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## Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings (Review)

Sloan D, Dlamini S, Paul N, Dedicoat M

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[Intervention Review]

# Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings

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## ABSTRACT

### Background

Despite the advent and increasingly wide availability of antiretroviral therapy, cryptococcal meningitis (CM) remains a significant cause of mortality and morbidity amongst individuals with HIV infection in resource-limited settings. The ideal management of CM remains unclear. The aim of this review is to assess the evidence for deciding on which antifungal regimen to use as well as other modalities of management to utilise especially resource poor settings in order to achieve the best possible outcome and enable an individual with CM to survive their acute illness and benefit from antiretroviral therapy.

### Objectives

To determine the most effective initial and consolidation treatment strategy for CM in HIV infected adults.

### Search methods

The Cochrane HIV/AIDS group search strategy was used. Key words in the search included, meningitis, cryptococcus neoformans, treatment, trial, human immunodeficiency virus, acquired immunodeficiency syndrome, antifungal agents, amphotericin, flucytosine, fluconazole, azole, lumbar puncture, cerebrospinal fluid (CSF) pressure and acetazolamide.

### Selection criteria

Randomised of HIV-infected adults with a first episode of CM diagnosed on CSF examination, by India ink staining, CSF culture or cryptococcal antigen testing.

### Data collection and analysis

Data were extracted using standardised forms and analysed using Rev Man 4.2.7 software.

### Main results

Six studies are included in the review. Five of the studies compared antifungal treatments and one study addressed lowering intracranial pressure. This study was stopped early due to excess adverse effects. The results of the other five studies as summarised as follows.

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**Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings (Review)**

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Mayanja-Kizza 1998 compared fluconazole to fluconazole with 5 flucytosine. The dose of fluconazole used 200mg initially is lower than the recommended initial dose of 400mg. No survival advantage was found with the use of 5 flucytosine in addition to fluconazole.

Two studies Brouwer 2004 and van der Horst 1997 compared Amphotericin (AmB) to AmB with 5 flucytosine. Both drugs were given at currently recommended doses for 2 weeks. No survival difference was found at 14 days or at 10 weeks (only recorded in Brouwer 2004). There were significantly more patients with sterile CSF cultures at 14 days in the group that received AmB with flucytosine.

Brouwer 2004 compared AmB given alone to AmB given with flucytosine and fluconazole alone or in combination. This was a small study and no differences in mortality were noted between the groups.

Bicanic 2008 compared high to standard dose AmB both with flucytosine. There was no difference in mortality between the two groups or adverse events.

Leenders 1997 compared standard AmB to liposomal AmB. There was no difference in death rates between the two groups. But there were significantly fewer side effects in the group treated with liposomal AmB.

### Authors' conclusions

The main aim of this review was to determine the best treatment for cryptococcal meningitis in resource-limited settings. In these settings usually only AmB and fluconazole are available. No studies suitable for inclusion in the review were found that compared these two drugs. Therefore we are unable to recommend either treatment as superior to the other. The recommended treatment for CM is a combination of AmB and flucytosine. The optimal dosing of AmB remains unclear. Liposomal AmB is associated with less adverse events than AmB and may be useful in selected patients where resources allow.

Future research into the management of cryptococcal meningitis in resource-limited settings should focus on the most effective use of medications that are available in these settings.

Flucytosine in combination with AmB leads to faster and increased sterilisation of CSF compared to using AmB alone. As Flucytosine is often not available in developing countries, policy makers and national departments of health should consider procuring this drug for HIV treatment programmes.

## PLAIN LANGUAGE SUMMARY

### Treatment of acute cryptococcal meningitis in HIV infected adults, with an emphasis on resource-limited settings

Despite the advent and increasingly wide availability of antiretroviral therapy for people with HIV/AIDS, cryptococcal meningitis remains a significant cause of death and illness amongst individuals with HIV infection in resource-limited settings (poor countries). The ideal way to manage cryptococcal meningitis remains unclear. The main aim of this review was to determine the best treatment for cryptococcal meningitis in resource-limited settings. In these settings, usually only Amphotericin and fluconazole are available. The authors didn't find any suitable studies that compared these two drugs. Because Flucytosine, which works well with Amphotericin, is often not available in poor countries, policy makers and government officials should consider using this drug for HIV treatment programmes. Future research into the management of cryptococcal meningitis in resource-limited settings should focus on the most effective use of medications that are available in these settings.

## BACKGROUND

Cryptococcal meningitis (CM) was first described in 1905. It is an infection of the brain parenchyma and sub-arachnoid space by the encapsulated saprophytic yeast organism *Cryptococcus neoformans*, of which there are three subtypes - var gatti, var neoformans

and var grubbi(Lee 1996). Before the global human immunodeficiency virus (HIV) pandemic the main pathogenic strain was *C. neoformans var gatti*, which is a rare cause of meningitis in immunocompetent individuals in several tropical countries.

Over the last twenty years, HIV has created a large and severely immunocompromised population to whom *C. neoformans* is a dangerous opportunistic infection. The major burden of disease is in South-East Asia and the African sub-continent. During the 1990's CM was the leading reported cause of adult meningitis in parts of Africa (Maher 1994, Moosa 1997, Mwaba 2001), and 10-30% of AIDS deaths are attributed to the disease (French 2002, Bicanic 2005, Day 2004). This makes it the second leading cause of death in HIV-infected individuals in Africa after tuberculosis. The majority of these patients are infected with sub-type *C. neoformans var grubbi* (Casadevall 2001) and infection predominantly occurs in patients with a CD4 counts of less than  $100 \times 10^6$  cells/l (French 2002, Saag 2000). CM is classified as a World Health Organisation HIV / AIDS stage 4 disease.

