DREAMM

Driving Reduced AIDS-associated Meningo-encephalitis Mortality

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EDCTP

Safe Administration of Amphotericin B deoxycholate

Treating Cryptococcal Meningitis

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Workshop Learning Objectives

- To demonstrate the safe administration of amphotericin B deoxycholate (AmB).
- To describe the management of meningo-encephalitis treatment toxicity.
- For more information see online Cryptococcal Meningitis module sections : *Treating HIV-associated Cryptococcal Meningitis*

Recommended CCM 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 week AmB (1mg/kg/day) + 5-FC (100mg/kg/day)**
  -gold standard for LMICs

- **2 weeks Fluconazole (1200mg daily) + 5-FC (100mg/kg/day)**
  -alternative

- 3rd line = 2 weeks AmB 1mg/kg/day + Fluconazole 1200mg daily

LMIC: Low- and middle-income countries, AmB: Amphotericin B deoxycholate, 5-FC: Flucytosine

Safe Administration of Amphotericin B deoxycholate

- Used for treating patients with confirmed cryptococcal meningo-encephalitis.

- Given as part of induction phase of therapy in conjunction with Flucytosine (5-FC), and where 5-FC unavailable fluconazole.

Please refer to the CCM poster, safe 5-FC administration poster and safe 5-FC administration workshop

How to Administer AmB?

- 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.

Please refer to the CCM poster on safe AmB administration

Pre-hydration before Administration

- AmB can cause LOW POTASSIUM – this can be FATAL.
- Administer 1L Normal Saline with Potassium chloride 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 minimum twice weekly.

Administration – Step 1

- AmB comes in 50mg vials of yellow powder which must be reconstituted with 10ml of water for injection.

- The dose is then drawn up according to the following table:

AmBd 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

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

AmB: Amphotericin B deoxycholate

Administration - Step 2

- 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.

AmB: Amphotericin B deoxycholate

Potassium (K) replacement

Please refer to the CCM poster on safe AmB administration

- 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 minimum twice weekly.
- 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% Dextrose
- See WHO 2018 guidelines for more details.

Hr: hour
IV: Intravenous
Max: Maximal
AmB: Amphotericin B deoxycholate

Potassium (K) 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.
- CAUTION-HCW training on safe KCl administration and adequate monitoring needs to be in place.
- Patients with hypokalaemia despite maximal oral K replacement may require additional IV KCl replacement if sufficient monitoring possible and training in place.

Hr: hour
IV: Intravenous
K: Potassium
KCL: Potassium Chloride
HCW: healthcare worker

Magnesium (Mg) 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.

K: Potassium
IV: Intravenous

Monitoring patients on AmB -Thrombophlebitis

- Common side effect of AmB. Lines must be checked for symptoms and signs of thrombophlebitis on a DAILY basis.
- Monitor the patient **daily** for symptoms & signs of thrombophlebitis – pain or tenderness.
- The peripheral line MUST be flushed with 5% dextrose for injection before and after administration of AmB.

Thrombophlebitis of right arm secondary to administration of Amphotericin B deoxycholate

AmB: Amphotericin B deoxycholate

Monitoring patients on AmB -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).

AmB: Amphotericin B deoxycholate

Thrombophlebitis of right arm secondary to administration of Amphotericin B deoxycholate

Monitoring patients on AmB - Rigors

- Monitor full blood count (minimum baseline & weekly) & renal function (minimum baseline & twice weekly).

- If AmB-induced rigors occur, the infusion length can be increased and/or acetaminophen/paracetamol (650-1000mg) PO/PR administered 30 minutes prior to AmB administration.

AmB: Amphotericin B deoxycholate

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

↓

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 creatinine still increasing: stop amphotericin B and switch to fluconazole (1200 mg +5-FC for first 2 weeks of antifungal therapy) adjusting its dose for renal impairment.
- AVOID other nephrotoxic agents such as aminoglycosides and NSAIDs if possible.

AmB: Amphotericin B deoxycholate

NSAIDS: Non-steroidal anti-inflammatory drugs

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 + 5-FC.
- Avoid nephrotoxic drugs such as NSAIDs including ibuprofen and aminoglycosides.
- Monitor electrolytes closely – acute renal failure can lead to life threatening hyperkalaemia.

AmB: Amphotericin B deoxycholate
5-FC: Flucytosine
NSAIDS: Non-steroidal anti-inflammatory drugs

AmB 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

AmB: Amphotericin B deoxycholate

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