health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: HIV and AIDS

MEDICINE REVIEW:

1. Executive Summary

Date: 26 October 2023 (Update of initial review of 28 November 2018)
Medicine (INN): Liposomal amphotericin B
Medicine (ATC): J02AA01
Indication (ICD10 code): Cryptococcal meningitis - B20.5 + (B45.1 + G02.1*)
Patient population: Immunocompromised patients with cryptococcal meningitis.
Prevalence of condition: In 2014, an estimated 223,100 incident cases and 181,100 deaths occurred globally, and cryptococcal meningitis is estimated to cause up to 15% of HIV-related deaths (Rajasingham 2017).
Level of Care: Adult Hospital Level
Prescriber Level: Medical officer
Current standard of Care: Amphotericin B deoxycholate
Efficacy estimates: (preferably NNT)
Nov 2018 summary
Regarding efficacy the trial by Hamill et al. gives the most informative findings and has the lowest risk of bias. Looking at mycological success at 2 weeks the NNT for benefit with liposomal amphotericin B 3 mg/kg/day over amphotericin B deoxycholate is 9 patients. Regarding mycological success at 2 weeks for liposomal amphotericin B 6 mg/kg/day versus amphotericin B deoxycholate, the **NNT is 200** patients. Looking at therapeutic success at 10 weeks the **NNT for benefit is 13** patients with amphotericin B deoxycholate versus liposomal amphotericin B 3 mg/kg/day, and for liposomal amphotericin B 6 mg/kg/day **NNT is 56** patients (note the inversion of comparison here). These findings did however not show statistical significance and the conclusions from the trial were the non-inferiority of liposomal amphotericin B versus amphotericin B deoxycholate.
The only safety outcomes available that were directly related to the review question also came from the RCT by Hamill et al. Regarding nephrotoxicity (creatinine level of 2 times baseline and >1.2 mg/dL), liposomal amphotericin B 3 mg/kg/day had an NNT for benefit of 5 patients versus amphotericin B deoxycholate. Similarly, for benefit with liposomal amphotericin B 6 mg/kg/day, **NNT was 8** patients versus amphotericin B deoxycholate. Hypokalaemia and anaemia were only significantly improved when using liposomal amphotericin B 3 mg/kg/day versus amphotericin B deoxycholate with an **NTT for benefit of 5** patients for both outcomes
May 2022 update
Authors of a phase III non-inferiority study (Jarvis 2022) comparing a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1 plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control) in patients with cryptococcal meningitis, reported that the 10-week mortality was 24.8% (95% confidence interval [CI], 20.7 to 29.3) in the liposomal amphotericin B group (101 of 407 participants had died) and 28.7% (95% CI, 24.4 to 33.4) in the control group (117 of 407 participants had died), based on their intention to treat analysis. The authors concluded that single-dose liposomal amphotericin B combined with flucytosine and fluconazole was non-inferior to the control (P<0.001 for non-inferiority) and was associated with fewer adverse events.
Motivator/reviewer name(s): *Initial review* (28 November 2022) - Dr R Griesel; Updated review (19 May 2022) – Dr H Dawood
PTC affiliation: RG: Groote Schuur Hospital

2. Name of author(s)/motivator(s)

Original document: Dr R Griesel, Dr H Dawood
August 2023 Update: Dr J Nel, Dr J Miot, Ms Z Adam

3. Author affiliation and conflict of interest details

RG: University of Cape Town, Pharmacology Department; Adult Hospital Level Committee (2017-2018); HD: Greys hospital and Caprisa, University of KwaZulu-Natal. RG and HD have no conflicts of interest pertaining to liposomal amphotericin B.

JM: Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand. JN: Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand. ZA: Consultant, Right to Care. The reviewers have no conflicts to declare.

4. Introduction/ Background

Cryptococcal meningitis is a severe fungal infection primarily seen in people with compromised cell-mediated immunity. Most cases occur in the context of advanced HIV disease with the risk increasing with decreasing CD4 cell count (Tenforde 2018). In 2014, an estimated 223,100 incident cases and 181,100 deaths occurred globally, and cryptococcal meningitis is estimated to cause up to 15% of HIV-related deaths (Rajasingham 2017). Approximately 73% of cases are estimated to occur in sub-Saharan Africa.

The World Health Organization (WHO) guidelines in 2018 recommend a 1-week course of amphotericin B plus flucytosine as the preferred regimen for the induction phase in the treatment of cryptococcal meningitis (WHO 2018). Flucytosine has historically not been freely available in South Africa and local guidelines still recommend a 2-week induction phase course of amphotericin B followed by fluconazole.

Conventional amphotericin B deoxycholate is a broad-spectrum antifungal that has been used as standard therapy for treatment of many invasive fungal infections since it was introduced to clinical practice in the 1950s (Bassetti 2011). The significant dose-limiting toxicity of amphotericin B deoxycholate (most notably nephrotoxicity and infusion-related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced (Bassetti 2011). This is due to the fact that when the liposome reaches the fungal cell, it is disrupted, and the drug is released into the fungal cell membrane where it binds to the ergosterol. The liposome keeps its integrity in the presence of mammalian cells resulting in minimal toxicity (Adler-Moore 2002).

This review will focus on the comparison of liposomal amphotericin B versus amphotericin B deoxycholate, specifically assessing efficacy and safety outcomes. This review may inform resource allocation decisions for liposomal amphotericin B use, particularly in our resource-limited setting.

Document History:

The original evidence review prepared in Nov 2018 was updated in May 2022 to include results from the Jarvis et al publication (March 2022) which concluded that the liposomal amphotericin B regimen was non-inferior to the control group (amphotericin B deoxycholate regimen) in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid. The study had a standardized 7-day inpatient monitoring in both arms, with some indication that liposomal amphotericin B could shorten hospital length of stay (LoS). However as liposomal amphotericin B was significantly more expensive than amphotericin B deoxycholate, the NEMLC did not support the inclusion of liposomal amphotericin B on the EML.

Following the announcement of a reduction in price of liposomal amphotericin B (R600 per 50mg vial)[1] in 2023, the cost analysis (Addendum A) has subsequently been updated and a revised recommendation was tabled at NEMLC on the 30th November 2023 for consideration. Furthermore, flucytosine is also now available on tender (NDoH contract HP02-2023AI). The updates to the cost analysis and recommendation are as detailed below.

[1] NDoH Communication Ref HP02-2023AI

5. Purpose/Objective i.e. PICO

Efficacy: *Is liposomal amphotericin B non-inferior to amphotericin B deoxycholate for the treatment of cryptococcal meningitis?*

Safety: *Is liposomal amphotericin B superior to amphotericin B deoxycholate for the treatment of cryptococcal meningitis?*

Population: Adult patients treated for cryptococcal meningitis with impaired renal function (defined as eGFR <60ml/L) at the onset of therapy, or those who develop intractable renal impairment or electrolyte disturbances (K^+) on amphotericin B deoxycholate.