Over 75% of patients with CM present with headache (Day 2004), usually evolving over 2-4 weeks. Fever, nausea, vomiting and seizures are common, but neck stiffness and classical signs of meningism are seen in less than 25% of cases; confusion or behaviour change may be the only sign of infection (French 2002, Day 2004). Sub-acute dementia can develop, which is reversible with treatment. Space occupying lesions such as cryptococcomas, sub-dural effusions and spinal cord granulomas are occasionally seen and present with focal neurological signs. Visual impairment can occur and blindness is a long-term complication of infection in some immunocompetent patients (Seaton 1997 (a), Seaton 1997 (b)). CM reduces the absorption of cerebrospinal fluid (CSF) leading to raised intracranial pressure (ICP). High ICP is responsible for many of the signs, symptoms and sequelae of CM.

Transmission of *C. neoformans* is usually by inhalation. A symptomatic respiratory illness may occur but this is rare in HIV-infected patients (Casadevall 2001). The skin is commonly involved as a manifestation of disseminated disease. Cutaneous lesions often resemble molluscum contagiosum but a wide spectrum of plaques and papules have been reported, especially in the immunocompromised population.

Diagnosing CM requires the examination of CSF. Indian Ink staining is the cheapest technique and is relatively easy to perform in developing countries. It has 75% sensitivity on a centrifuged sample (Day 2004). A more reliable but expensive test is Cryptococcal antigen detection, which has 99% sensitivity in subjects with titres  $> 1:2048$  (Van der Horst 1997). Fungal culture has a sensitivity of 90%. Microscopic and biochemical features of positive CSF analysis may include a moderate mononuclear leucocytosis, mildly elevated protein and slightly low CSF/blood glucose ratio. These parameters may be normal in 17% of HIV patients with known cryptococcal disease (Moosa 1997). Computer tomography brain imaging is of limited supportive diagnostic value as the scan is normal in 50% of proven cases. It can be justified in some cases, however, to exclude mass lesions and other HIV-related pathology (e.g. toxoplasmosis, CNS lymphoma).

HIV associated CM carries a high mortality even when treated appropriately, a study from Thailand reported 43% mortality in patients treated in a tertiary facility, with the majority of the deaths occurring in the first two weeks of therapy (Imwidthaya 2000). Three main groups of anti-fungal drugs are used in treatment, amphotericin B (AmB), flucytosine and the azoles. Drug toxicity has been found to be a problem and is reported in up to 60% of patients (Day 2004).

AmB, the traditional mainstay of therapy, can be given intravenously, or, rarely, intrathecally, but it has poor oral bioavailability. Although actively fungicidal, it is associated with significant nephrotoxicity. This can be reduced by giving intravenous normal saline pre-medication. Liposomal amphotericin preparations are associated with fewer side effects but are very expensive not available in resource poor settings.

Intra-venous or oral flucytosine displays synergy with AmB. It cannot be used as monotherapy because of rapidly developing drug resistance and significant gastro-intestinal side effects may develop (Saag 2000, Graybill 1997). Drug levels or haematological markers need to be monitored.

The azole compounds (e.g. fluconazole, itraconazole, ketoconazole) were introduced in the 1980s as effective, well tolerated oral and intravenous anti-fungals. Their action against cryptococcal disease has been well described.

Most modern treatment protocols for CM involve combinations of the above drugs. The Infectious Diseases Society of America recommends a 3 step treatment approach - induction (2 weeks of AmB 0.7-1mg/kg/day plus flucytosine 100mg/kg/day) followed by consolidation (8 weeks of fluconazole 400mg/day) and then maintenance (fluconazole 200mg/day for life) (Saag 2000) but some commentators have questioned the scientific evidence behind this (Day 2004). Other proposed regimes include prolonged courses of AmB and flucytosine, fluconazole and flucytosine dual therapy and the use of AmB alone. In much of the developing world fluconazole is the only drug available, via a donation programme and azole based monotherapy is widely used. A number of these regimes are based on anecdotal reports of open-label phase II clinical trials and the rationale for their use has never been rigorously reviewed.

Raised ICP, is common in CM occurring in more than 50% of patients (Graybill 1997). Raised ICP during the first 2 weeks of treatment is associated with a poor clinical response and careful management of ICP is thought to reduce mortality and long term sequelae. Proposed mechanisms to reduce ICP include repeated lumbar puncture, drain insertion and ventriculo-peritoneal shunting (Denning 1991). Mannitol, acetazolamide and corticosteroids have also been tried, but the effects of these interventions are, at best, unproven.

Initial antifungal treatment rarely eradicates *C. neoformans* in HIV infected patients but symptoms may improve and control of infec-

tion is obtainable with secondary prophylaxis. With the advent of antiretroviral therapy this picture may change with patients that are initially treated with antifungal agents being established on antiretroviral therapy and no longer needing secondary prophylaxis as their immune system improves (Vibhagool 2003). Combination antiretroviral therapy (ART) is becoming increasingly available in the developing world, many patients in these setting still present with a major opportunistic infection such as CM having not known they were HIV infected. Defining effective evidence based protocols for treatment of CM is important in these patients if they are to benefit from subsequent ART. The timing of initiating ART after acute CM has not been well studied.

