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Treatment of Cryptococcal Meningitis in Resource Limited Settings

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Abstract

Purpose of review—Cryptococcal meningitis most commonly occurs in advanced HIV.

Although diminishing in the developed world with antiretroviral therapy (ART), it remains a major problem in resource-limited settings. ART roll-out will improve long-term HIV survival if opportunistic infections are effectively treated. Considering cryptococcal meningitis in that context, this review addresses excess morbidity and mortality in developing countries, treatment in areas of limited drug availability and challenges posed by combined anti-cryptococcal and HIV therapy.

Recent Findings—From Early Fungicidal Activity (EFA) studies, Amphotericin B-flucytosine is best induction therapy but often unavailable; high dose Amphotericin B monotherapy may be feasible in some settings. Where fluconazole is the only option, higher doses are more fungicidal. Serum cryptococcal antigen testing may identify patients at highest disease risk and primary prophylaxis is effective; the clinical role of such interventions needs to be established. Timing of ART introduction remains controversial; early initiation risks Immune Reconstitution Disease (IRD), delays may increase mortality.

Summary—Amphotericin B based treatment is appropriate where possible. More studies are needed to optimise fluconazole monotherapy doses. Other research priorities include management of raised intracranial pressure, appropriate ART initiation and IRD treatment. Studies should focus on developing countries where problems are greatest.

Keywords

Cryptococcal meningitis; resource-limited setting; HIV; Antiretroviral therapy; Immune Reconstitution Disease

Introduction

Cryptococcal Meningitis (CM) is caused by the encapsulated saprophytic yeast *Cryptococcus neoformans*. The vast majority of cases occur in patients with HIV infection; as 95% of CM cases in developing countries are HIV associated [1*] HIV-CM will be the focus of this review. The disease burden in resource-limited settings, treatment in areas of

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reduced drug availability and challenges posed by combined CM and HIV treatment will be discussed.

Disease Burden in Resource Limited Settings

There are marked differences in CM incidence and outcome between developed and resource limited countries.

Incidence: Developed vs Resource-limited Countries

HIV-CM particularly affects patients with CD4+ counts < 100 cells/ μ l [2,3]. Incidence has declined in developed countries since the advent of Antiretroviral Therapy (ART) [4]. In developing countries, with limited ART access, it remains a major problem; often the commonest in-patient cause of meningitis [5,6] or a key 'AIDS-defining' diagnosis [1,7*] or cause of death [8,9]. Although generally a disease of adults, one recent Brazilian study reported 2.3% of CM cases in patients under 12 years [10*].

By retrospectively reviewing published cohort studies of CM in the international literature, Park *et al* estimated a global incidence of 957,900 (range 371,700-1.54 million) cases per year and described regional distribution (Table 1) [11**].

Incidence may be underestimated in resource-limited settings due to under-reporting and lack of diagnostic tools. Diagnosis requires lumbar puncture (LP) but in one Ugandan series LPs were performed in only 54% of patients with presumed Central Nervous System (CNS) infections; inadequate equipment was cited [12]. Cerebrospinal Fluid (CSF) should be examined by Indian Ink staining or Cryptococcal Antigen (CRAG) detection but in 2007 many Tanzanian hospitals relied on private imports of reagents for these tests, with CRAG costing over \$5 per test in a country with per capita health expenditure of only \$12 [3]. Advanced radiology may detect space occupying cryptococcomas but is normally unavailable [13*].

The inequitable global distribution of CM strains developing world health service capacity. In 2006-7 in Malawi, 2.6% of patients with HIV required CM treatment [14]. In Cape Town, South Africa, CM accounts for 31% of all in-patient days in patients commencing ART [15].

