# Management of cryptoccocal meningitis in resource-limited settings: A systematic review

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**To the Editor:** Cryptococcal meningitis (CM) remains a serious cause of mortality and morbidity in individuals infected with the human immunodeficiency virus (HIV). The optimal treatment of CM is unknown. We conducted a systematic review to determine the best treatment for CM with an emphasis on resource-poor settings. Six studies met the inclusion criteria; none was found that compared amphotericin B with fluconazole. From the available evidence, it is not possible to determine which treatment is superior for CM.

## Background

Despite the increasingly wide availability of antiretroviral therapy (ART), CM remains a significant cause of mortality and morbidity among HIV-infected individuals; untreated, its outcome is universally fatal.[1] In South Africa, despite the availability in the public sector of antifungal therapy (fluconazole (FLU) and amphotericin B (AmB)) for treating CM, inpatient mortality is around 25%.[2] The ideal management of CM remains unclear. Many patients with HIV infection who present for the first time to health services with a major opportunistic infection such as CM are unaware of their status. We aimed to assess the evidence for which antifungal regimen and other management to use, emphasising resource-poor settings, for treating CM in HIV-infected individuals to enable them to survive and benefit from ART.

## Methods

Relevant studies were identified using the Cochrane HIV/AIDS group search strategy from databases from January 1980 to June 2008. Key search words included meningitis, *Cryptococcus neoformans*, treatment, trial, human immunodeficiency virus, acquired immunodeficiency syndrome, antifungal agents, AmB, flucytosine (FLC), FLU, azole, lumbar puncture, cerebrospinal fluid (CSF) pressure and acetazolamide. Trials deemed suitable were randomised trials of HIV-infected adults with a first episode of CM diagnosed on CSF examination, by India ink staining, CSF culture or cryptococcal antigen testing. The authors extracted data using standardised forms and performed analysis using Rev Man 4.2.7 software.

## Results

Six studies are included in the review;[3-8] 5 compared antifungal treatments.[4-8] One study that addressed lowering intracranial pressure using oral acetazolamide to lower intracranial pressures was stopped early because of excessive metabolic acidosis[3] (Table I). No study demonstrated differences in survival between groups.

## Conclusions

We aimed to determine the best treatment for CM in resource-limited settings in which only AmB and FLU were usually available. No suitable studies comparing these two drugs were found; therefore, we cannot recommend either treatment as superior to the other. Although AmB-containing regimens have caused more rapid sterilisation of CSF compared with FLU,[9] we found no evidence of improved survival. The optimal dosing and duration of AmB remains unclear; the Southern African HIV Clinicans Society recommended dose is 1 mg/kg daily for 14 days, followed by FLU 400 mg daily for 8 weeks, then FLU 200 mg daily for life; if AmB is not available or its use is contraindicated, then FLU should be used as first-line treatment.[10]

Liposomal AmB is associated with less adverse events than AmB and may be useful in selected patients where resources allow.

FLC (not available in South Africa) in combination with AmB leads to faster and increased sterilisation of CSF compared with using AmB alone. This finding does not correlate with improved clinical outcomes. Infectious Diseases Society of America guidelines recommend that AmB be given in combination with FLC.[11]

Future research into the management of CM in resource-limited settings should focus on the most effective use of medications available in these settings as well as other management modalities such as control of intracranial pressure. The other major issue is the optimal timing of initiation of ART either during or after initial treatment of CM, with the aim of maximising early immunological benefit and reducing the incidence of immune reconstitution-related complications.

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**Table I. Summary of included studies**