The mainstay of treatment for CM in the developing world is fluconazole, which in many cases is the only drug available. The aim of this review will be to look at trials comparing the current gold standard of treatment AmB (often with flucytosine) to fluconazole. Liposomal and standard AmB will be compared, although liposomal AmB is usually not available outside well resourced countries and centres. Also combinations of treatment will be compared and interventions to manage raised ICP.

This review will not look at primary or secondary prophylaxis against cryptococcal infection.

## OBJECTIVES

To determine the most effective initial and consolidation treatment strategy for CM in HIV infected adults with an emphasis on resource-limited countries.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled blinded and unblinded trials

#### Types of participants

HIV-infected adults (Aged >18) with a first episode of CM diagnosed on CSF examination, by India ink staining, CSF culture or cryptococcal antigen testing.

Acute CM will be defined as a first episode of CM, for which no treatment has been given prior to study entry and which has been diagnosed no longer than two weeks before commencing therapy. Studies including patients receiving antiretroviral therapy were allowed and are commented on in the results and discussion section.

#### Types of interventions

1. Antifungal agents that may be available in resource-limited and other settings (AmB, liposomal AmB, flucytosine and fluconazole) given alone or in combination for the initial treatment and consolidation treatment of acute CM.
2. Drugs and procedures used to reduce raised ICP in patients with acute CM.

#### Types of outcome measures

##### Primary outcomes

1. Proportion of patients alive two weeks after commencing therapy.
2. Proportion of patients alive at the end of the follow up period.
2. Major adverse events secondary to treatment.

##### Secondary outcomes

1. Proportion of patients with sterile CSF after two weeks of therapy
2. Proportion of patients who have symptomatic improvement after two weeks of therapy

##### Exclusion criteria

Studies were excluded if the treatment and control groups were not well matched, if retreatment patients were included (as this may affect the organisms sensitivity to the drug under test), if intention to treat analysis was not used, if there was a large loss to follow up or if the methodological quality of the study was felt to be poor.

### Search methods for identification of studies

See: Cochrane HIV/AIDS Group search strategy

The following databases were searched: MEDLINE, EMBASE, AIDSLINE, AIDSTRIALS, AIDSDRUGS, CINAHL, LILACS, Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane HIV/AIDS Group register, and the Cochrane Controlled Trials Register (CENTRAL/CCTR) from the date the database started or from 1980 which ever is later. Abstracts were reviewed from the relevant conferences. Reference lists of relevant articles were hand searched. The searches were completed in July 2008. Unpublished data were not included. Journals in languages other than English were included in the searches if they were indexed in the databases used.

Key words used included: Meningitis, cryptococcus neoformans, treatment, trial, human immunodeficiency virus, acquired immunodeficiency syndrome, antifungal agents, amphotericin, flucytosine, fluconazole, azole, lumbar puncture, cerebrospinal fluid pressure and acetazolamide,

### Data collection and analysis

Trials identified by the search were assessed for inclusion in the review. Abstracts of all studies identified were screened by the reviewers. Those felt to meet the criteria for inclusion were reviewed

by the reviewers in full. Where there was a conflict between the reviewers as to the suitability of a study to be reviewed this was resolved by discussion or the involvement of a third party (a member of the Cochrane HIV AIDS group). Identified studies were reviewed by the reviewers as to their methodological quality which was graded as A - adequate, B-unclear, C-inadequate and D-not done. The assessment of methodological quality was based on quality of randomisation, allocation concealment, blinding, baseline characteristics of patients, use of intention to treat analysis and completeness of follow-up.

Data was extracted from the selected studies by the reviewers using a standard data extraction form.

Summary ratio measures between trials (odds ratios, relative risks with 95% confidence intervals), were calculated where appropriate using Cochrane REV Man software. Heterogeneity between trials was tested.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Six studies were found that meet the inclusion criteria for the review and were felt to be of sufficient quality to be included. The studies are described below divided into groups by the type of intervention tested. A list of excluded studies with the reason for exclusion is given in the table "Characteristics of excluded studies."

#### Studies looking at methods to treat raised intracranial pressure.

One study [Newton 2002](#) was found that looked at treating raised ICP. In this study conducted between 1998 and 2000, 22 adult Thai patients were randomised to receive either acetazolamide (dose adjusted for weight and serum creatinine) or placebo in addition to AmB (1mg/kg) for 14 days. Eligible patients had CM confirmed on Indian Ink staining, headache, GCS>11/15 and CSF opening pressure >200mm/H<sub>2</sub>O. Exclusion criteria were; weight <35kg, renal or electrolyte disturbance, pregnancy or breast feeding, hypersensitivity to sulphonamides, contraindications for acetazolamide therapy, systolic blood pressure <100mm Hg, a known intracerebral lesion or any infection apart from cryptococcosis and HIV. Lumbar puncture and blood tests were performed on days 2, 4, 7 and 14 after commencement of the acetazolamide/placebo regime. Primary outcome measures were CSF opening pressure, headache severity and serum potassium and bicarbonate levels at 14 days. 21/22 recruited patients were HIV positive. 10 received placebo and 12 received acetazolamide. 2 additional patients were enrolled in the study but had to be withdrawn as they were underweight.

#### Studies comparing different antifungal drugs.

Five other studies were included. [Brouwer 2004](#) compared AmB to AmB and flucytosine to AmB, flucytosine and fluconazole. [Mayanja-Kizza 1998](#) compared fluconazole to fluconazole and flucytosine, [van der Horst 1997](#) compared AmB to AmB and flucytosine, [Bicanic 2008](#) compared standard dose AmB and flucytosine to high dose AmB and flucytosine and [Leenders 1997](#) compared liposomal AmB to standard AmB.