Outcomes & mortality: Developed vs Resource-limited Countries

Using data from clinical trials, case series and surveillance reports, Park *et al* estimated 10 week case-fatality rates of 9% in developed countries, 55% in regions with primarily less developed countries and 70% in sub-Saharan Africa and used these to calculate annual mortality (Table 1) [11]. Some trials informing Park's analysis (particularly from North America [16]) excluded recruitment of the sickest patients, potentially confounding the assumptions underpinning this data. Additionally, well-conducted recent studies using amphotericin B (AmB) in South Africa and Thailand reported early mortality of 20-33% [17,18**,19] and a retrospective review from a tertiary referral facility in northern India described a 10 week fatality rate of 10% [7*], showing that outcomes in resource limited settings are sometimes better than predicted. Nevertheless, unacceptable early mortality in poorer countries remains common.

Long term developed world cryptococcal outcomes have been revolutionised by ART. In France mortality has fallen from 63.8 (95% CI 53.0-94.9) to 15.3 (95% CI 12.2-18.4) per 100 person-years over the ART era [20]. In Italy 5 year survival probability has risen from 2.8% to 87.2% [21*]. These improvements have not been replicated in developing countries; the 51.8% case-fatality rate in Brazil was unchanged from 1994-2006 [10] and 1 year survival in Uganda remains four-fold worse than in France. Of 44 patients from Kampala

followed by Kabugu *et al* in 2007, 24 (55%) patients survived long enough to initiate ART and only 18 (40%) remained alive 6 months later [22**].

Anti-fungal therapy

Infectious Diseases Society of America (IDSA) guidelines outline 3 treatment stages for CM; 2 week induction with amphotericin B (AmB) 0.7mg/kg/day and flucytosine 100mg/kg/day, 8-10 week consolidation with fluconazole 400mg/day and long-term maintenance (secondary prophylaxis) with fluconazole 200mg/day [23]. Similar guidelines exist in resource poor settings [24] but access to drugs compromises implementation [25].

Induction & Consolidation Therapy

Table 2 summarises case series and clinical trials in resource limited countries published from 2006-9. Induction therapy with fluconazole monotherapy or a variety of AmB based regimes is described. Developing countries studies often include small patient numbers with high overall mortality making it difficult to demonstrate significant differences in therapeutic strategies. Surrogate mycological outcomes are sometimes used (e.g. CSF sterilisation at 2 weeks or rates of cryptococcal elimination from fungal cultures, often described as early Fungicidal Activity [EFA]). No direct association has been demonstrated between EFA and outcome but more efficient fungal clearance may ultimately reduce the risks of treatment failure, relapse and Immune Restoration Disease (IRD).

Donated fluconazole (200-400mg/day for 8-10 weeks) often the only treatment option, especially in Africa [14], but little evidence supports its efficacy. An old American study showed non-inferiority between fluconazole and AmB (0.3mg/kg/day) but excluded severely ill patients, and the low AmB dose is outdated [35]. In Uganda only 3/25 (12%) patients survived 2 months of fluconazole 200mg/day [36], in Zambia only 13/130 (10%) survived 6 weeks [37] and in South Africa doubling the dose to 400mg did not improve in-hospital mortality (Table 2) [26].

Fluconazole 400mg/day is fungistatic not fungicidal [38], predisposing towards clinical relapse and drug resistance through prolonged high fungal burden. In 2006 Bicanic *et al* reported that, of 21 culture-positive relapsed South African patients initially treated with this regime, 2 (10%) had reduced fluconazole susceptibility and 14 (67%) were fully resistant [39]. In 2007 a Kenyan study reported reduced susceptibility in 65% and full resistance in 11.2% of isolates [40].

These data question the dosing of donated fluconazole for cryptococcal disease [41]. Dose escalation may accelerate CSF sterilisation and some African countries have adopted 800mg for initial treatment [42,43]. Extending this approach in an EFA study in Uganda, Longley *et al* demonstrated greater fungicidal activity at 1200mg than 800mg (Table 2). There was no mortality difference but the study was not powered for this and excess severe disease in the 1200mg group may have confounded outcomes [31**]. From pilot data, Milefchik *et al* suggested that dose-dependent incremental mycological and clinical responses improve up to 2000mg daily for 10 weeks. At fluconazole 1600mg daily, 10/16(62.5%) patients survived treatment and had negative CSF cultures [44*]. Higher dose toxicity did not occur.