Intervention: Initiate liposomal amphotericin B or substitute conventional amphotericin B deoxycholate with liposomal amphotericin B

Comparator: Amphotericin B deoxycholate. An advantage of the comparator is cost. Disadvantages are related to severe thrombophlebitis and infusion related reactions, nephrotoxicity, electrolyte disturbances, and anaemia.

Outcome:

Efficacy: Mortality benefit or rate of clearance of CSF (surrogate marker)

Safety:

- Renal impairment (decrease in estimated glomerular filtration or increase in serum creatinine)
- Infusion related reactions
- Electrolyte disturbances (K^+)
- Anaemia

6. Methods:

a. Data sources Medline (PubMed) and Cochrane database

b. Search strategy

(((("amphotericin b"[MeSH Terms] OR "amphotericin b"[All Fields]) OR ("amphotericin B, deoxycholate drug combination"[Supplementary Concept] OR "amphotericin B, deoxycholate drug combination"[All Fields] OR "amphotericin b deoxycholate"[All Fields])) AND (("cryptococcus"[MeSH Terms] OR "cryptococcus"[All Fields]) OR ("meningitis, cryptococcal"[MeSH Terms] OR ("meningitis"[All Fields] AND "cryptococcal"[All Fields]) OR "cryptococcal meningitis"[All Fields] OR ("cryptococcal"[All Fields] AND "meningitis"[All Fields])))) AND ("liposomal amphotericin B"[Supplementary Concept] OR "liposomal amphotericin B"[All Fields] OR "liposomal amphotericin b"[All Fields]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

The search revealed 9 publications. Going through these individually to check for applicability, 2 systematic reviews and meta-analyses were relevant. Two applicable randomised control trials (RTCs) were isolated. Both RCTs were included in the systematic reviews and meta-analyses. No new RCTs had been published since the publication of the systematic reviews and meta-analyses.

c. Excluded studies:

Four publications from the literature search was excluded (see below).

Author, date	***Type of study***	***Reason for exclusion***
Hadley 2009	RCT	Wrong indication and wrong intervention and comparator
Jadhav 2010	RCT	Wrong comparison
Luke 1998	RCT	Wrong intervention
Sharkey 1996	RCT	Wrong intervention
Coker 1993	Observational	Non-comparative study

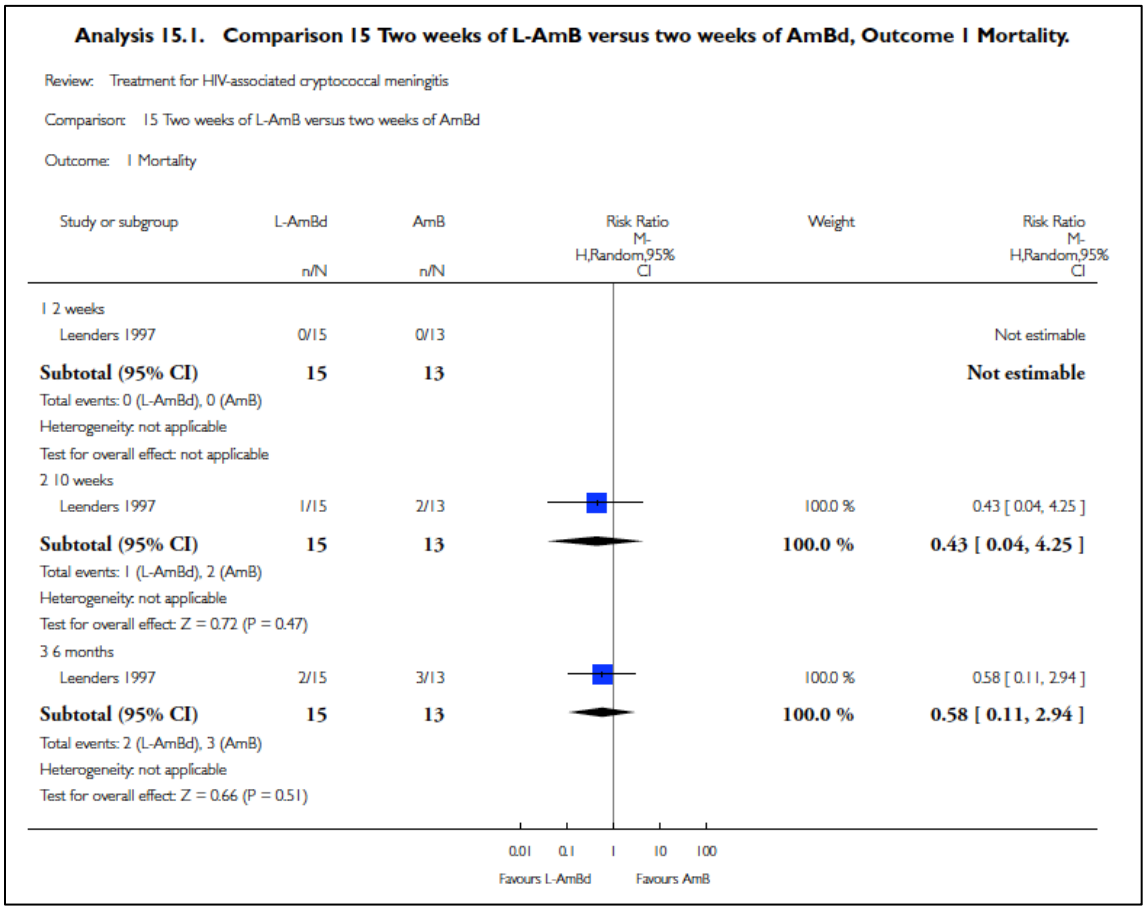
7. Evidence synthesis:

Assessing the treatment of cryptococcal meningitis in HIV-infected patients, Tenforde et al. (Tenforde 2018) specifically assessed the comparison of 2 weeks treatment with liposomal amphotericin B versus 2 weeks treatment with amphotericin B deoxycholate.

Only 1 RCT by Leenders et al. compared a lipid-based amphotericin B preparation to conventional amphotericin B (Leenders 1997). They assessed the outcome of mortality at 10 weeks (primary outcome) and 6 months (secondary

outcome) between the treatment of liposomal amphotericin B for 3 weeks and amphotericin B deoxycholate for 3 weeks (Table 1). The evidence from this RCT was classified as very low by the GRADE classification. There was no significant difference in either of these outcomes (10 weeks: RR 0.43, 95% CI 0.04 to 4.25; 6 months: RR 0.58, 95% CI 0.11 to 2.94), however the trend was toward a benefit (Figure 1). No clinical relapses were observed during the 10-week study period. No proven clinical relapses occurred during the 6-month or further follow-up.

