Treatment of HIV-associated cryptococcal meningitis

Which combination treatment regimens should be used?

Training module structure

- This training module is organised into 7 sections which can be accessed individually.
- This is section 5: Treatment of HIV-associated cryptococcal meningitis
- It is recommended to complete all sections and access them sequentially from 1 to 7.
- All references and acknowledgments can be found in the notes section of each slide as well as more information and external links to resources.

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ACTA trial results

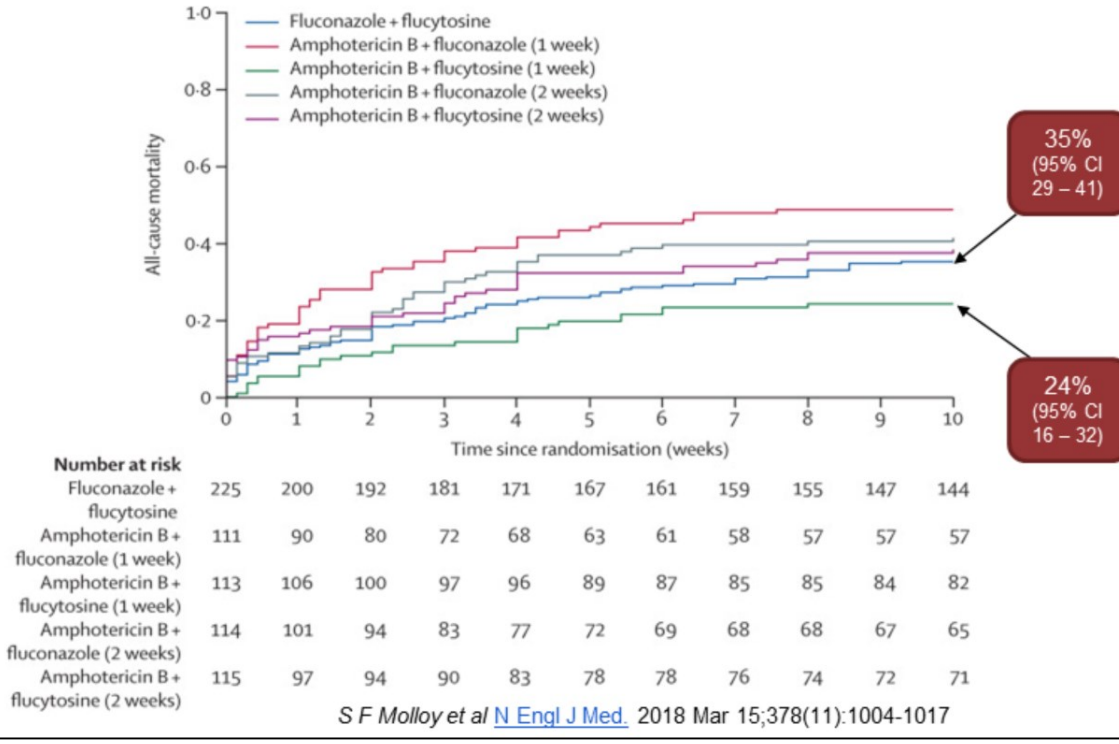

Figure used with permission from *S F Molloy et al* N Engl J Med. 2018 Mar 15;378(11):1004-1017

The results of the ACTA trial showed that short course (1-week) amphotericin B and flucytosine could decrease 10-week mortality to 24% (95% CI −16 to 32). (24.2%; 95% CI, 16.2 to 32.1),
They also showed that 2 weeks of flucytosine and fluconazole performed well and reduced mortality to 35% 35.1 (28.9 – 41.3)

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March 2018 updated WHO guidance on cryptococcal disease

Source: Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

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Treatment principles

Induction phase 1-2 weeks:

- Rapidly clear the organism from the body.

Consolidation phase 8 weeks:

- Ensure disease is fully suppressed.

Maintenance phase until CD4> 100:

- Prevent recurrence of disease after treatment; this phase is also known as secondary prophylaxis.

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Recommended CM induction regimens for LMICs as a result of ACTA – WHO Guidance 2018

In order of recommendation (depending on possibility of safe AmB administration and availability of 5-FC):

- **1/52 AmB (1mg/kg/day) + 5-FC (100mg/kg/day) -gold standard for LMICs**
- **2/52 Fluconazole (1200mg daily) + 5-FC (100mg/kg/day) -alternative**
- 3rd line = 2/52 AmB 1mg/kg/day + Fluconazole 1200mg daily

1/52: 1 week
2/52: 2 week

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Safe AmB administration

AmB dose	Amount drawn up from vial(s)	Number of vials
25mg	5ml	1
30mg	6ml	1
35mg	7ml	1
40mg	8ml	1
45mg	9ml	1
50mg	10ml	1
55mg	11ml	2
60mg	12ml	2
65mg	13ml	2
70mg	14ml	2
75mg	15ml	2
80mg	16ml	2

Pre-hydration

Aim: Avoid hypokalaemia and renal toxicity associated with AmB administration. Administer 1L N. Saline with KCl (20mmol) over 2 hours minimum prior to AmB infusion.
Do not supplement K if patient has pre-existing renal impairment or hyperkalaemia.