| Interventions | Study (reference) | Results |
|---|---|---|
| Acetzolamide v. placebo | Newton *et al*.[3] | Study terminated early owing to excess deaths 2/12 v. 0/10 relative risk (RR) 4.23 95% confidence interval (95% CI) 0.23 - 79.1 and FLU v. excess acidosis 5/12 v. 0/10 RR 9.31 95% CI 0.58 - 150.25 in the intervention group. |
| FLU v. FLU and FLC | Mayanja-Kizza *et al*.[4] | The dose of FLU used (200 mg daily) was lower than the currently recommended 400 mg daily. FLC was given at a dose of 150 mg/kg daily. There was no difference in death rate at 2 weeks: 4/25 v. 10/25 RR 0.4 95% CI 0.14 - 1.11 or at 6 months: 17/25 v. 22/25 RR 0.77 95% CI 0.57 - 1.05; there was no difference in number of patients with sterile CSF at 2 months after treatment: 4/8 v. 12/15 RR 0.4 95% CI 0.11 - 1.36. No major adverse events occurred in either group. |
| AmB v. AmB and FLC | Brouwer *et al*.[5] and van der Horst *et al*.[6] | AmB 0.7 mg/kg daily was compared with AmB 0.7 mg/kg/day with FLC 100 mg/kg/day. The studies were analysed together for the outcomes of death at 14 days and sterility of CSF culture at 14 days. There was no difference in the proportion of deaths at 14 days: 12/195 v. 12/217 RR 1.1 95% CI 0.51 - 2.4, but there was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving FLC: 93/195 v. 128/217 RR 0.81 95% CI 0.68 - 0.98. There was no difference in major adverse events between the two treatment arms: 5/195 v. 6/217 RR 0.94 95% CI 0.29 - 3.03.<br>Brouwer *et al*.[5] recorded deaths at 10 weeks; there was no difference between the two groups: 3/16 v. 1/16 RR 2.81 95% CI 0.33 - 24.16.<br>Van der Horst *et al*.[6] found no difference in symptomatic improvement at 14 days between the two groups: 149/179 v. 157/202 RR 1.07 95% CI 0.97 - 1.18. |
| AmB v. AmB, FLC and FLU | Brouwer *et al*.[5] | AmB was compared with AmB, FLC and FLU. AmB 0.7 mg/kg daily was given, FLC 100 mg/kg daily and FLU 400 mg daily. There was no significant difference in the proportion of patients dying at 2 or 10 weeks: 2/16 v. 1/16 RR 2.0 95% CI 0.2 - 19.91 and 3/16 v. 3/16 RR 1.0 95% CI 0.24 - 4.23. There was no difference in the proportion of patients with sterile CSF at 14 days: 2/16 v. 4/16 RR 0.5 95% CI 0.11 - 2.35. Neither group had serious adverse events. |
| AmB and FLC v. AmB, FLC and FLU | Brouwer *et al*.[5] | AmB and FLC were compared with AmB, FLC and FLU. There was no difference in death at 14 days or 10 weeks between the groups: 1/15 v. 1/16 RR 1.07 95% CI 0.07 - 15.57 and 1/15 v. 3/16 RR 1.07 95% CI 0.07 - 15.57. There was no difference in the proportion of patients with sterile CSF at 14 days: 6/15 v. 4/16 RR 1.6 95% CI 0.56 - 4.58. There were no serious adverse events in either group. |
| AmB and FLC v. AmB and FLU | Brouwer *et al*.[5] | AmB and FLC were compared with AmB and FLU. There was no difference in the proportion of deaths at 14 days or 10 weeks: 1/15 v. 5/16 RR 0.21 95% CI 0.03 - 1.62 and 1/15 v. 7/16 RR 0.15 95% CI 0.02 - 1.1. There was no difference in the amount of patients with sterile CSF at 14 days: 6/15 v. 3/16 RR 2.13 95% CI 0.65 - 7.04. There were no serious adverse events in either group. |
| AmB v. AmB and FLU | Brouwer *et al*.[5] | AmB was compared with AmB and FLU. There was no difference in the proportion of deaths at 14 days or 10 weeks: 2/16 v. 5/16 RR 0.4 95% CI 0.09 - 1.77 and 3/16 v. 7/16 RR 0.43 95% CI 0.13 - 1.37. Also, there was no difference in the number of patients with sterile CSF at 14 days: 2/16 v. 3/16 RR 0.67 95% CI 0.13 - 3.47. There were no serious adverse events in either group. |
| AmB and FLU v. AmB, FLU and FLC | Brouwer *et al*.[5] | AmB and FLU were compared with AmB, FLC and FLU. There was no difference in the proportion of deaths at 14 days or 10 weeks: 5/16 v. 1/16 RR 5.0 95% CI 0.66 - 38.15 and 7/16 v. 3/16 RR 2.33 95% CI 0.73 - 7.45. Also, there was no difference in the number of patients with sterile CSF at 14 days: 3/16 v. 4/16 RR 0.75 95% CI 0.2 - 2.83. There were no serious adverse events in either group. |

**Table I. Summary of included studies - continued**

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| Standard-dose AmB and FLC v. high-dose AmB and FLC | Bicanic *et al*.[7] | AmB 0.7 mg/kg and FLC 0.25 mg/kg for 2 weeks was compared with AmB 1 mg/kg with FLC 0.25 mg/kg for 2 weeks. There was no difference in the proportion of deaths at 14 days or 10 weeks: 1/30 v. 3/34 RR 0.34 95% CI 0.04 - 3.44 and 6/30 v. 9/34 RR 0.76 95% CI 0.03 - 1.83. The proportion of patients with sterile CSF at 14 days was not different between the two treatment groups: 6/29 v. 7/28 RR 1.13 95% CI 0.43 - 2.94. There was no major difference in major adverse events defined as side-effects of treatment leading to the study interventions being terminated: 1/30 v. 5/34 RR 0.23 95% CI 0.03 - 1.83. |
| AmB v. liposomal AmB | Leenders *et al*.[8] | AmB 0.7 mg/kg daily for 21 days was compared with liposomal AmB 4 mg/kg daily for 21 days. There was no difference in the proportion of patients who had a clinical response after 3 weeks' treatment: 12/15 in the liposomal AmB group v. 11/13 in the AmB group RR 0.95 95% CI 0.67 - 1.33. There was no difference in the proportion of deaths at 14 days, 10 weeks or 6 months. At 6 months, 2/15 patients who received liposomal AmB had died and 1/13 patients who received AmB: RR 1.73 95% CI 0.12 - 59.4. Major adverse events were less common in patients who received liposomal AmB: 2/15 v. 9/13 RR 0.19 95% CI 0.05 - 0.74. There was no statistically significant difference in the proportion of patients with sterile CSF at 14 days in either group but the trend suggests that liposomal AmB was superior, with 10/15 patients having sterile CSF v. 1/9 in the AmB group RR 6.0 95% CI 0.91 - 39.41. |

A full version of this review is available in the Cochrane database.[12]

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*Accepted 17 December 2008.*