Figure 1



Regarding mycological outcomes, liposomal amphotericin B resulted in a CSF culture conversion within 7 days in 6 out of 15 patients versus 1 out of 12 for amphotericin B deoxycholate (P = 0.09). Within 21 days 11 out of 15 patients treated with liposomal amphotericin B versus 3 out of 8 patients treated with amphotericin B deoxycholate had responded mycologically (P = 0.18). When Kaplan–Meier estimates were used to compare time to CSF culture conversion, liposomal amphotericin B was significantly more effective than for amphotericin B deoxycholate (P < 0.05) (Figure 2). The median time to CSF culture conversion was between 7 and 14 days for liposomal amphotericin B versus > 21 days for amphotericin B deoxycholate. A significant correlation was found between the time to CSF culture conversion and the time to clinical response (r = 0.63; P < 0.001) (Figure 3).

Both treatment regimens were well tolerated. Concerning nephrotoxicity, when increases from baseline of serum creatinine (SCr) levels at the various timepoints were analysed with repeated measurements ANOVA, it was found that this increase was on average a factor of 1.37 (P = 0.003) greater in the amphotericin B deoxycholate treated patients. Three patients treated with liposomal amphotericin B and four patients treated with amphotericin B deoxycholate experienced hypokalaemia, but none of these patients had to discontinue therapy for this reason.

The systematic review and meta-analysis by Botero Aguirre et al. (Botero Aguirre 2015) looked at the benefit of using liposomal amphotericin B, as compared to conventional amphotericin B regarding a two-fold increase in SCr from baseline (Table 1). In this systematic review and meta-analysis comparisons were made using all indications for the use of amphotericin B (Table 1). The risk was significantly reduced (RR 0.49, 95% CI 0.40 – 0.59) with a moderate quality of evidence (GRADE classification). The number needed to treat for this benefit (NNTB) is 6 patients (Figure 4).

Figure 2

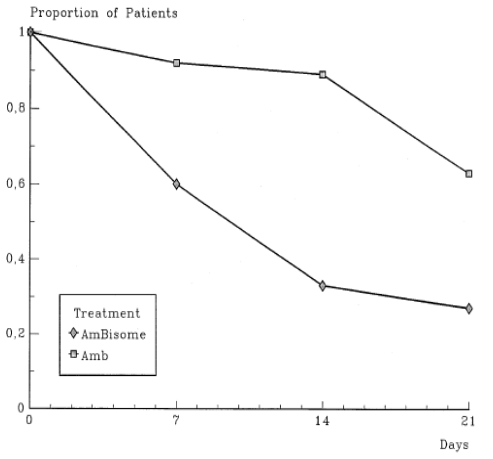


Fig. 1. Kaplan–Meier estimates of the proportion of patients who had positive cerebrospinal fluid cultures during the first 3 weeks of treatment, according to treatment group.

Figure 3

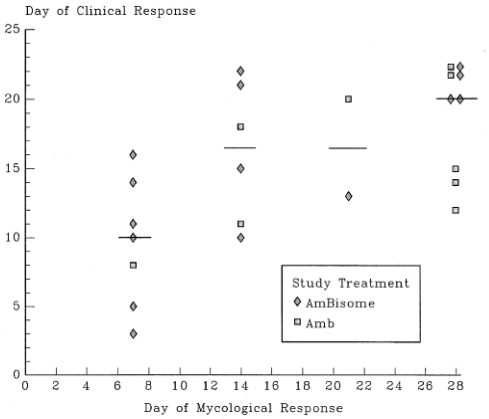


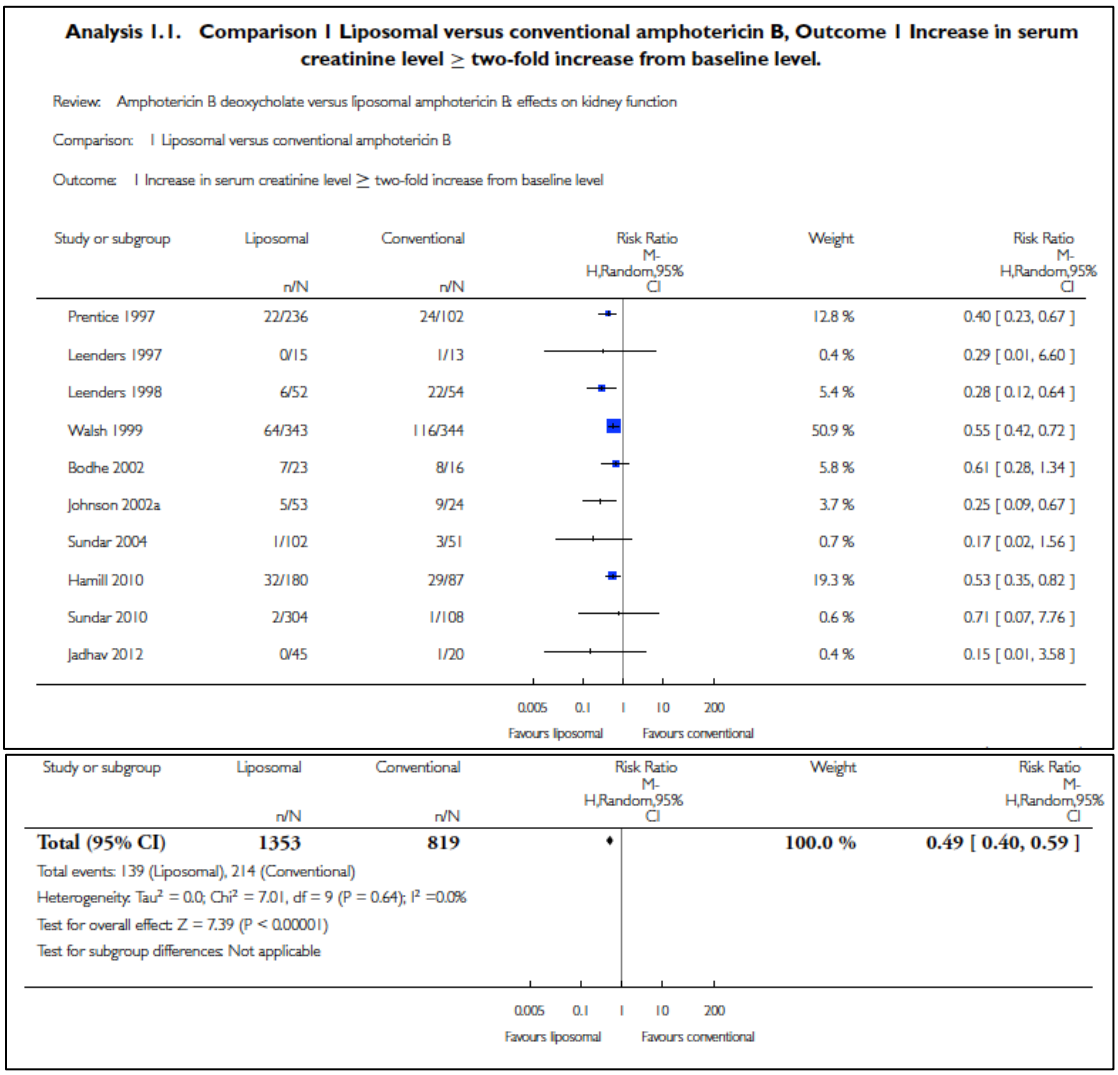
Fig. 2. Correlation between the time to mycological response and the time to clinical response. The times to mycological and clinical response show a significant correlation in AIDS patients with crytococcal meningitis treated with AmBisome or amphotericin B (P = 0.0009 by Spearman rank correlation test).