No studies directly compare high dose fluconazole and AmB but it is widely accepted that, where available, AmB is better induction therapy. An EFA study from Thailand suggested AmB (0.7mg/kg/day) in combination with flucytosine (100mg/kg/day) [29] was more fungicidal than AmB alone or in combination with fluconazole 400mg/day. Despite no drug level monitoring flucytosine was not excessively toxic and oral flucytosine was as fungicidal as intravenous; important because oral administration is simpler when resources are

stretched [30]. These conclusions are corroborated by studies indicating absent or incomplete flucytosine therapy is associated with treatment failure [38,45*] or relapse [46].

Unfortunately, flucytosine is expensive (\$120/day in Uganda [22]) and licensing issues complicate availability [25] so alternatives to AmB-flucytosine induction merit consideration. EFA analysis suggested AmB-fluconazole (400mg/day) was unsatisfactory [37] but higher fluconazole dosing (800mg) may be better [34**]. Alternatively, in Cape Town increasing AmB doses to 1mg/kg/day improved EFA, albeit with slightly greater toxicity [18**]. An ongoing clinical trial in Vietnam comparing AmB (1mg/kg/day) alone, in combination with flucytosine (100mg/kg/day) or with fluconazole (800mg/day) will provide more information [ISRCTN95123928; www.controlled-trials.com] [47].

Concern exists about AmB in developing countries due to nephrotoxicity [48]. Various reports, however, refute this [22,32*] and it has been used to safely manage visceral leishmaniasis in poor rural communities in Africa and India [49*].

Liposomal AmB preparations reduce toxicity but are expensive and no more efficacious than standard preparations [45*,50,51], making them unrealistic for resource-limited settings. In Uganda, Kambugu *et al* reduced 14 day CM mortality by 22% from 2002-7. Protocol changes included intravenous hydration before AmB administration, suggesting simpler toxicity-reduction measures are useful [22]. Alternatively a small Thai study shortened induction phase AmB treatment to one week without compromising CSF sterilisation or survival, though analysis was confounded by a high lost to follow-up rate [27]. Reducing dose frequency to alternate days has also been considered [28] (data in Table 2).

If oral flucytosine becomes available in developing countries, an all-oral fluconazole-flucytosine option may emerge. In 1998, in Uganda this combination out-performed fluconazole monotherapy but low dose fluconazole (200mg) was used and 68% mortality at 6 months on combination treatment was unacceptable [36]. Milefchik *et al* showed 75% clinical and mycological treatment success at 10 weeks using fluconazole 2000mg/day and flucytosine 100mg/kg/day with no further relapses during prolonged follow-up [44*].

Innovative treatments, including adjunctive recombinant interferon gamma (IFN- γ) have been investigated at sites in Peru [52] but are unlikely to impact in resource-limited countries in the near future.

Maintenance/Secondary Prophylaxis

Pre-ART, disease relapses prompted recommendation of lifelong secondary prophylaxis with fluconazole 200mg/day [23,53]. International data [54] now allows discontinuation of this in ART patients with CD4+ count ≥ 200 cells/ μ l for 6 months, presuming AmB was used for induction therapy [24]. No specific guidelines exist for stopping prophylaxis after initial fluconazole monotherapy but recent reports describe late CM relapse on discontinuation at CD4 counts of ≥ 495 cells/ μ l [55*]. It seems likely that less fungicidal initial regimes carry higher risk of long-term sub-clinical cryptococcal persistence and relapse.

Ensuring adherence to long-term secondary prophylaxis may be difficult. A pharmacy study in East London, South Africa, showed diminishing collection of fluconazole prescriptions by patients over time (31.5% at 2 months, 23% at 4 months, 6% at 1yr) [56]. Many defaulters may have died, but observations about difficulties in long-term therapy in resource limited settings remain prescient.

