Managing HIV-associated crytococcal meningitis

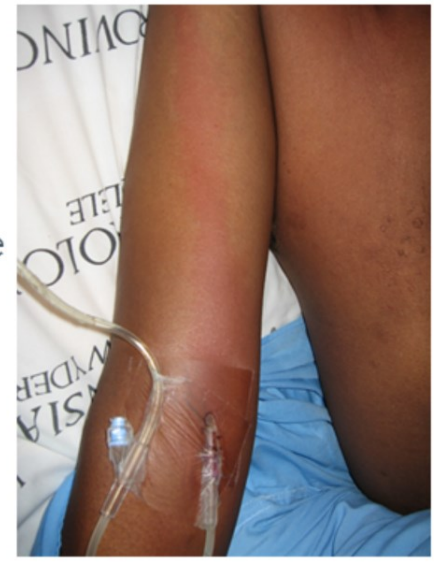
Monitoring and complications

Training module structure

- This training module is organised into 7 sections which can be accessed individually.
- This is section 6: Managing 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.

Thrombophlebitis

- Common side effect of AmB.
- Flush line with 5% dextrose for injection before and after administration.
- Lines must be checked for symptoms and signs of thrombophlebitis on a DAILY basis.



Thrombophlebitis of right arm secondary to administration of Amphotericin B deoxycholate

Thrombophlebitis

- Re-site line at first report of pain or tenderness.
- Swab site of thrombophlebitis.
- Send blood cultures.
- If severe thrombophlebitis give antibiotics – Flucoxacillin first line but check local antibiotic sensitivities.
- Flucolaxacillin covers Methicillin Sensitive Staphylococcus Aureus (MSSA) + Methicillin Sensitive Coagulase Negative Staphylococcus (MS CNS).

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Treatment Monitoring

Schedule for minimum laboratory monitoring required for 1 week AmB + 5FC gold standard regimen for CCM

	Week 1 AmB administration				
Day of Treatment	1	3	4	5	7
Minimum Laboratory Monitoring	Potassium (K) Creatinine (Creat) Haemoglobin (HB)		K Creat HB		K Creat HB

WHO guidance on safe AmB administration (1-2 weeks duration)-WHO guidelines

Monitoring (adults, adolescents and children)	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly

5FC combination therapy

- 5FC may be combined with AmB or fluconazole as recommended induction therapies for CCM.
- Dosing for the induction stage is 100mg/kg/day in 4 divided doses over a 6 hour period
- Note that 5-FC level monitoring for HIV-associated CCM is not routinely required.
- Flucytosine can cause bone marrow depression leading to neutropaenia and thrombocytopenia.
- Nausea and vomiting may occur; this can be prevented by giving capsules individually during a 15 minute window.

Flucytosine dosing schedule

Weight of Patient	Quarterly 6 Hour 5-FC Dosing (mg)	500mg Tablets
30 - 39 kg	500-1000-500-1000	1-2-1-2
40 - 49 kg	1000	2-2-2-2
50 - 59 kg	1000-1500-1000-1500	2-3-2-3
60 - 69 kg	1500	3-3-3-3
70 - 79 kg	1500-1200-1500-2000	3-4-3-4

The majority of patients will be over the 40- 49kg weight band

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5FC dosing in case of renal impairment & neutropaenia

5-FC dose interval adjustment in renal impairment

Creatinine Clearance ml/ min	Individual dose (mg/kg)	Dose Interval (hours)
>40	25	6
20-40	25	12
10-20	25	24
<10	25	>24

Est. Creatinine Clearance =

(140 – age) * (weight in kg) / (72 * Cr in mg/dL)

[Multiply result by 0.85 for women]

5FC dosing in case of neutropaenia

Platelets < 50,000 cells/mm³ or **Neutrophils < 750 cells/mm³**	If grade III range* monitor closely + if worsens then halve dose of flucytosine (50%).
Platelets < 25,000 cells/mm³ or **Neutrophils < 500 cells/mm³**	Monitor closely and halve dose of flucytosine (50%).