Nine RCTs included in the systematic review and meta-analysis by Botero Aguirre et al. (Botero Aguirre 2015) assessed infusion related reactions between liposomal amphotericin B and conventional amphotericin B (sodium deoxycholate). There was significant decrease in all infusion-related reactions in the liposomal group compared with the conventional amphotericin B group (Figure 5).

The RCT by Leenders et al. was included in this systematic review and meta-analysis. Only one other included RCT specifically looked at efficacy and safety outcomes in comparing liposomal amphotericin B with amphotericin B deoxycholate for the management of cryptococcal meningitis (Hamill 2010) (Table 1).

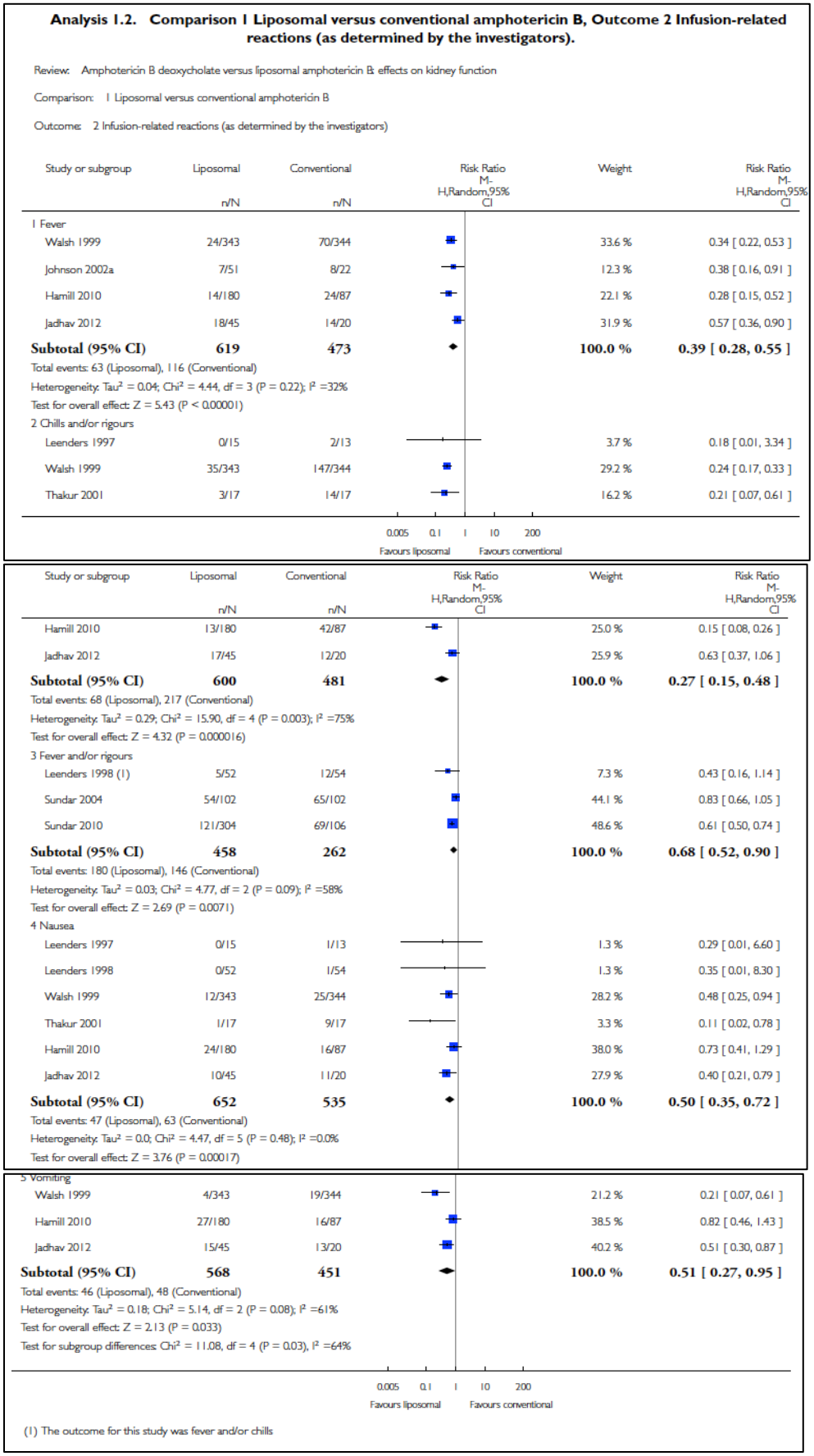
Table 2 reports the primary efficacy end point for the comparison of liposomal amphotericin B versus amphotericin B deoxycholate from Hamill et al. CSF culture results were negative at 2 weeks in 47.5% of patients who received amphotericin B deoxycholate, in 58.3% of those who received liposomal amphotericin B 3 mg/kg/day and in 48.0% of those who received liposomal amphotericin B 6 mg/kg/day. None of these differences among the groups were statistically significant. The lower bounds of the 95% CIs for the treatment differences (liposomal amphotericin B versus amphotericin B deoxycholate) were all greater than -20% but not greater than 0. Consequently, liposomal amphotericin B (combined, 3 and 6 mg/kg/day) was at least as effective as, but not superior to, amphotericin B deoxycholate with regard to mycological success at week 2.

Figure 4



The incidence of infusion-related reactions, as well as the individual frequencies of fever, chills or rigors and respiratory events, were significantly lower for patients administered either dose of liposomal amphotericin B compared with amphotericin B deoxycholate (Table 3). Significant anaemia, as indicated by a hemoglobin concentration <8 g/dL, occurred less frequently in the liposomal amphotericin B 3 mg/kg/day arm (Table 4). Significantly fewer patients who received liposomal amphotericin B 3 mg/kg/day developed nephrotoxicity, as indicated by a doubling of the SCr level (P = 0.04) (Table 4); the difference for liposomal amphotericin B 6 mg/kg/day was not significant, although there was a trend towards less nephrotoxicity (P = 0.066). Significantly fewer patients in the liposomal amphotericin B 3 mg/kg/day arm developed serum potassium values <3 mmol/L than in the other 2 arms (Table 4).