Primary Prophylaxis

Poor treatment outcomes from advanced disease prompted Thai guidelines to recommend primary fluconazole prophylaxis for high risk HIV patients with CD4+ count < 100 cells/ μ l. A Cochrane review of five trials, including two from Thailand, demonstrated reduced CM incidence on prophylaxis with fluconazole or itraconazole. No beneficial effect was shown on mortality, but ART availability was low [57]. Unfortunately, emergent fluconazole resistant *Candida albicans* [58] has subsequently been associated. Recent data from a large Ugandan trial demonstrated fluconazole primary prophylaxis to be highly effective in preventing cryptococcal disease prior to and during the first few months of ART [59]. WHO guidelines suggest cost-effectiveness of primary prophylaxis may be affected by regional incidence and prevalence of disease [60].

Serum CRAG testing may more specifically target prophylaxis to those at highest risk of clinical disease; untreated asymptomatic CRAG positivity is associated with increased mortality [61,62]. Positive titres precede symptoms by a median of 22 days [9], and improve detection of non-neurological cryptococcosis especially in the lungs. [63,64].

In South Africa, Jarvis *et al* showed serum CRAG positivity to be independently associated with onset of new CM and mortality during the first year of follow-up. Death correlated with CRAG titre ($19\% < 1:512$, $53\% > 1:512$, $p < 0.04$). The authors estimated that screening 52 asymptomatic individuals with CD4 count < 100 cells/ μ l and no prior history of cryptococcal disease would pre-emptively identify one CM case at a cost per detected case of \$206.44 [65**]. This would be worthwhile only if intervention clearly reduced mortality and it may be necessary to perform LP on serum CRAG positive patients to exclude active CM before prophylaxis. The precise role of selective primary prophylaxis based on CRAG screening in resource-limited settings remains to be delineated.

Raised intracranial pressure

Intracranial pressures (ICP) > 250 mm H₂O are associated with reduced short-term survival and impaired treatment response [32*,66]. Measured ICP appears related to fungal burden at baseline and 14 days [67*]. Repeated therapeutic drainage by LP may improve outcome [64,65]. A Peruvian case series described gradual pressure reduction from a median of 250 mmH₂O at diagnosis to 155 mm H₂O at 10 weeks, citing aggressive ICP management as a factor in mortality reduction. [32*]. For intractable ICP elevation, short-term external lumbar drains may allow gradual resolution at a set rate or when pressure exceeds a stated threshold. These drains require strict aseptic insertion technique and meticulous nursing. An encouraging report from Thailand describes 61 drainage procedures in 54 HIV-CIM patients with only 3 (4.9%) secondary infections [68*]. This was, however, done in a tertiary facility. Given the difficulty of performing simple LPs in some settings it is clearly not universally feasible. Optimal duration of drain placement is unclear and rare complications include brain herniation and subdural haematoma from over-vigorous CSF removal. These problems may be unmanageable without neurological imaging and neurosurgical expertise.

In the developed world, patients with persistent ICP elevation occasionally undergo ventriculo-peritoneal shunt insertion [69]. This is impossible in most developing world centres.

Combined Cryptococcal Meningitis and HIV Treatment

Challenges to combined treatment of HIV and associated opportunistic infections include optimal timing of ART initiation and managing the risk of IRD.

Anti-retroviral Therapy

Long-term survival requires ART but timing of initiation remains controversial. Early introduction may potentiate IRD [70] but delayed therapy in the developing world is associated with significant mortality; in South Africa 67-87% early ART deaths occurred between patient enrolment and initiation with low CD4 count and WHO Stage 4 disease cited as specific risk factors [71*]. CM patients are particularly vulnerable prompting support for ART initiation during the first month of anti-fungal treatment [24]. Data from Zolopa *et al* advocates this approach, indicating that immediate ART after opportunistic infections reduced death and AIDS progression over 48 weeks but only 13% of their patients had cryptococcosis [72]. A recent retrospective cohort analysis of only CM patients showed no mortality difference in early versus delayed ART in Bangkok [73*] and a prospective randomised trial in Zimbabwe described higher mortality in CM patients initiating ART within 72 hours of diagnosis than those delaying for 10 weeks (hazard ratio 2.36 [95%CI 1.12 to 4.97]) [74]. Further studies are essential.