[Brouwer 2004](#) carried out their study in Thailand. Between May and December 2002, 64 HIV positive adult patients with a first episode of culture positive cryptococcal meningitis were randomised to receive one of four treatments for 14 days: intravenous AmB (0.7mg/kg/day), AmB plus oral flucytosine (100mg/kg/day), AmB plus oral fluconazole (400mg/day) or triple therapy with AmB, flucytosine and fluconazole. Unless contraindicated, 11 0.9% NaCl was administered intravenously to patients before every AmB infusion to reduce nephrotoxicity. After 2 weeks, all patients were treated with oral fluconazole 400mg daily for 8 weeks, and 200mg daily thereafter. Exclusion criteria were ALT more than five times the upper limit of normal, neutrophil count <500x10<sup>6</sup>/l, platelet count <50,000x10<sup>6</sup>/l, pregnancy or previous adverse reaction to study drugs.

Lumbar puncture (LP) was performed on days 3, 7 and 14 of the study. Additional LPs were done as required on patients with high CSF pressures. Semi-quantitative cultures were done on CSF samples at each time point. This allowed the rate of reduction in the number of colony forming units (CFUs) to be calculated for each patient. The mean rate of fall in CSF log CFU counts was used as a marker of early fungicidal activity (EFA) in each study arm.

16 patients were treated with each of these regimes; AmB alone, AmB plus fluconazole (AmB+F) and triple therapy (AmB+5TC+F). Although 16 patients were randomised to receive AmB plus flucytosine (AmB+5TC) only 15 patients actually participated in this study arm as one patient turned out to be HIV negative. Follow-up of all participants who received study drugs was done at an established HIV clinic and was complete to 10 weeks.

[Mayanja-Kizza 1998](#) carried out their study in Uganda. Between January 1994 and May 1994, 58 HIV positive adults were randomised to receive primary therapy with either oral fluconazole (400mg od on Day 1 then 200mg daily for 2 months) or oral fluconazole plus flucytosine (150mg/kg/day in 3 split doses for 14 days). All patients who responded to primary therapy were continued on maintenance therapy with fluconazole at a dose of 200mg three times per week for 4 more months.

Eligible patients all had positive CSF cultures for *C. neoformans* and either a positive India Ink test or cryptococcal antigen test by latex agglutination. Pregnant and comatose patients were excluded from the study. 5 patients were diagnosed with tuberculosis had anti-tuberculous therapy administered. No adjustment of fluconazole dose was made during co-prescription of rifampicin.

30 patients received combination therapy, whilst 28 patients re-

ceived fluconazole alone. Clinical assessments were done weekly for the first 2 months and every two weeks thereafter. Patients were asked to grade their headache as none, mild, moderate or severe at each review. Repeat lumbar puncture was done at 2 months and 6 months of therapy. Outcomes measured were survival, CSF sterilisation, clinical success (improvement or resolution of headache) and occurrence of adverse events.

[van der Horst 1997](#) carried out their study in the United States. The study had two steps. Step One: Between October 1991 and August 1994, 381 HIV positive adult patients were randomised to receive two weeks of AmB 0.7mg/kg daily along with either flucytosine 100mg/kg/day in four divided doses or placebo. Patients were eligible if they presented with a first episode of culture-proven CM and no concurrent opportunistic infections. Patients were excluded if they had been pre-treated with anti-fungals or were co-prescribed agents (including rifampicin) which affected the absorption or metabolism of azole drugs. Comatose patients were also excluded, as were pregnant women, and those with haematologic, renal and hepatic dysfunction. Outcomes measured at 2 weeks were clinical success (fever, headache and meningism improved or no worse) and mycological success (sterile CSF fungal culture). 202 patients received AmB and flucytosine, whilst 179 received AmB alone.

Step Two: At two weeks all patients who were clinically stable with no hepatic dysfunction were randomised to receive oral fluconazole (800mg daily for two days, then 400mg daily for eight weeks) or oral itraconazole (600mg daily for three days, then 300mg daily for eight weeks). Outcomes measured after this time were clinical success (absence of fever, headache and meningism) and mycological success (sterile CSF fungal culture). 75 patients dropped out before this part of the study due to withdrawal of consent (21 patients), death (19 patients), clinical deterioration (11 patients), inability to take oral medications (1 patient), adverse drug events (11 patients), co-prescription of prohibited drugs (7 patients) concurrent opportunistic infections (4 patients) and inadequate total dose of amphotericin B (1 patient). 151 patients received fluconazole and 155 received itraconazole. Due to the large drop out rate this second portion of the study is not included in the analysis below.

[Bicanic 2008](#) carried out their study in Cape Town, South Africa between May 2005 and June 2006. Sixty four HIV infected patients with culture proven *C. neoformans* meningitis were randomised to receive either AmB 0.7mg/Kg daily (standard dose AmB) with flucytosine 0.25mg/Kg four times a day for two weeks or AmB 1 mg/Kg daily (high dose AmB) with flucytosine 0.25mg/Kg four times a day for two weeks. This initial treatment was followed by fluconazole 400mg daily for a month then fluconazole 200mg daily afterwards.