Figure 5


Analysis 1.2. Comparison 1 Liposomal versus conventional amphotericin B, Outcome 2 Infusion-related reactions (as determined by the investigators).
Review: Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function
Comparison: 1 Liposomal versus conventional amphotericin B
Outcome: 2 Infusion-related reactions (as determined by the investigators)
Study or subgroup
Liposomal n/N
Conventional n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
1 Fever
Walsh 1999 24/343 70/344 33.6 % 0.34 [0.22, 0.53]
Johnson 2002a 7/51 8/22 12.3 % 0.38 [0.16, 0.91]
Hamill 2010 14/180 24/87 22.1 % 0.28 [0.15, 0.52]
Jadhav 2012 18/45 14/20 31.9 % 0.57 [0.36, 0.90]
Subtotal (95% CI) 619 473 100.0 % 0.39 [0.28, 0.55]
Total events: 63 (Liposomal), 116 (Conventional)
Heterogeneity: Tau² = 0.04; Chi² = 4.44, df = 3 (P = 0.22); I² =32%
Test for overall effect: Z = 5.43 (P < 0.00001)
2 Chills and/or rigours
Leenders 1997 0/15 2/13 3.7 % 0.18 [0.01, 3.34]
Walsh 1999 35/343 147/344 29.2 % 0.24 [0.17, 0.33]
Thakur 2001 3/17 14/17 16.2 % 0.21 [0.07, 0.61]
0.005 0.1 1 10 200
Favours liposomal
Favours conventional
Hamill 2010 13/180 42/87 25.0 % 0.15 [0.08, 0.26]
Jadhav 2012 17/45 12/20 25.9 % 0.63 [0.37, 1.06]
Subtotal (95% CI) 600 481 100.0 % 0.27 [0.15, 0.48]
Total events: 68 (Liposomal), 217 (Conventional)
Heterogeneity: Tau² = 0.29; Chi² = 15.90, df = 4 (P = 0.003); I² =75%
Test for overall effect: Z = 4.32 (P = 0.000016)
3 Fever and/or rigours
Leenders 1998 (1) 5/52 12/54 7.3 % 0.43 [0.16, 1.14]
Sundar 2004 54/102 65/102 44.1 % 0.83 [0.66, 1.05]
Sundar 2010 121/304 69/106 48.6 % 0.61 [0.50, 0.74]
Subtotal (95% CI) 458 262 100.0 % 0.68 [0.52, 0.90]
Total events: 180 (Liposomal), 146 (Conventional)
Heterogeneity: Tau² = 0.03; Chi² = 4.77, df = 2 (P = 0.09); I² =58%
Test for overall effect: Z = 2.69 (P = 0.0071)
4 Nausea
Leenders 1997 0/15 1/13 1.3 % 0.29 [0.01, 6.60]
Leenders 1998 0/52 1/54 1.3 % 0.35 [0.01, 8.30]
Walsh 1999 12/343 25/344 28.2 % 0.48 [0.25, 0.94]
Thakur 2001 1/17 9/17 3.3 % 0.11 [0.02, 0.78]
Hamill 2010 24/180 16/87 38.0 % 0.73 [0.41, 1.29]
Jadhav 2012 10/45 11/20 27.9 % 0.40 [0.21, 0.79]
Subtotal (95% CI) 652 535 100.0 % 0.50 [0.35, 0.72]
Total events: 47 (Liposomal), 63 (Conventional)
Heterogeneity: Tau² = 0.0; Chi² = 4.47, df = 5 (P = 0.48); I² =0.0%
Test for overall effect: Z = 3.76 (P = 0.00017)
5 Vomiting
Walsh 1999 4/343 19/344 21.2 % 0.21 [0.07, 0.61]
Hamill 2010 27/180 16/87 38.5 % 0.82 [0.46, 1.43]
Jadhav 2012 15/45 13/20 40.2 % 0.51 [0.30, 0.87]
Subtotal (95% CI) 568 451 100.0 % 0.51 [0.27, 0.95]
Total events: 46 (Liposomal), 48 (Conventional)
Heterogeneity: Tau² = 0.18; Chi² = 5.14, df = 2 (P = 0.08); I² =61%
Test for overall effect: Z = 2.13 (P = 0.033)
Test for subgroup differences: Chi² = 11.08, df = 4 (P = 0.03), I² =64%
0.005 0.1 1 10 200
Favours liposomal
Favours conventional
(1) The outcome for this study was fever and/or chills

REVIEW UPDATE (19 MAY 2022)

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis.

Background: A recent publication (Jarvis et al, March 2022) of single dose of liposomal amphotericin B for the treatment of cryptococcal meningitis was reviewed.

The phase 3 trial evaluated the efficacy and safety of a single dose of liposomal amphotericin B (10mg/kg), followed by 14 days of flucytosine (100mg/kg/day) and fluconazole (1200mg/day) compared to a control treatment of amphotericin B deoxycholate (1mg/kg/day) plus flucytosine (100mg/kg/day) for 7 days, followed by 1 week of fluconazole (1200mg/day). This was followed with fluconazole at 800mg/day for 8 weeks, then 200mg/day fluconazole in all patients. The study was conducted in five African countries (8 hospitals).

814 participants with cryptococcal meningitis were included in the intention-to-treat analysis. Those who previously received more than two doses of fluconazole or amphotericin B, pregnancy or breastfeeding, history of adverse reaction to study drugs, elevated alanine aminotransferase, leukopenia, and thrombocytopenia were excluded. All were treated in hospital for at least 7 days.

The mortality rate was 24.8% for the intervention group (95% CI, 20.7 to 29.3) and 28.7% (95% CI, 24.4 to 33.4) for the control group at 10 weeks and the fungal clearance in CSF was similar. Grade 3 or 4 adverse events within the first 21 days of treatment was 50.0% vs 62.3% in the liposomal amphotericin B group compared to the control group. Similarly adverse events such as anaemia, creatinine elevation, and thrombophlebitis were less prevalent in the intervention group.

Conclusion: The liposomal amphotericin B regimen was non-inferior to the control group in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid. The study had a standardized 7-day inpatient monitoring in both arms. The study authors indicated that there may be potential to shorten length of hospital stay with liposomal amphotericin B.