For patients commencing ART prior to CM presentation, long-term prognosis seems better; one Cape Town cohort described lower baseline fungal burdens and better 1 year survival amongst those initiating ART a median of 30 days before cryptococcal diagnosis [17] and observational data from Botswana showed lower in-hospital mortality amongst ART-established CM patients [33**]. Improved outcomes amongst ART-established patients may simply reflect more regular medical care and faster diagnosis in this group, but also suggest that overall survival from CM is more likely where effective HIV programmes permit early diagnosis and treatment.

Most ART regimes in resource limited countries contain nevirapine. Fluconazole inhibits the liver enzymes responsible for nevirapine metabolism raising concerns about nevirapine hepatotoxicity during co-therapy. Recent Thai and Ugandan studies have shown that low dose fluconazole increases plasma nevirapine levels without precipitating transaminitis or adverse events [75,76]. Toxicity may emerge at higher doses, but in the Thai study 400mg/day fluconazole was not different to 200mg.

Immune Reconstitution Disease

IRD occurs during ART as recovering host immunity recognises previously neglected pathogens and antigens [77]. Prospective South African data demonstrated cryptococcus to cause IRD less commonly than tuberculosis; nevertheless it constituted 3/44(7%) cases [78*]. Retrospective review of an Ethiopian cohort reported a higher incidence of 12/74(16%) cases [79*] and data from Cape Town showed that one-third of patients with previous cryptococcosis developed IRD after ART initiation [80]. In all these cohorts, cryptococcal IRD carried higher mortality than tuberculosis immune reconstitution; it has been reported elsewhere that CNS IRD causes greatest morbidity and mortality [81*].

Timing of onset of cryptococcal IRD is difficult to predict; Thai authors reported cases 3-27 months after ART initiation [82]. The only prospective study of cryptococcal IRD, from Cape Town, suggests no factors identifiable at first CM presentation (including fungal burden, rate of clearance or HIV parameters) predict IRD occurrence but rapid rise in CD4 count after ART initiation is a risk factor [83**]. Retrospective studies implicate low presenting CD4 count, high fungal burden and ART commenced within 2 months of initiating CM treatment [70]. Clinical presentation is normally recurrent meningitis but unusual manifestations have also been reported including ocular abnormalities [84] and breast abscess [85].

The evidence base for management is limited, relying on observational studies and expert opinion. ART is continued where possible with intensified anti-fungal therapy and CSF lowering LPs. Anti-inflammatory drugs and short-course corticosteroids have been tried [30].

Conclusions

HIV-CM disproportionately affects resource-limited settings. AmB based induction therapy, combined with flucytosine, has greatest EFA. Although it is not always possible to relate mycological outcome measures directly to clinical end-points this treatment should be used where possible. If fluconazole monotherapy is the only option dose escalation should be investigated. The role of primary prophylactic anti-fungal therapy, best management of raised ICP, appropriate initiation time for ART and optimal management of IRD remain unclear and require further study, particularly in the developing world where problems are greatest.