Amb infusion was preceded by infusion of 1L of normal saline to reduce nephrotoxicity, electrolytes were supplemented as necessary. Patients developing renal failure were switched from AmB to fluconazole. Lumbar punctures were performed on days 3, 7

and 14 of treatment. Additional lumbar punctures were done in patients with raised ICP or headache.

Eligible patients had to be HIV infected, over 18 years of age, *C. neoformans* culture positive in their CSF and have a first episode of CM. Patients were excluded if they were pregnant or lactating, if they were taking ARVs, if they had experienced a serious reaction to AmB or flucytosine, had a platelet count under 50 cells/mm<sup>3</sup>, neutrophil count <0.5 cell / mL or an alanine transaminase level greater than five times normal. Patients with reduced level of consciousness were included in the study if a relative was available to give consent. Including these patients meant the investigators were including very sick patients not normally involved in CM trials which is highly commendable as these type of patients commonly present in clinical practice.

Sixty four patients were randomised, 30 received AmB 0.7mg/Kg with flucytosine 0.25mg/Kg and 34 received AmB 1 mg/Kg with flucytosine 0.25mg/Kg. Patients were followed up for one year. Antiretroviral therapy was commenced after 4 weeks of antifungal treatment.

The primary outcome measure was the mean rate of decrease of *C. neoformans* colony forming units in the CSF, secondary outcome measures were adverse events related to treatment namely anaemia and renal failure, mortality at 2 weeks, 10 weeks and long term survival.

[Leenders 1997](#) conducted their study in the Netherlands and Australia between June 1992 and June 1995. 28 HIV infected patients with culture proven CM were randomised to either 21 days of AmB 0.7mg/Kg daily or liposomal AmB (AmBisome) 4mg/Kg daily for 21 days. Both treatments were followed by 7 weeks of fluconazole 400mg daily then fluconazole 200mg daily indefinitely. Patients were prehydrated with normal saline prior to AmB infusions. Lumbar punctures were performed on days 7, 14 and 21, also after 10 weeks.

Eligible patients had to be aged over 18, give informed consent, have a first episode of CM and have culture proven *C. neoformans* infection. Exclusion criteria are not clearly stated.

28 patients were randomised, 13 received AmB and 15 liposomal AmB. Patients were followed up for six months. Combination ART was not available at the time of this trial.

The outcome measures were mortality, toxicity and adverse events leading to discontinuation of therapy.

### Risk of bias in included studies

The quality of the trials was assessed by the reviewers independently. The assessment was based on the quality of allocation concealment, blinding, baseline characteristics of patients, use of intention to treat analysis and completeness of follow-up. They are graded A - adequate, B - unclear, C - inadequate, D - not done.

#### Quality of allocation concealment:

The study by [Bicanic 2008](#), [Brouwer 2004](#), [Leenders 1997](#) and [Mayanja-Kizza 1998](#) used sealed envelopes for treatment allocation.



tion and were graded A. In the other three studies [Newton 2002](#) and [van der Horst 1997](#) allocation concealment was unclear therefore these studies were graded B.

#### **Blinding:**

The study by [Newton 2002](#) was double blind and graded A. The study by [van der Horst 1997](#) had two phases the first phase was unblinded and the second phase was double blind therefore the study was graded D/A. The other three studies [Bicanic 2008](#), [Brouwer 2004](#), [Leenders 1997](#) and [Mayanja-Kizza 1998](#) were unblinded and graded D.

#### **Baseline characteristics of patients:**

In all Six studies attempts were made to carefully match patients in all groups for baseline characteristics. All studies were graded A.

#### **Use of intention to treat analysis:**

All Six trials used intention to treat analysis and were graded A.

#### **Completeness of follow-up:**

Loss to follow up of less than 5% of the total number of patients enrolled was reported in [Brouwer 2004](#) and [Leenders 1997](#). [Bicanic 2008](#) reported 1/64 patients lost to follow up at 10 weeks and 3/64 at 1 year. These three studies were graded A. [Mayanja-Kizza 1998](#) reported 8/58 patients lost to follow up, [Newton 2002](#) reported 12/24, these trials were graded C. [van der Horst 1997](#) reported 21/306 patients were lost to follow up in stage 2 of their study, this trial was graded C.

### **Effects of interventions**

#### **Acetazolamide vs placebo**

Only one study addressed treating raised intracranial pressure, [Newton 2002](#). This study used acetazolamide. No studies of repeated lumbar puncture were found. The study by [Newton 2002](#) was terminated early by the safety monitoring committee due to the observation of excess deaths 2/12 vs 0/10 relative risk (RR) 4.23 95% confidence interval (95% CI) 0.23 to 79.1 and excess serious adverse events 5/12 vs 0/10 RR 9.31 95% CI 0.58 to 150.25 in the group of patients receiving acetazolamide. Although these excess events did not reach statistical significance in this small study, acetazolamide can not be recommended for the management of increased intracranial pressure.

#### **Fluconazole and flucytosine vs fluconazole**

[Mayanja-Kizza 1998](#) compared fluconazole to fluconazole and flucytosine. The dose of fluconazole used 200mg daily is lower than the currently recommended dose of 400mg daily. Flucytosine was given at a dose of 150mg/kg daily. There was no difference in death rate at two weeks 4/25 Vs 10/25 RR 0.4 95% CI 0.14 to 1.11 or at six months 17/25 Vs 22/25 RR0.77 95%CI 0.57 to 1.05. Also there was no difference in number of patients with ster-

ile CSF at 2 months after treatment 4/8 Vs 12/15 RR 0.4 95%CI 0.11 - 1.36. There were no major adverse events in either group.