Table 1

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Botero Aguirre 2015	Cochrane systematic review and meta-analyses	2298 participants (2172 participants included in the meta-analysis)	Patients diagnosed with proven, probable or possible invasive fungal infection were included, as well as those with documented or suspected neutropenia (absolute neutrophil count < 500 cells/ mm^3), those considered at high risk for developing invasive fungal infection by investigators, and those with other infectious diseases where amphotericin B is used as primary treatment.	Conventional amphotericin B deoxycholate	<u>Primary outcomes:</u> • Increase in serum creatinine (SCr) level ≥ than two-fold from baseline. <u>Secondary outcomes:</u> • 50% increase in SCr occurring at any time during the study period • Discontinuation of amphotericin B therapy due to nephrotoxicity as determined by the investigators • Increase in SCr > 2 mg/dL at any time during the study period • Change in creatinine clearance (CrCl) from beginning to end of the study • Infusion-related reactions as determined by the investigators.	<u>Increase in serum creatinine:</u> There was a significant increase in SCr level: ≥ two-fold from baseline level with conventional amphotericin B compared to liposomal amphotericin B (10 studies, 2172 participants): RR 0.49, 95% CI 0.40 - 0.59; I2 = 0%). <u>Infusion-related reactions:</u> There was significant decrease in all infusion-related reactions in the liposomal group compared with the conventional group (Analysis 1.2): fever (4 studies, 1092 participants): RR 0.39, 95% CI 0.28 to 0.55; I2 = 32%); chills and/or rigours (5 studies, 1081 participants): RR 0.27, 95% CI 0.15 to 0.48; I2 = 75%); fever and/or rigours (2 studies, 720 participants): RR 0.68, 95% CI 0.52 to 0.90; I2 = 58%); nausea (6 studies, 1187 participants): RR 0.50, 95% CI 0.35 to 0.72; I2 = 0%); and vomiting (3 studies, 1019 participants): RR 0.51, 95% CI 0.27 to 0.95; I2 = 61%).	Overall, risk of bias in included studies was low or unclear for most domains. However, blinding of participants and personnel, blinding of outcome assessment and other bias (funding) tended to have a high risk of bias. Summary of findings for the main comparison provides a concise overview and synthesis of the volume and quality of the evidence for the comparison between liposomal and conventional amphotericin B respect to the increase in SCr level ≥ two-fold from baseline level. Publication bias was not detected and several sensitivity analyses were performed to check the robustness of the effect estimate.
Leenders 1997	Unblinded RCT	30 (2 excluded after randomization including	Inclusion criteria: HIV infected; ≥18 years of age;	3 weeks of conventional amphotericin B deoxycholate	<u>Primary outcome</u> • Clinical and mycological response at the completion of 10 weeks (including	10-week mortality RR 0.43 (95% CI 0.04 – 4.25) and 6-month mortality RR 0.58 (95% CI 0.11 – 2.94)	Certainty of evidence for this trial was classified as GRADE very low (the true effect is likely to be different from the estimate of effect).

		comatose patient without written informed consent from family and patient with negative CSF culture)	positive CSF India ink or CrAg with confirmation by positive CSF culture or CSF CrAg with positive blood culture Exclusion criteria: previous cryptococcal meningitis; SCr >250 µmol/L	vs 3 weeks of liposomal amphotericin B Consolidation: fluconazole 400 mg/day up to 10 weeks, then 200 mg/day maintenance dose	mortality and sterile CSF culture) <u>Secondary outcomes</u> • Mortality up to 6 months		

Table 2

Efficacy of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Parameter	No. (%) of patients, by regimen			Treatment difference, % (95% CI)[a]	
	L-AmB 3	L-AmB 6)	AmB	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Mycological success[b]					
Week 2	35 (58.3)	36 (48)	29 (47.5)	10.8 (−6.9 to 28.5)	0.5 (−16.4 to 17.3)
Week 10	36 (60)	53 (70.7)	48 (78.7)		
Therapeutic success:[c] week 10	27 (67.5)	42 (73.7)	40 (75.5)	−8.0 (−26.5 to 10.6)	−1.8 (−18.1 to 14.5)
Clinical success					
Week 2[d]	48 (65.8)	64 (75.3)	50 (65.8)	…	…
Week 10[e]	31 (70.5)	43 (72.9)	44 (81.5)	…	…
Survival:[f] week 10	74 (86)	85 (90.4)	77 (88.5)	…	…

NOTE. CI, confidence interval; L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

[a] Treatment difference for 1° end point for incidence of mycological success at week 2.

[b] All randomized patients who received ≥1 dose of study drug, had a positive baseline culture result, and underwent ≥1 follow-up culture.

[c] All randomized patients who received ≥1 dose of study drug, had a positive baseline culture result, and underwent ≥1 follow-up culture (ie, mycological evaluable patients) and who completed therapy or died during weeks 2–10.

[d] All randomized patients who received ≥1 dose of study drug and had a positive baseline culture result.

[e] All randomized patients who received ≥1 dose of study drug and had a positive baseline culture result who completed therapy or died during weeks 2–10.

[f] Among the modified intent-to-treat population, the Kaplan-Meier estimate of patient survival was 83.6% (95% CI, 75.7%–91.6%) for the combined liposomal amphotericin B groups and 87% (95% CI, 79.5%–95.6%) for the amphotericin B group.

Table 3

Table 3. Incidence of Infusion-Related Reactions among Recipients of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Infusion-related reaction	No. (%) of patients, by regimen			*P*[a]	
	L-AmB 3 (*n* = 86)	L-AmB 6 (*n* = 94)	AmB (*n* = 87)	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Increase in temperature ≥1.0°C	6 (7)	8 (8.5)	24 (27.6)	<.001	<.001
Chills and/or rigors	5 (5.8)	8 (8.5)	42 (48.3)	<.001	<.001
Nausea	11 (12.8)	13 (13.8)	18 (20.7)	.222	.241
Vomiting	14 (16.3)	13 (13.8)	16 (18.4)	.841	.425
Respiratory system (any adverse event)	0 (0)	1 (1.1)	8 (9.2)	.007	.015
Overall	27 (31.4)	35 (37.2)	58 (66.7)	<.001	<.001

NOTE. AE, adverse event; L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

[a] Determined using the Fisher exact test.

Table 4

Table 4. Adverse Events among Recipients of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Adverse event	No. (%) of patients, by regimen			*P*	
	L-AmB 3	L-AmB 6	AmB	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Creatinine level of 2.0 times baseline and >1.2 mg/dL	12 (14.9)	20 (21.3)	29 (33.3)	.004	.066
Serum potassium level, <3.0 mmol/L	8 (9.3)	33 (35.1)	26 (29.9)	.001	.529
Hemoglobin concentration, ≤8 g/dL	20 (23.3)	39 (41.5)	38 (43.7)	.006	.650

NOTE. L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

a. Evidence quality:

The quality of evidence from the RCT by Leenders et al. was classified as very low by the GRADE classification in the Cochrane systematic review. Hamill et al. was classified as a low risk of bias in the Cochrane systematic review.