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Table 1
Estimated global incidence and mortality from cryptococcal meningitis amongst 10 United Nations Programme on HIV/AIDS global regions by using published incidence rates on studies conducted in those regions from 1996–2007

Region	HIV prevalence in 1000s	Estimated yearly cryptococcal meningitis cases (range) in 1000s	Assumed 90-day case fatality (%)	Estimated yearly mortality (range) in 1000s
Sub-Saharan Africa	22 500	720 (144.0–1296.0)	70	504 (100.8–907.2)
East Asia	800	13.6 (2.7–24.5)	9	1.2 (0.2–2.2)
Oceania	75	0.1 (0.0–0.1)	0	0.009 (0.0–0.009)
South and South-east Asia	4000	120 (24.0–216.0)	55	66 (13.2–118.8)
Eastern Europe and Central Asia	1600	27.2 (5.4–49.0)	55	15 (3.0–27.0)
Western and Central Europe	760	0.5 (0.1–1.0)	9	0.045 (0.009–0.09)
North Africa and Middle East	380	6.5 (1.3–11.6)	55	3.6 (0.7–6.4)
North America	1300	7.8 (1.6–14.0)	9	0.7 (0.1–1.3)
Caribbean	230	7.8 (1.6–14.1)	9	4.3 (0.9–7.8)
Latin America	1600	54.4 (10.9–97.9)	55	29.9 (6.0–53.8)
Global	33 200	957.9 (371.7–1544.0)	Not done	624.7 (125.0–1124.9)

Data adapted with permission from [11••].

Table 2
Published observational studies and clinical trials of antifungal agents used to treat cryptococcal meningitis exclusively in resource poor countries, 2006–2009

Study author	Site	Study type	Induction regime (duration)	Consolidation regime	Severity exclusion	ART available	CSF sterilization (time)	Mortality (study duration)
Schaars [26]	Cape Town, South Africa	Retro OS	F 200 mg/day (2 week)	F 100 mg/day	'Poor prognosis patients'	No	Not reported	18/77 (23.4%) (in hospital deaths)
Tansuphaswadikul [27]	Nonthaburi, Thailand	Pros R, OLT	F 400 mg/day (2 week) AB 0.7 mg/kg/day (1 week) AB 1 mg/kg/day (2 week)	F 200 mg/day F 400 mg/day F 400 mg/day	GCS 8 excluded	Yes	Not reported 19/30 (63.3%) (6 week) 19/27 (70.4%) (6 week)	34/128 (26.6%) (in hospital deaths) 2/30 (7%) (10 week) 6/30 (21%) (10 week)
Bicanic [17]	Cape Town, South Africa	Pros OS	AB 1 mg/kg/day (1 week) F 400 mg/day (1 week)	F 400 mg/day	None, but treatment based on GCS ^d	Yes	8/49 (16%) (2 week) 0/5 (0%) (2 week)	16/48 (33%) (10 week) 3/4 (7.5%) (10 week)
Techapornroong [28]	Bangkok, Thailand	Pros R, OLT	AB 1 mg/kg/day (2 week) AB 2mg/kg/alt day (2week)	F 400 mg/day F 400 mg/day	None stated	Not stated	3/9 (33%) (2 week) 1/10 (10%) (2week)	2/9 (22.2%) (12 week) 3/12 (25%) (12week)
Brouwer [29,30]	Ubon Ratchathani, Thailand	Pros R, OLT	AB 0.7 mg/kg/day, (2 week) AB 0.7 mg/kg/day + 5TC 100 mg/kg/day, (2 week) AB 0.7 mg/kg o.d. + F 400 mg/day (2 week) AB 0.7 mg/kg o.d. + 5TC 100 mg/kg/day + F 400 mg/day (2 week)	F 400 mg/day F 400 mg/day F 400 mg/day F 400 mg/day	None stated	No	2/16 (12%) (2 week) 6/15 (40%) (2 week) 3/16 (19%) (2 week)	2/16 (12%) (10 week) 1/15 (7%) (10 week) 5/16 (31%) (10 week)
Bicanic [18•]	Cape Town, South Africa	Pros R, OLT	AB 0.7 mg/kg/day + 5TC 100 mg/kg/day (2 week) AB 1 mg/kg/day + 5TC 100 mg/kg/day (2 week)	F 400 mg/day F 400 mg/day	None stated	Yes	4/16 (24%) (2 week) Not stated ^c	1/16 (6%) (10 week) 6/30 (21%) (10 week)
Kambugu [22••]	Kampala, Uganda	Pros OS	AB 0.7 mg/kg/day	F 400 mg/day	'Comatose' excluded	No	Not stated ^c	9/34 (26%) (10 week) 39/92 (42%) (2 week); Not stated (10 week)
Longley [31••]	Mbarara, Uganda	Pros OLT	F 800 mg/day (2 week)	F 400 mg/day	None	Yes	Not reported	9/44 (20%), (2 week) 26/44 (59%) (10 week)
Oamert [32•]	Lima, Peru	Pros OS	F 200 mg/day (2 week) AB 0.7 mg/kg/day (2 week)	F 400 mg/day F 800 mg/day (2 days) then 400 mg/day	'Comatose' excluded	Not stated	Not stated ^d 12/47 (25%) (2 week)	18/30 (60%) (10 week) 13/27 (48%) (10 week)
Bisson [33••]	Gaborone, Botswana	Pros OS	Ab 1 mg/kg/day (2 week)	F 400 mg/day	None stated	No	Not reported	9/47 (19%) (10 week) 14/66 (21%) (in hospital deaths)
Kumar [7•]	Chandigarh, India	Retro OS	AB 0.7 mg/kg/day (2 week)	F 400 mg/day	None stated	Yes	Not reported	2/26 (8%) (in hospital deaths)
					None stated	Yes	Not reported	3/40 (8%) (10 week)

