

# Recent advances in management of cryptococcal meningitis: commentary

Tania C Sorrell\* and Sharon C-A Chen

Address: Centre for Infectious Diseases and Microbiology and the University of Sydney at Westmead Hospital, Darcy Road, Westmead, NSW 2145, Australia

\* Corresponding author: Tania C Sorrell (tania.sorrell@sydney.edu.au)

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## Abstract

Cryptococcal meningitis remains a substantial health burden with high morbidity, particularly in developing countries. Antifungal treatment regimens are guided by host factors, severity of illness (including presence of complications), and causative cryptococcal species. Recent clinical studies indicate the need for rapidly fungicidal induction therapy regimens using amphotericin B in combination with flucytosine for optimal outcomes. Maintenance therapy with fluconazole is necessary until recovery of immune function. *Cryptococcus gattii* meningitis requires prolonged induction/eradication therapy. Prompt control of raised intracranial pressure or hydrocephalus is essential. Clinicians should be vigilant for immune restoration-like features. Adjuvant surgery, corticosteroids, and/or recombinant interferon-gamma may be required for large cryptococcomas, cerebral edema, or refractory infection.

## Introduction and context

Human cryptococcosis is most commonly caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, with *C. neoformans* var. *grubii* in patients with AIDS accounting for the majority of infections worldwide. Clinical features and complications of infection caused by the two species are influenced by differences in epidemiology and host association (reviewed in [1,2]). For example, there is a greater propensity for *C. gattii* than for *C. neoformans* to cause disease in immunocompetent hosts and to be associated with large mass lesions or cryptococcomas [3]. These differences may influence intervention strategies.

Cryptococcal meningoencephalitis (CM), the most severe form of cryptococcosis, typically affects the high-risk population groups of HIV/AIDS and organ transplantation patients but also affects individuals without apparent immunocompromise [3-5]. Key management issues include the employment of rapidly fungicidal regimens in the induction phase of antifungal treatment followed by adequate suppressive therapy, as well as early recognition and treatment of complications of CM

such as raised intracranial pressure (ICP) and the immune response inflammatory syndrome (IRIS) [1,6,7], optimal management of large cerebral cryptococcomas, and treatment strategies in resource-limited settings [8,9].

## Recent advances

Recent advances in clinical research include those directed at better defining prognostic determinants of outcome, especially in HIV-infected individuals, and the application of these findings to treatment algorithms [10,11]. The overall management of cryptococcosis is detailed in the new clinical practice guidelines of the Infectious Diseases Society of America [1]. These include specific recommendations for unique risk populations such as children, pregnant women, those with *C. gattii* infection, and those in resource-limited environments.

## Meningoencephalitis in HIV/AIDS

Randomized controlled trials (RCTs) of drug therapy of CM due to *C. neoformans* in HIV/AIDS formalized the concept of induction, consolidation (eradication), and

**Table 1. Antifungal treatment for cryptococcal meningoencephalitis and disseminated disease**

Clinical setting	Induction therapy	Duration	Consolidation/maintenance therapy	Duration
HIV-infected individuals	c-AMB (0.7-1 mg/kg daily) plus flucytosine (100 mg/kg daily)	2 weeks	Consolidation: fluconazole (400 mg daily) Maintenance: fluconazole (200 mg daily)	8 weeks
	L-AMB (3-4 mg/kg daily) or ABLC (5 mg/kg daily) (if there are renal function concerns) plus flucytosine (100 mg/kg daily)	2 weeks	Itraconazole (400 mg daily) <sup>a</sup> c-AMB (1 mg/kg per week) <sup>a</sup>	≥1 year <sup>b</sup>
	c-AMB or L-AMB or ABLC (doses as above) for flucytosine-intolerant patients	4-6 weeks		≥1 year <sup>b</sup>
Organ transplant recipients	L-AMB (3-4 mg/kg daily) or ABLC (5 mg/kg daily) plus flucytosine (100 mg/kg daily)	2 weeks	Consolidation: fluconazole (400-800 mg daily) Maintenance: fluconazole (200-400 mg daily)	8 weeks
	L-AMB (6 mg/kg daily) or ABLC (5 mg/kg daily) or c-AMB (0.7 mg/kg daily)	4-6 weeks		6-12 months
Non-HIV, non-transplant patients	c-AMB (0.7-1 mg/kg daily) plus flucytosine (100 mg/kg daily)	≥4 weeks	Consolidation: fluconazole (400-800 mg daily) Maintenance: fluconazole (200 mg daily)	8 weeks
	L-AMB (3-4 mg/kg daily) or ABLC (5 mg/kg daily) plus flucytosine c-AMB or L-AMB or ABLC (in above doses) without flucytosine	≥6 weeks		6-12 months