8. Alternative agents:

None

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [x] Uncertain: [ ]	Very few trials available that looked at this specific treatment comparison of liposomal amphotericin B versus amphotericin B deoxycholate for the management of cryptococcal meningitis. The available evidence is moderate regarding risk of bias. The recent RCT by Jarvis et al (2022) likewise considered to be of moderate risk of bias.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	The benefits of using liposomal amphotericin B outweigh the risks, specifically regarding safety outcomes: nephrotoxicity, infusion related reactions, electrolyte disturbances, and anaemia. Jarvis et al (2022) found liposomal amphotericin B regimen to be non-inferior to the control group (amphotericin B deoxycholate regimen) in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid - mortality rate of 24.8% (95% CI, 20.7 to 29.3) vs 28.7% (95% CI, 24.4 to 33.4) at 10 weeks and the fungal clearance in CSF was similar. Grade 3 or 4 adverse events within the first 21 days of treatment was 50.0% vs 62.3% in the liposomal amphotericin B group compared to the control group. Similarly adverse events such as anaemia, creatinine elevation, and thrombophlebitis were less prevalent in the intervention group.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [x]	There are no other alternatives available in South Africa for Amphotericin B in the management of cryptococcal meningitis.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [x] **Is the option acceptable to key stakeholders?** Yes: [x] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [x*] Uncertain: [ ] *Similar or less intensive costs with Liposomal amphotericin B compared to current standard of care.	Cost of medicines/unit: **Medicine** / **SEP (ZAR)*** / **MHPL**** AmpB deoxylate 50 mg inj / 155.02 / n/a AmpB liposomal 50 mg inj / 3078.83 / 600 *SEP database, 14 August 2023 ** MHPL 1 Dec 2023 **Induction phase** / **Cost (ZAR)*** 1 week AmpBd/Flucytosine / 5,156 2 week Liposomal AmpB (single dose) Flucytosine/fluconazole / 10,487 **Additional resources:** Refer to cost analysis (Addendum A)
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [x]	Significantly higher cost of liposomal amphotericin B could impact health equity.

FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Implementation is feasible, particularly if restricted to specific patients that will benefit from the improved safety benefits of this agents.

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	[ ]	[ ]	[ ]	[X]	[ ]

Recommendation: Based on the updated evidence review, the PHC/Adult Hospital Level Committee suggests the use of liposomal amphotericin B for treating patients with cryptococcal meningitis.

Liposomal amphotericin B is non-inferior to current standard of care in terms of efficacy and is safer. Liposomal amphotericin B has a similar or lower cost compared to current standard of care, at the latest price of R600 per 50mg vial taking length of hospital stay into account in the costing.

Rationale: The current evidence of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate.

Level of Evidence: Low to moderate certainty evidence

Review indicator: Price reduction

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[ ]	[X]

VEN status: n/a

Vital	Essential	Necessary
[ ]	[ ]	[ ]

NEMLC MEETING OF 21 FEBRUARY 2019:

NEMLC ratified the medicine review and accepted the recommendation not to include liposomal amphotericin B in the Adult Hospital Level EML as although small and of moderate risk of bias, it shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, however it is currently not affordable.

NEMLC MEETING OF 23 JUNE 2022:

NEMLC upheld the previous recommendation not to include liposomal amphotericin B on the national EML, but amended the strength of recommendation from “strong” to “conditional”, with a review indicator of “price reduction”. The NEMLC further recommended that the proposed Gilead price of $16.25 per 50 mg vial be added as a threshold price.

NEMLC MEETING OF 30 NOVEMBER 2023: NEMLC supports the ERC’s recommendation to include the use of liposomal amphotericin B on the EML for the management of cryptococcal meningitis in line with the treatment regimen included in the cost analysis (Addendum A). The Committee supported this recommendation on the basis of the better safety profile of liposomal amphotericin B compared to amphotericin B deoxycholate as well as the potentially lower overall cost with liposomal amphotericin B. The committee however, acknowledged the limitations of modelling the benefits of the better safety profile of liposomal amphotericin B in the cost analysis.

Monitoring and evaluation considerations

Need for restriction and monitoring if allowed for use in patients that require it.

Research priorities

None

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Jarvis JN, Lawrence DS, Meya DB, Kagimu E, Kasibante J, Mpoza E, et al.; Ambition Study Group. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

Mashau 2022

Mashau, R., Meiring, S., Quan, V., Nel, J., et al.; Outcomes of flucytosine-containing combination treatment for cryptococcal meningitis in a South African national access programme: a cross-sectional observational study. The Lancet Infectious Diseases, Volume 22, Issue 9, 1365 - 1373

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	28 Nov 2018	RG and HD	
V3.0	29 may 2022	JM	Updated Jarvis et al, March 2022 and BIA
V4.0	26 October 2023	JM	BIA updated with reduced price of Liposomal amphotericin B and hospitalisation costs

ADDENDUM A:

Liposomal amphotericin B cost analysis

Date of Update: 19 October 2023

Authors: Jacqui Miot, Trudy Leong, Lise Jamieson, Danleen Hongoro

Affiliation(s) and declaration: JM, LJ and DH (Health Economics and Epidemiology Research Office (HE^2RO), University of Witwatersrand) and TL (Essential Drugs Programme, National Department of Health) have no interests pertaining to liposomal amphotericin B.

A cost analysis was conducted based on the data available from the Jarvis et al. publication. A single dose of Liposomal amphotericin B (10mg/kg) followed by 14 days of flucytosine 100mg/kg/day and fluconazole 1200mg/day (Lipo AmB/5FC/Flu) was compared to 1 week of amphotericin B (1mg/kg/day) and flucytosine 100mg/kg/day (1wk AmBd/5FC) followed by 1 week of fluconazole (1200mg/day). This was followed with fluconazole at 800mg/day for 8 weeks, then 200mg/day fluconazole in all patients. The model also presents data from other treatment regimens used in cryptococcal meningitis in South Africa, however, these are simply cost comparisons and not cost-effectiveness analyses (i.e. they don't take into account any differences in clinical benefits).

The model has been updated to reflect recent price changes. Flucytosine is now available on SEP at R1,764.89 per pack of 100 x 500mg tablets, Amphotericin B is available at an SEP of R155.02 per vial and Liposomal amphotericin B was recently awarded on tender at R600 per 50mg vial. Each treatment arm included the cost of the medicines, administration, and infusion costs, consumables, supportive medicines, laboratory monitoring, and hospital stays. In the Jarvis paper, patients in each treatment arm stayed in the hospital for 7 days. Since amphotericin B is given as an infusion, it is necessary for the patients to remain in the hospital in the treatment arm for at least 1 week with flucytosine. In a local cross-sectional observational study of patients with CM, those on flucytosine regimens were compared to other regimens the majority of which was a combination of amphotericin B deoxycholate and fluconazole (Mashau 2022). In this study patients on the flucytosine regimens (of which the majority were flucytosine plus amphotericin B) the median length of stay was 10 days compared to 14 days in the other regimens. Therefore, it is reasonable to assume that in South Africa, the 1-week AmBd/5FC treatment cohort would have a LOS of 10 days. It is possible that patients in the Liposomal amphotericin B arm would be able to leave the hospital sooner and be treated at home, however given the severity of the nature of cryptococcal meningitis this is unlikely to be less than 7 days and so the baseline LOS was assumed to be 7 days.