Administration

Inject AmB dose into 1000ml bag of 5% Dextrose or 10% Dextrose (*never* N.Saline as medicine will precipitate).
Administer over 4 hours to avoid arrhythmias.
Routine supplements: 1-2 8mEq KCL tablets twice daily, 2x 250mg magnesium glycerophosphate twice daily.

Monitoring

Monitor daily for symptoms & signs of thrombophlebitis.
Monitor full blood count (baseline & weekly) & renal function (baseline & twice weekly).
If amphotericin B-induced rigors occur, the infusion length can be increased. Anti-histamines or hydrocortisone may rarely be required.
If significant hypokalaemia (K<3.3mmol/L), increase K supplementation to one or two 8mEq KCl tablets three times daily, monitor K twice weekly*.
If hypokalaemia remains uncorrected, consider doubling Mg oral supplementation.
*If monitoring facilities allow, consider increased IV KCl supplementation (e.g. additional ampoule of 20 mmol KCl under careful monitoring).

AmB: Amphotericin B deoxycholate

The AmB dose is drawn up according to the table above.

(*Aseptic technique should be observed during this process)*

All patients, unless contraindicated, should routinely receive oral K and Mg supplementation whilst receiving amphotericin B therapy

Note: Routine oral supplementation with magnesium can be with either magnesium glycerophosphate or magnesium chloride.

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Pre-hydration before administration

⚠ DANGER

- AmB can cause LOW POTASSIUM – this can be FATAL.
- Administer 1L Normal Saline with KCl (20mmol) **over a minimum 2 hour** period prior to AmB infusion. Ideally, pre-hydration should be given first thing in the morning.
- Do not supplement with potassium if the patient has pre-existing renal impairment or hyperkalaemia.
- If significant hypokalaemia (K <3.3mmol/L), increase potassium supplementation to one or two 8mEq KCL tablets three times daily. Monitor potassium twice weekly.
- If hypokalaemia remains uncorrected, consider doubling magnesium oral supplementation.

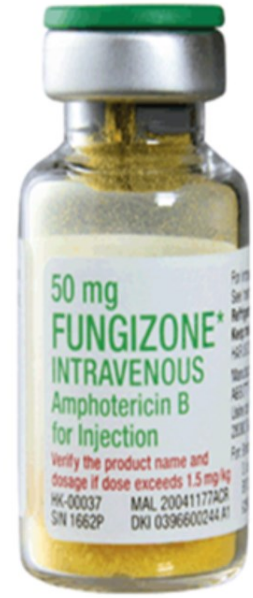
If patients experience AmB-induced rigors, length of administration can be increased. Anti-histamines or hydrocortisone may rarely be required.

If hyperkalaemia is persistent and severe, increased intravenous KCL prehydration may be considered (for e.g. adding an additional 20mml KCl ampoule), however HCW training and careful patient and laboratory monitoring needs to be in place.

Safe Amphotericin B deoxycholate administration

Refer to Safe Administration of Amphotericin B Workshop

- The dose of AmB to be administered daily is **1mg/kg/day**
- Doses usually range between 25mg and 80mg based on patient weight.
- A single infusion is given once daily **over 4 hours.**
- AmB comes in 50mg vials of yellow powder which must be reconstituted with 10ml of water for injection.



DREAMM training, Dar Es Salaam November 2017 - Lead Sister Nurse Amana Hospital, Dar Es Salaam holding a drip infused with the essential antifungal medicine amphotericin B and supportive safe amphotericin B administration poster.
Image courtesy of EDCTP

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Safe Amphotericin B deoxycholate administration

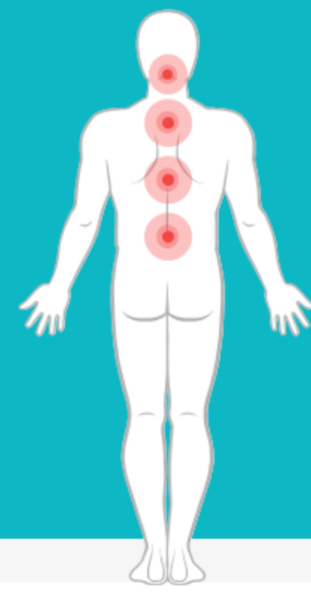
Please refer to the CCM poster and safe AmB administration workshop

- Inject the AmB dose into a 1000ml bag of 5% dextrose or 10% dextrose. Shake to mix.
- ***NEVER* mix AmB with Normal Saline as the drug will precipitate.**
- Administer AmB over **4 hours (no faster)** to avoid arrhythmias, ideally in the morning.
- Once mixed, the bag must be administered within 24 hours or else discarded.
- The line used for AmB should not be used for administering any other drugs.

See Safe Administration of Amphotericin B Workshop for further information.

DREAMM Clinical Training

HIV-associated cryptococcal meningitis



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Education programme topics

- General meningo-encephalitis patient management
- Cryptococcal meningitis - CCM
- Tuberculous meningitis – TBM
- Bacterial meningitis – BM
- Toxoplasmic encephalitis - Toxo
- Neurosyphilis – NS