#### **AmB vs AmB and flucytosine**

[Brouwer 2004](#) and [van der Horst 1997](#) compared AmB 0.7mg/kg daily to AmB 0.7mg/kg daily with flucytosine 100mg/kg per 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 deaths at 14 days 12/195 Vs 12/217 RR1.1 95%CI 0.51 to 2.4, but there was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving flucytosine 93/195 Vs 128/217 RR0.81 95%CI 0.68 to 0.98. There was no difference in major adverse events between the two treatment arms 5/195 Vs 6/217 RR 0.94 95% CI 0.29 to 3.03.

[Brouwer 2004](#) recorded deaths at 10 weeks there was no difference between the two groups 3/16 Vs 1/16 RR 2.81 95%CI 0.33 to 24.16.

[van der Horst 1997](#) found no difference in symptomatic improvement at 14 days between the two groups 149/179 Vs 157/202 RR 1.07 95%CI 0.97 to 1.18.

#### **AmB vs AmB, flucytosine and fluconazole**

[Brouwer 2004](#) compared AmB to AmB, flucytosine and fluconazole. AmB was given at a dose of 0.7mg/kg daily, flucytosine 100mg/kg daily and fluconazole was given at a dose of 400mg daily. There was no significant difference in the proportion of patients dying at two weeks or ten weeks 2/16 Vs 1/16 RR2.0 95%CI 0.2 to 19.91 and 3/16 Vs 3/16 RR 1.0 95%CI 0.24 to 4.23. There was also no difference in the proportion of patients sterile CSF at 14 days 2/16 Vs 4/16 RR0.5 95%CI 0.11 to 2.35. There were no serious adverse events in either group.

#### **AmB and flucytosine vs AmB, flucytosine and fluconazole**

[Brouwer 2004](#) compared AmB and flucytosine to AmB, flucytosine and fluconazole. There was no difference in death at 14 days or 10 weeks between the groups 1/15 Vs 1/16 RR 1.07 95%CI 0.07 to 15.57 and 1/15 Vs 3/16 RR 1.07 95%CI 0.07 to 15.57. Also there was no difference in the proportion of patients with sterile CSF at 14 days 6/15 Vs 4/16 RR 1.6 95%CI 0.56 to 4.58. There were no serious adverse events in either group.

#### **AmB and flucytosine vs AmB and fluconazole**

[Brouwer 2004](#) compared AmB and flucytosine to AmB and fluconazole. There was no difference in the proportion of deaths at 14 days or 10 weeks 1/15 Vs 5/16 RR 0.21 95%CI 0.03 to 1.62 and 1/15 Vs 7/16 RR 0.15 95%CI 0.02 to 1.1. Also there was no difference in the amount of patients with sterile CSF at 14 days 6/15 Vs 3/16 RR 2.13 95%CI 0.65 to 7.04. There were no serious adverse events in either group.

#### **AmB vs AmB and fluconazole**

[Brouwer 2004](#) compared AmB to AmB and fluconazole. There was no difference in the proportion deaths at 14 days or 10 weeks 2/16 Vs 5/16 RR 0.4 95%CI 0.09 to 1.77 and 3/16 Vs 7/16 RR 0.43 95% CI 0.13 to 1.37. Also there was no difference in the

amount of patients with sterile CSF at 14 days 2/16 Vs 3/16 RR 0.67 95%CI 0.13 to 3.47. There were no serious adverse events in either group.

#### **AmB and fluconazole vs AmB, flucytosine and fluconazole**

[Brouwer 2004](#) compared AmB and fluconazole to AmB, flucytosine and fluconazole. There was no difference in the proportion of deaths at 14 days or 10 weeks 5/16 Vs 1/16 RR 5.0 95%CI 0.66 to 38.15 and 7/16 Vs 3/16 RR 2.33 95%CI 0.73 to 7.45. Also there was no difference in the amount of patients with sterile CSF at 14 days 3/16 Vs 4/16 RR 0.75 95%CI 0.2 to 2.83. There were no serious adverse events in either group.

#### **Standard dose AmB and Flucytosine Vs high dose AmB and flucytosine.**

[Bicanic 2008](#) compared AmB 0.7mg/Kg with flucytosine 0.25mg/Kg for 2 weeks with AmB 1 mg/Kg with flucytosine 0.25mg/Kg for 2 weeks. There was no difference in the proportion of deaths at 14 days or 10 weeks 1/30 Vs 3/34 RR 0.34 95% CI 0.04 - 3.44 and 6/30 Vs 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 Vs 7/28 RR 1.13 95% CI 0.43 - 2.94. There was also no major difference in major adverse events defined as side effects of treatment leading the study interventions being terminated 1/30 Vs 5/34 RR 0.23 95% CI 0.03 - 1.83.

#### **AmB Vs liposomal AmB**

[Leenders 1997](#) compared AmB 0.7mg/Kg daily for 21 days with liposomal AmB 4mg/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 Vs 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 Vs 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 Vs 1/9 in the AmB group RR 6.0 95% CI 0.91 - 39.41.

#### **In Summary.**

[Newton 2002](#) compared acetazolamide to placebo for reducing raised ICP. This study was terminated due to safety concerns and therefore acetazolamide can not be recommended for management of raised ICP in CM.

[Mayanja-Kizza 1998](#) compared fluconazole to fluconazole with 5 flucytosine. The dose of fluconazole used 200mg initially is lower than the recommended initial dose of 400mg. No survival advantage was found with the use of 5 flucytosine in addition to fluconazole.