*Grade III Platelets: 25,000 ≤ 50,000 cells/mm³

*Grade III Neutrophils: 400—599 cells/mm³

Link to DAIDS AE Grading Table V2.1 July 17

Dose of 5FC may need to be adjusted in case of neutropaenia and also renal impairment (see treatment toxicity section)

If dose adjusting or stopping 5-FC does not cause the neutropaenia to improve or reverse, consider stopping co-trimoxazole.

5-FC monitoring

Minimum 5-FC laboratory monitoring two weeks fluconazole + 5FC regimen

	2 Weeks oral regimen administration				
Day of Treatment	**1**	**3**	**7**	**10**	**14**
Minimum Laboratory Monitoring	**Haemoglobin (HB)** **Neutrophils (N)** **Platelets (P)**		**HB** **N** **P**		

If results abnormal on day 7, repeat on day 10

Treatment toxicity management

- Potassium deficiency
- Magnesium deficiency
- Anaemia
- Neutropaenia
- Renal toxicity

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Potassium replacement

- ALL patients on AmB should receive oral potassium supplementation (except if contraindicated – hyperkalaemia or pre-existing renal impairment).
- IV 20 mmol KCl mixed in 1litre Normal saline infused over minimum 2 hours before AmB administration, ideally first thing in the morning.
- If significant hypokalaemia (K <3.3mmol/l), increase potassium supplementation to one or two 8mEq KCL tablets three times daily. Monitor potassium twice weekly.
- See WHO 2018 guidelines for more details.

Max infusion rate 10mmol /hr by peripheral IV (or 20mmol per hour by central IV). Ampoule should be diluted in at least 100mL of normal saline or 5%.

Administering the pre-hydration first thing means that the AmB can then also be administered during the day, ensuring in part that patients receive careful monitoring of both IV KCl prehydration and AmB administration by routine nursing staff.

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Potassium replacement

- Patients with hypokalaemia despite oral K replacement may require additional IV KCl replacement.*
- Remember –Maximal infusion rate KCl 10mmol /hr by peripheral IV.
- Routine prehydration with IV KCl 20mmol must be given over a minimum period of 2 hours.
- 1 KCl ampoule should be diluted in at least 100mL of normal saline.

See safe administration of amphotericin B workshop for more information

* CAUTION-HCW training on safe KCl administration and adequate monitoring needs to be in place.

Magnesium replacement

- ALL patients (unless contraindicated) should be routinely given oral magnesium supplementation
- 3 tablets daily (12mmols/day Mg glycerophosphate or chloride) to prevent hypomagnesaemia.
- If persistently low serum potassium for >2 days (serum K+ levels <3.0 mmol/L) request Mg measurement (if available).
- Hypokalaemia despite adequate replacement - ASSUME HYPOMAGNESEMIA.
- Patients receive 5g Magnesium sulfate IV daily until serum K+ levels normalize.
- If new seizure develops in setting of hypokalaemia, consider giving Mg Sulfate IV.

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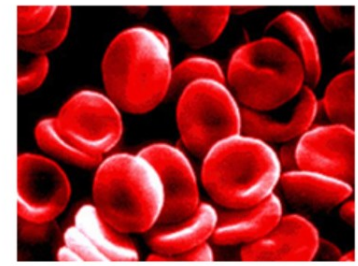
Anaemia management

- Symptoms include shortness of breath, fatigue, tachycardia and chest pain.
- If the haemoglobin <6.5 g/dL or symptomatic consider blood transfusion within local guidelines and practice.
- Risk of sustained severe anaemia must be weighed against the risk of blood transfusion on an individual patient basis.



If baseline Hb is low and patient is receiving amphotericin be vigilant as to likely further reduction in Hb. It may be advisable to make preparations for possible transfusion if this is within practice.

