures or ventriculoperitoneal shunts to alleviate increased ICP and anticonvulsants or antiemetics if necessary. Corticosteroids may be used for severe symptoms, though there is a lack of studies supporting this, and a randomized controlled trial of dexamethasone for adjunctive cryptococcal meningitis treatment did not show a reduced incidence of IRIS in the treatment arm [58].

Relapsed cryptococcal meningitis, defined as a second onset of symptoms and *Cryptococcus* growth on CSF culture following normalization of prior cryptococcosis (including improvement in symptoms and negative CSF cultures), may occur when primary induction therapy is inadequate or with inconsistent adherence to consolidation or maintenance therapy. A recent study found 90% of PLWH with relapsed cryptococcal meningitis to be on ART, with a median of five months from primary to relapsed infection. Opening ICPs were significantly higher in relapse compared with primary infections, though mortality was lower after relapse [70].

Despite advances in ART and antifungal regimens, long-term mortality from cryptococcal meningitis remains high. A study of PLWH with cryptococcosis in the United States found a 1-year mortality of 28% and a mortality of 48% by the end of the study period with median follow-up of 3.7 years [71•]. An earlier study of PLWH with cryptococcal meningitis in Uganda demonstrated a 1-year survival

of 45% and 5-year survival of 42%, showing higher early mortality with lower rates of late mortality past one year [72]. Additional analyses have found mortality rates of 30% at three years post-diagnosis in Taiwan and 60% at two years post-diagnosis in Uganda [73, 74]. In the United States study, long-term mortality for patients in the modern ART era (defined as 2008 onward) was significantly lower than those diagnosed prior to 2008, with a hazard ratio of 0.5 for mortality. Viral load suppression was associated with substantially higher rates of survival [71•]. These results demonstrate high mortality after cryptococcal meningitis even in the years after cessation of antifungal therapy, though increased access and adherence to ART may improve long-term survival.

Conclusions

While mortality due to cryptococcal meningitis in PLWH remains very high, clinical studies continue to demonstrate improved methods for its management. Understanding of optimal induction therapies continues to evolve, though it will be critical to ensure that liposomal amphotericin B and flucytosine become more accessible in resource-limited settings. Beyond antifungal drugs, management of ICP is an important component of treatment, and therapeutic lumbar punctures are critical tools for reducing mortality from cryptococcal meningitis. With evidence for high ongoing mortality even after completion of antifungal therapy, long-term follow-up of PLWH with cryptococcal meningitis and increased access and adherence to ART should be emphasized to further decrease risks in these populations.

Declarations

Conflict of Interest M.R.O. and P.B.M. declare that they have no conflicts of interest.
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