Medicines costs assumed a patient weight of 60kg and also included pre-emptive hydration and potassium and magnesium supplements in the amphotericin B arm. The medicine and consumable costs were mostly obtained from the Master Health Products Price list (April 2022). Hospital, laboratory, blood transfusion and administration costs were taken from the relevant price lists of 2018 and inflation-adjusted to 2023. We further present two scenarios of costing hospital costs, procedures, supportive medicines: 1) using costs from the Uniform Patient Fee Schedule (UPFS), and 2) using the expenditure per patient day equivalent (PDE) to represent the hospital costs. The PDE hospital cost is a top-down average and therefore includes any consultations, supporting medicines, consumables etc. so these were removed from the PDE analysis.

Table 1: Total medicine Costs

1 week AmBd/5FC									
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**	
Induction phase	Amphotericin B	7	1mg/kg daily	310.04	1.00	310.04	2170.28		
	Dextrose 5%	7	1litre	12.71	1.00	12.71	88.97		
	Flucytosine	7	100mg/kg daily	211.79	1.00	211.79	1482.51		
	Infusions	7		202.00	1.00	202.00	1414.00	**5155.76**	week 1
	Fluconazole	7	1200mg daily	2.25	3.00	6.74	47.18	**47.18**	week 2
Consolidation phase	Fluconazole	56	800mg daily	2.25	2.00	4.49	251.60	**251.60**	**Total**
Maintenance phase	Fluconazole	294	200mg daily	1.12	1.00	1.12	330.23	**330.23**	**R 5,784.76**

2 week 5FC/Flu with single dose Liposomal amphotericin B									
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**	
Induction phase	Liposomal AmB	1	10mg/kg daily	7200.00	1.00	7,200.00	7200.00		
	Dextrose 5%	1	1litre	12.71	1.00	12.71	12.71		
	Flucytosine	14	100mg/kg daily	211.79	1.00	211.79	2965.01		
	Infusions	1		215.37	1.00	215.37	215.37	**10487.44**	
	Fluconazole	14	1200mg daily	2.25	3.00	6.74	94.35		week 2
Consolidation phase	Fluconazole	56	800mg daily	2.25	2.00	4.49	251.60	**251.60**	**Total**
Maintenance phase	Fluconazole	294	200mg daily	1.12	1.00	1.12	330.23	**330.23**	**R 11,069.26**

Total medicine cost for the full regimen including maintenance phase fluconazole was R5,784.76 per patient for the 1-week AmBd/5FC regimen compared to R11,069.26 per patient for the liposomal AmB/5FC regimen.

Table 2: Total Costs Summary

Total Costs Summary (ZAR)				
	UPFS-based		**Expenditure per PDE**	
Per Patient	**2wk 5FC LipAmB**	**1wk AmBd/5FC**	**2wk 5FC LipAmB**	**1wk AmBd/5FC**
Medicine Costs				
Induction (week 1)	10487	5156	10487	5156
Induction (week 2)	-	47	-	47
Consolidation	252	252	252	252
Maintenance	330	330	330	330
ART costs	3319	3319	3319	3319
Total Medicine Costs	**14388**	**9103**	***14388***	***9103***
Hospital Costs				
Secondary level	8433	12048	25816	36881
Other costs				
Supportive Medicines	0	212		
Laboratory Costs (Monitoring)	1675	1675	1675	1675
Lumbar puncture	1570	1570		
ADR Costs				
Blood transfusions	186	442		
Antibiotics	93	75		
Total ADR costs	**280**	**517**		
Total Costs (per patient)	**R26,346**	**R25,125**	**R41,879**	**R47,659**

In our cost analysis, we employed two distinct methodologies, UPFS-based and PDE-based, to assess the overall cost of Liposomal amphotericin B in comparison to two alternative treatments: the 1-week AmBd/5FC course and the standard

2-week AmBd/Flu regimen. When evaluated from the UPFS-based perspective, the total cost analysis, which considered laboratory monitoring, adverse drug reactions (ADRs), hospitalization, and other relevant costs, revealed that Liposomal amphotericin B tends to be relatively more expensive per patient, with a per-patient cost of R26,346 in comparison to the 1-week AmBd/5FC course (R25,125) and the standard 2-week AmBd/Flu treatment (R31,670) (Table 3a). Conversely, when we considered the PDE-Based perspective, the total cost analysis indicated that Liposomal amphotericin B presents as a less expensive choice (R41,879) when contrasted with the 1-week AmBd/5FC course (R47,659) and the standard 2-week AmBd/Flu treatment (R63,753) (Table 3b). Adverse drug reactions that were considered were anaemia requiring blood transfusions and antibiotics for neutropaenia and thrombophlebitis. Dosing and the likelihood of these specific ADRs were sourced from the Jarvis et al. publication. For comprehensive insights into the cost breakdowns for the 1-week AmBd/5FC and 2-week AmBd/5FC (SC) courses, refer to the economic analysis of flucytosine.[2]

The model was sensitive to the LOS. In the UPFS-based costing, where a difference of one day LOS (either 6 days in LipAmB/5FC or 11 days in AmBd/5FC) brought the total costs to neutral (i.e. no cost difference). In the PDE-based costing, if the LOS of LipAmB/5FC increased beyond 8 days (compared to 10 days in the AmBd/5FC arm) or the AmBd/5FC LOS decreased below 8 days (compared to 7 days in the LipAmB/5FC) then the model was no longer cost-neutral and the Liposomal amphotericin B arm because more expensive.

Table 3a: Cost analysis (using UPFS cost for hospital and procedures)

Total Costs (ZAR)	2wk 5FC LipAmB	1wk AmBd/5FC	1wk AmBd/Flu	2wk AmBd/Flu (SC)	Oral
Per pt costs (at 1 year)					
Medicine costs	14,388	9,103	7,548	11,163	6,960
Hospital costs	8,433	12,048	16,867	16,867	20,481
Lumbar puncture	1,570	1,570	734	1,570	1,570
Laboratory costs	1,675	1,675	1,675	957	535
Supportive medicines	0	212	212	225	0
ADR treatment costs	280	517	675	888	396
Total	**26,346**	**25,125**	**27,711**	**31,670**	**29,942**

Table 3b: Cost analysis (using expenditure per PDE for hospital and procedures)

Total Costs (ZAR)	2wk 5FC LipAmB	1wk AmBd/5FC	1wk AmBd/Flu	2wk AmBd/Flu (SC)	Oral
Per pt costs (at 1 year)					
Medicine costs	14,388	9,103	7,548	11,163	6,960
Hospital costs	25,816	36,881	51,633	51,633	62,697
Laboratory costs	1,675	1,675	1,675	957	535
Total	**41,879**	**47,659**	**60,855**	**63,753**	**70,192**

[2] Miot J, Leong T, Takuva S, Parrish A, Dawood H. Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa. BMC Health Serv Res. 2021 Apr 6;21(1):305. https://pubmed.ncbi.nlm.nih.gov/33823842/