Study author	Site	Study type	Induction regime (duration)	Consolidation regime	Severity exclusion	ART available	CSF sterilization (time)	Mortality (study duration)
Pappas [34**]	Multisite, Thailand	Pros, OLT	AB 0.7 mg/kg/day (2 week)	F 400 mg/day	'Comatose' & likely survival <14 days excluded	Yes	10/32(31.3%) ^e	8/32(25%) (10 week) ^e
			AB 0.7 mg/kg/day + F 400 mg/day (2 week)	F 400 mg/day		Yes	7/34(20.6%) ^e	8/24(76.5%) (10 week) ^e
			AB 0.7 mg/kg/day + F 800 mg/day (2 week)	F 400 mg/day		Yes	21/41(51.6%) ^e	7/41(17%) (10 week) ^e

5TC, flucytosine; AB, amphotericin B; F, fluconazole; GCS, Glasgow Coma Scale; OLT, Open label trial; OS, observational study; Pros, prospective; R, randomized; Retro, retrospective.

^aPatients with GCS at least 10 received AB 0.7mg/kg/day induction. Patients with GCS less than 10 received F 400mg/day induction.

^bBrouwer 2007 is subset analysis of Brouwer 2004 data indicating no significant difference in mycological & clinical outcomes between regimes containing oral or intravenous 5TC.

^cRate of CSF clearance of infection was measured by Early Fungicidal Activity (EFA). For AB 0.7 mg/kg/day + 5TC, EFA was -0.45 ± 0.16 log cfu/ml of CSF/day; for AB 1 mg/kg/day + 5TC, EFA was -0.56 ± 0.24 log cfu/ml of CSF/day. Rate of clearance was associated with AB dose (difference 0.11 log cfu/day, 95% CI 0–0.22 log cfu/ml of CSF, $P < 0.05$).

^dRate of CSF clearance of infection was measured by EFA. For F 800 mg/day, EFA was -0.07 ± 0.17 log cfu/ml of CSF; for F 1200 mg/day, EFA was -0.18 ± 0.11 log cfu/ml of CSF/day. Rate of clearance was associated with F dose (difference 0.10 log cfu/day, 95% CI 0.03–0.16 log cfu/ml of CSF, $P = .007$).

^eOutcome data not subdivided to CSF sterilization and mortality but reported on the basis of a composite end-point defined as CSF culture conversion, stable neurological function and survival at day 14, 42 and 70.