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Renal toxicity Amphotericin B

- If creatinine rises up to 2.5 mg/dl (220 µmol/l):

Miss one dose. Check adequate hydration. Check creatinine next morning:

↓

If stable or improving and creatinine < 2.5 mg/dl: restart daily dosing (1 mg/kg) paying close attention to adequate hydration

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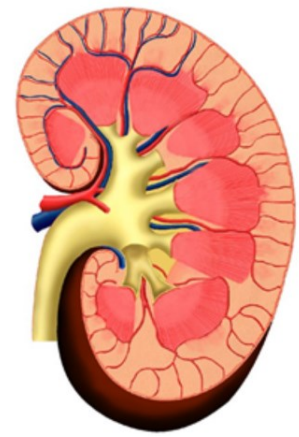
If stable or improving, but still above 220 µmol/l: institute alternate day dosing (1 mg/kg q 4 hours)



If creatinine is increasing do not give amphotericin B and check again after 24 hours:

If stable or improving institute daily or alternate day dosing as above

If still increasing: stop amphotericin B and switch to fluconazole (1200 mg for first 2 weeks of antifungal therapy) adjusting its dose for renal impairment.

AVOID other nephrotoxic agents such as aminoglycosides, NSAIDS if possible.

Amphotericin B renal impairment

- Ensure adequate hydration.
- If creatinine remains high or climbs despite increased hydration then switch to second line induction regimen – 2 weeks fluconazole + 5FC.
- Avoid nephrotoxic drugs such as NSAIDs including ibuprofen and aminoglycosides.
- Monitor electrolytes closely – acute renal failure can lead to life threatening hyperkalaemia.

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Safe administration of Fluconazole

- Oral antifungal available in 50, 100, 150, or 200 mg tablets.
- The 200mg tablet formulation is preferred for CCM treatment – other formulations will be too high pill burden
- Fluconazole is used for the maintenance and consolidation phases of cryptococcal meningitis treatment (different dosage to induction phase).
- Can also be taken as an oral suspension.
- Taken with or without food and taken at any time of day.
- Also used to treat vaginal and oropharyngeal candidiasis.

Note: Fluconazole dosage for 2nd or 3rd line induction treatment of CCM: 1200mg daily in combination with either 5-FC or AmB for 2 weeks.

See safe administration of 5-F and Fluconazole workshop

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Safe administration of Fluconazole

- Fluconazole may increase level of phenytoin, warfarin and sulfonylurea derivatives. If concomitant use of warfarin: check INR.

- If concomitant use of sulfonylurea derivatives there is a risk of hypoglycaemia, so check glucose levels more often.

- Category D risk in pregnancy:
FDA - Chronic, high doses fluconazole(400-800mg/day) may be associated with rare and distinct set of birth defects in infants whose mothers were treated with fluconazole during 1st trimester.

See safe administration of 5-F and Fluconazole workshop

Side effects and drug interactions

Side effects - rare

- Abdominal pain
- Headache, dizziness
- Rash
- Liver toxicity

- HIV medications – nevirapine: Fluconazole increases nevirapine levels.
- Monitor patients closely for signs of liver toxicity.
- TB medications - rifampicin Concomitant use of rifampicin and fluconazole decreases levels of fluconazole in the blood. In practice, fluconazole dose increased by 50% in induction phase. Consider increase 50% fluconazole dose during consolidation and maintenance phases of treatment.

Treatment practicalities in LMICs

- Amphotericin B (AmB) and flucytosine (5-FC) are often not readily available, expensive or avoided over toxicity and safe administration concerns.
- High dose fluconazole commonly used for induction phase treatment but this is inadequate – amphotericin B clears organism much faster.
- Short course AmB and flucytosine is safe and effective when administered and monitored correctly at current recommended dosages.
- Two weeks of 5FC and fluconazole is an effective and well tolerated alternative regimen where AmB therapy is not available or can not be administered safely.

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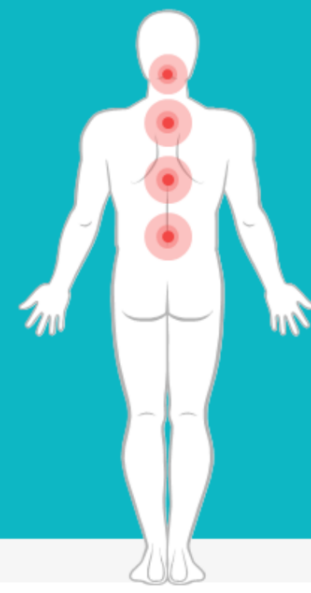
HIV-associated cryptococcal meningitis



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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