ABLC, amphotericin B lipid complex; c-AMB, amphotericin B deoxycholate; L-AMB, liposomal amphotericin B. <sup>a</sup>Inferior to fluconazole. <sup>b</sup>With CD4 count at least 100 cells per microliter and undetectable viral load for at least 3 months with a minimum of 1 year of antifungal therapy.

maintenance (suppression) antifungal therapy in the severely immunosuppressed (Table 1) [1]. Rapidly fungicidal induction therapy regimens are essential for favorable outcomes [12]. In particular, combined amphotericin B (AMB)-flucytosine regimens result in faster sterilization of cerebrospinal fluid (CSF) and superior clinical or mycological outcomes at 2 weeks and at 3 months in comparison with AMB alone, AMB plus fluconazole, or fluconazole alone [10,11,13]. This difference has been most evident in patients with high initial CSF fungal burdens or abnormal neurological features (or both) at presentation. Conversely, receipt of initial flucytosine for fewer than 14 days has been independently linked with treatment failure at 3 months of therapy [11]. Nonetheless, the only large randomized phase III study of AMB with and without flucytosine (in patients with AIDS) failed to demonstrate a clinical benefit of combination therapy [14]. Conventional AMB (c-AMB) at a daily dose of 1 mg/kg (in combination with flucytosine) is more rapidly fungicidal than a dose of 0.7 mg/kg [10]; duration of therapy depends on clinical response and treatment regimen (Table 1). Although there are fewer reports of lipid AMB formulations in combination with flucytosine for treating CM, clinical experience strongly suggests that such combination therapy is effective (reviewed in [1]) and there is consensus that either liposomal AMB (3-4 mg/kg daily) or AMB lipid complex (5 mg/kg daily) could be substituted for c-AMB in patients with or predisposed to renal dysfunction [1].

Induction regimens with fluconazole plus flucytosine or with fluconazole monotherapy have been used,

especially in resource-limited areas (see below), but are less effective and are indicated only when first-line drugs cannot be used [1]. If fluconazole is to be used as a single agent, a daily dose of 1200-2000 mg is recommended [15,16]. Following induction/consolidation therapy, fluconazole should be continued until immune reconstitution with HAART (highly active antiretroviral therapy) [1]. Voriconazole and posaconazole can be used as salvage therapy for all patient groups (see below) [1].

When *C. gattii* affects patients with AIDS, clinical features appear to be similar to those of *C. neoformans* var. *grubii* [17], suggesting that management should also be similar. There are retrospective data showing that the course and outcomes of CM (without cerebral mass lesions or hydrocephalus) are independent of causative cryptococcal species [1].

#### **Meningoencephalitis in organ transplantation**

Given the likelihood of nephrotoxicity with concurrent use of c-AMB and calcineurin inhibitors and given that approximately 25% of all organ recipients with cryptococcosis have renal dysfunction, lipid AMB formulations are often employed as induction therapy in combination with flucytosine (Table 1). The median time to CSF sterilization is approximately 10 days, and 2-6 weeks of induction therapy (depending on whether flucytosine is given) are recommended [1]. Recently, it was documented for the first time in solid-organ transplant recipients that the use of lipid AMB formulations to treat CM independently predicted better outcomes (compared with c-AMB) [5]. However, clinical outcomes were measured at 90 days,

did not include late complications, and did not specifically evaluate efficacy of different antifungal therapies. There are data to suggest that calcineurin inhibitors demonstrate synergistic effects *in vitro* with antifungal agents and may be associated with better outcomes in solid-organ transplant patients with cryptococcosis [18].

Since most relapses in patients not prescribed maintenance therapy occur within 6 months [1,19], consolidation/maintenance fluconazole therapy for 6-12 months (relapse rate of 1.3%) is recommended. Azole-drug interactions may be problematic. Reduction of immunosuppressive therapy should be gradual to minimize the risk of allograft loss and development of IRIS [6,19].