Two studies [Brouwer 2004](#) and [van der Horst 1997](#) compared

AmB to AmB with 5 flucytosine. Both drugs were given at currently recommended doses for 2 weeks. No survival difference was found at 14 days or at 10 weeks (only recorded in [Brouwer 2004](#)). There were significantly more patients with sterile CSF cultures at 14 days in the group that received AmB with flucytosine.

[Brouwer 2004](#) compared AmB given alone to AmB given with flucytosine and fluconazole alone or in combination. This was a small study and no differences in mortality were noted between the groups.

[Bicanic 2008](#) compared high to standard dose AmB both with flucytosine. There was no difference in mortality between the two groups or adverse events.

[Leenders 1997](#) compared standard to liposomal AmB. There was no difference in death rates between the two groups. But there were significantly fewer side effects in the group treated with liposomal AmB.

## **DISCUSSION**

Six studies were found that met the inclusion criteria. Five of the studies compared antifungal treatments and one study [Newton 2002](#) addressed lowering intracranial pressure, this study was terminated prematurely by the safety monitoring committee due to concerns over excess mortality in the intervention group who received acetazolamide. Therefore acetazolamide can not be recommended for the management of raised ICP in CM. No studies were found that examined the use of repeated lumbar puncture in the management of raised ICP. A limitation of the studies of antifungal therapy reviewed is that different approaches to controlling raised intracranial pressure were used. It is felt that aggressive management of raised ICP has an important impact on mortality and long term neurological disability [Pappas 2005](#); [Saag 2000](#). This difference in management may have impacted on survival differences between the studies, for example [van der Horst 1997](#) used a combination of repeat lumbar punctures and acetazolamide to lower raised ICP, acetazolamide has subsequently been associated with adverse outcomes [Newton 2002](#). The method of optimal management of raised ICP remains an important unanswered question that could significantly impact on survival.

The main aim of this review was to determine the best treatment for cryptococcal meningitis with an emphasis on resource-limited settings. In these settings usually only AmB and fluconazole are available. No study suitable for inclusion was found that directly compared AmB to Fluconazole for primary treatment of CM. Therefore we are unable comment or to recommend either treatment as superior to the other.

The addition of flucytosine to AmB increased the proportion of patients with sterile CSF cultures at 14 days but this did not translate into a survival benefit during the follow up period of the studies reviewed. It is not known if over a longer period faster sterili-

sation of CSF will confer a survival advantage but it may well do so, therefore it is recommended where possible to treat patients with a combination of AmB and flucytosine. High dose AmB did not impact on early mortality even though there was a trend to wards better fungicidal activity. There is insufficient evidence to recommend to recommend high dose AmB over standard dose AmB when combined with flucytosine.

Liposomal AmB was found to be associated with less adverse events compared to standard AmB but the overall outcome as the same. Liposomal AmB in view if its high cost is not available in public facilities in resource-limited settings. But this formulation does have a role where resources are not an issue and especially in patients with co morbidities such as renal impairment.

## AUTHORS' CONCLUSIONS

### Implications for practice

No evidence was found to recommend the use of fluconazole in place of AmB as first line therapy for CM. No evidence was found to recommend the frequency of lumbar punctures necessary to control raised ICP. In view of the superior antifungal activity of AmB / flucytosine combination therapy, policy makers in national

departments of health should consider making flucytosine available to public HIV treatment programmes in all settings.

### Implications for research

Future research into the management of cryptococcal meningitis in resource-limited settings should focus on the most effective use of medications that are available in these settings. For example the combination of AmB and fluconazole could be compared to AmB alone. Also studies looking at the best time to initiate ART in relation to an acute episode of CM are needed. Optimal dosing of both fluconazole and amphotericin also needed to be elucidated, namely doses that improve survival without causing excessive toxicity.

Also ideal management of raised intracranial pressure needs to be determined. A trial looking at various regimens for repeat lumbar puncture to control raised ICP is warranted.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Bicanic 2008

Methods	Randomised trial	
Participants	HIV infected adults with cryptococcal meningitis in South Africa	
Interventions	Amphotericin 0.7mg/Kg and flucytosine Vs Amphotericin 1mg/Kg and flucytosine	
Outcomes	Death Mycological outcome Adverse events	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Low risk	A - Adequate

#### Brouwer 2004

Methods	Randomised trial	
Participants	HIV infected adults with cryptococcal meningitis in Thailand	
Interventions	Amphotericin B Vs amphotericin B and flucytosine Vs amphotericin B and fluconazole Vs amphotericin B, flucytosine and fluconazole	
Outcomes	Death, mycological outcome	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Low risk	A - Adequate

**Leenders 1997**

Methods	Randomised trial	
Participants	HIV infected adults with cryptococcal meningitis in Holland and Australia	
Interventions	Ambisome Vs amphotericin	
Outcomes	Death Mycological outcome Adverse events	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Low risk	A - Adequate

**Mayanja-Kizza 1998**

Methods	Randomised trial	
Participants	HIV infected adults with cryptococcal meningitis in Uganda	
Interventions	Fluconazole and flucytosine Vs fluconazole	
Outcomes	Death, headache severity, mycological response	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Low risk	A - Adequate

**Newton 2002**

Methods	Randomised double blind trial	
Participants	HIV infected adults with cryptococcal meningitis in Thailand	
Interventions	Acetazolamide Vs placebo	
Outcomes	CSF opening pressure, headache severity, serum potassium and bicarbonate levels	
Notes		

**Newton 2002** (Continued)

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Unclear risk	D - Not used

**van der Horst 1997**

Methods	Randomised double blind trial
Participants	HIV infected adults with cryptococcal meningitis in the USA
Interventions	Step one - amphotericin B and flucytosine Vs. amphotericin B. Step 2. Maintenance therapy with fluconazole Vs maintenance therapy with itraconazole
Outcomes	Death, resolution of headache, meningism and fever. Mycological response at 2 weeks and 10 weeks
Notes	

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Unclear risk	D - Not used

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Brouwer 2007	This is a substudy of Brouwer 2004.
Chotmongkol 1997	This study included retreatment patients, which may have biased the results
Chotmongkol 2005	Control and study group not well matched for severity of disease
de Gans 1992	Several patients were lost to follow up and several patients were switched from the itraconazole to amphotericin treatment arm due to deterioration in their clinical condition. In such a small study this factors may have affected the conclusions reached about treatment efficacy
Larsen 1990	This was a small study where many patients were excluded before randomisation. Also intention to treat analysis was not used meaning 6/26 patients were excluded from the final analysis. Also the two groups were not well matched for CD4 counts



(Continued)

Saag 1992	This study included 8 patients who were retreatment patients. This may bias the results as the patients may have <i>C. neformans</i> infection that is resistant to the treatments under trial due to previous exposure
Sharkey 1996	Control and study groups are poorly matched for baseline characteristics
Tansuphaswadikul2006	Large loss to follow at end of 10 week period. Fifteen patients (50%) lost in group of individuals given 1 week treatment with amphotericin

## DATA AND ANALYSES

### Comparison 1. Acetazolamide Vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	22	Risk Ratio (M-H, Fixed, 95% CI)	4.23 [0.23, 79.10]
2 Serious adverse event	1	22	Risk Ratio (M-H, Fixed, 95% CI)	9.31 [0.58, 150.25]

### Comparison 2. Fluconazole and flucytosine Vs fluconazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 2 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.14, 1.11]
2 Death at six months	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.57, 1.05]
3 Major adverse events	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 2 months	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.12, 1.36]

### Comparison 3. Amphotericin Vs fluconazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Death after 10 weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Major adverse events	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

### Comparison 4. Amphotericin Vs amphotericin and flucytosine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	2	412	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.60, 2.85]
2 Death at 10 weeks	1	31	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [0.33, 24.16]
3 Major adverse events	2	412	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.29, 3.03]
4 Sterile CSF culture at 14 days	2	412	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.68, 0.98]
5 Symptomatic improvement at 14 days	1	381	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.97, 1.18]

**Comparison 5. Amphotericin Vs amphotericin, flucytosine and fluconazole**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.20, 19.91]
2 Death at 10 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.24, 4.23]
3 Major adverse event	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.11, 2.35]

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**Comparison 6. Amphotericin and flucytosine Vs amphotericin, flucytosine and fluconazole**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 15.57]
2 Death at 10 weeks	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 15.57]
3 Major adverse event	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 14 days	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.56, 4.58]

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**Comparison 7. Amphotericin and flucytosine Vs amphotericin and fluconazole**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.62]
2 Death at 10 weeks	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.10]
3 Major adverse events	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 14 days	1	31	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.65, 7.04]

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**Comparison 8. Amphotericin Vs amphotericin and fluconazole**

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.77]
2 Death at 10 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.13, 1.37]
3 Major adverse events	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.13, 3.47]

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### Comparison 9. Amphotericin and fluconazole Vs amphotericin, flucytosine and fluconazole

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.66, 38.15]
2 Death at 10 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.73, 7.45]
3 Major adverse event	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Sterile CSF culture at 14 days	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.20, 2.83]

### Comparison 10. Standard dose amphotericin and flucytosine Vs high dose amphotericin and flucytosine

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.04, 3.44]
2 Death at 10 weeks	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.30, 1.87]
3 Major adverse event	1	64	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 1.83]
4 Sterile CSF at 14 days	1	57	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.43, 2.94]

### Comparison 11. Amphotericin Vs liposomal amphotericin

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 14 days	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Death at 10 weeks	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.12, 59.40]
3 Death at 6 months	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.18, 16.99]
4 Major adverse events	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.05, 0.74]
5 Sterile CSF culture at 14 days	1	24	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.91, 39.41]
6 Proportion of patients responding clinically after 3 weeks treatment	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.67, 1.33]

## WHAT'S NEW

Last assessed as up-to-date: 30 July 2007.

Date	Event	Description
5 September 2011	Amended	Minor amendment to title of plain language summary

## HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 4, 2008

Date	Event	Description
13 August 2008	Amended	Converted to new review format.
31 July 2007	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

All reviewers contributed equally to the design of the protocol

## DECLARATIONS OF INTEREST

None of the reviewers has any potential conflict of interest to declare.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acetazolamide [adverse effects]; Acute Disease; Amphotericin B [supply & distribution; therapeutic use]; Antifungal Agents [supply & distribution; \*therapeutic use]; Antihypertensive Agents [adverse effects]; Developing Countries; Fluconazole [supply & distribution; therapeutic use]; Flucytosine [supply & distribution; therapeutic use]; HIV Infections [\*complications]; Health Resources [\*supply & distribution]; Intracranial Hypertension [drug therapy]; Meningitis, Cryptococcal [\*drug therapy]

### MeSH check words

Adult; Humans