#### **Neurocryptococcosis in non-immunocompromized hosts**

In uncomplicated *C. neoformans* meningitis, opinion (there are no RCT data) favors induction with c-AMB or a lipid formulation and flucytosine for 2 weeks (in the absence of adverse prognostic factors such as abnormal neurological findings or altered mental status) or 4-6 weeks provided that 2-week CSF cultures are negative [1] (Table 1). One recent retrospective study of 154 patients without HIV/AIDS, of whom 103 had no immune compromise, reported that initial therapy with non-AMB-containing regimens was independently associated with increased mortality [20]. Experts treating *C. gattii* meningitis also favor 4-6 weeks of therapy on the basis of clinical experience [1]. Although fluconazole (with or without flucytosine) is not recommended for induction therapy, it is the drug of choice (400 mg/day) for eradication (8 weeks) and maintenance (6-12 months) therapy to prevent relapse. Compared with *C. neoformans*, intracranial *C. gattii* infection is associated with a greater number of neurological sequelae and delayed responses to therapy, primarily because of a higher proportion of cerebral mass lesions (cryptococcomas) and late presentations [1,3].

#### **Other management**

Another important determinant of outcome is control of raised ICP by repeated lumbar puncture and/or by early shunting; symptomatic hydrocephalus requires antifungal therapy plus early shunting [1,2]. In the absence of cryptococcomas, the antifungal regimen should be the same as for meningitis. Large cryptococcomas should be treated with combination antifungal therapy and early surgical removal as response to antifungal drugs is poor. Multiple lesions require prolonged induction/eradication therapy [3]. Corticosteroids may be required if there is substantial surrounding edema, especially in the presence of neurological deficits [1].

The duration of induction/eradication antifungal therapy depends on clinical and mycological responses.

Re-imaging in cases of apparent relapse may reveal new/enlarging lesions, with increased perilesional edema despite antifungal therapy. This appears to result from IRIS, as has been reported for *C. gattii* infection and organ transplant/HIV-positive patients following recovery of immune function. Apart from enhancing central nervous system (CNS) lesions, *C. neoformans*-associated IRIS may manifest in the CNS as increased ICP and inflammatory lesions within the spinal cord and typically also presents as lymphadenitis, skin, or soft tissue lesions [6,7]. Short-course corticosteroids have been used successfully alongside antifungal therapy [6,21,22]. Adjunctive recombinant interferon-gamma therapy has been tried in *C. gattii* infection unresponsive to repeated/prolonged courses of antifungal drugs [1,2]. Its contribution to outcomes is uncertain.

#### **Resource-limited settings**

Treatment of CM in areas where only c-AMB and fluconazole are widely available has been recently assessed. Donated fluconazole (200-400 mg daily) for 8-10 weeks is often the only treatment option, especially in Africa [23], but there are no data to recommend fluconazole as first-line therapy [9]. The only study comparing the efficacy of fluconazole and c-AMB is an older American study that showed non-inferiority between the two agents. This study, however, had excluded severely ill patients, included patients who were undergoing re-treatment of their infection, and had employed a low dose of c-AMB (0.3 mg/kg daily) [24].

In developed countries, flucytosine-AMB combinations are the preferred induction treatment regimens in HIV/AIDS. Where flucytosine-AMB combinations are not available, relevant authorities should consider procuring flucytosine for CM treatment programs. Antifungal prophylaxis programs have shown mixed results [22].

#### **Implications for clinical practice**

Major determinants of outcome of CM include neurological status, ICP, presence of cerebral mass lesions, and cryptococcal load at presentation. CSF pressure should always be assessed and raised ICP relieved promptly. Rapidly fungicidal induction treatment regimens are the key to optimal outcomes in all patients. Flucytosine, in combination with AMB, remains the induction regimen of choice; the importance of flucytosine has been demonstrated in a number of studies and RCTs. In organ transplant patients, use of lipid AMB, over c-AMB, has been linked with superior outcomes. Longer courses of induction/eradication therapy are required in *C. gattii* infection. Shunting to relieve symptomatic hydrocephalus, and resection of large cryptococcomas, usually due to *C. gattii*, may be necessary. In patients with substantial

cerebral edema and/or IRIS, corticosteroids may be required to control the pathogenic process.

## Abbreviations

AMB, amphotericin B; c-AMB, conventional amphotericin B; CM, cryptococcal meningoencephalitis; CNS, central nervous system; CSF, cerebrospinal fluid; ICP, intracranial pressure; IRIS, immune response inflammatory syndrome; RCT, randomized controlled trial.

## Competing interests

The authors declare that they have no competing interests.

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