REAMM

Driving Reduced AIDS-associated Meningo-encephalitis Mortality

France REcherche Nord & sud Sida-hiv Hépatites

Agence autonome de l'Inserm

E D C T P

Safe Administration of Amphotericin B deoxycholate

Treating Cryptococcal Meningitis

St George's University of London

Centre for Global Health

St. George's University of London

Institute for Infection and Immunity

National Institute for Medical Research

UNC Project Lilongwe, Malawi

Hôpital Central de Yaoundé

Institution Hospitalo-Universitaire

Institut Pasteur

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

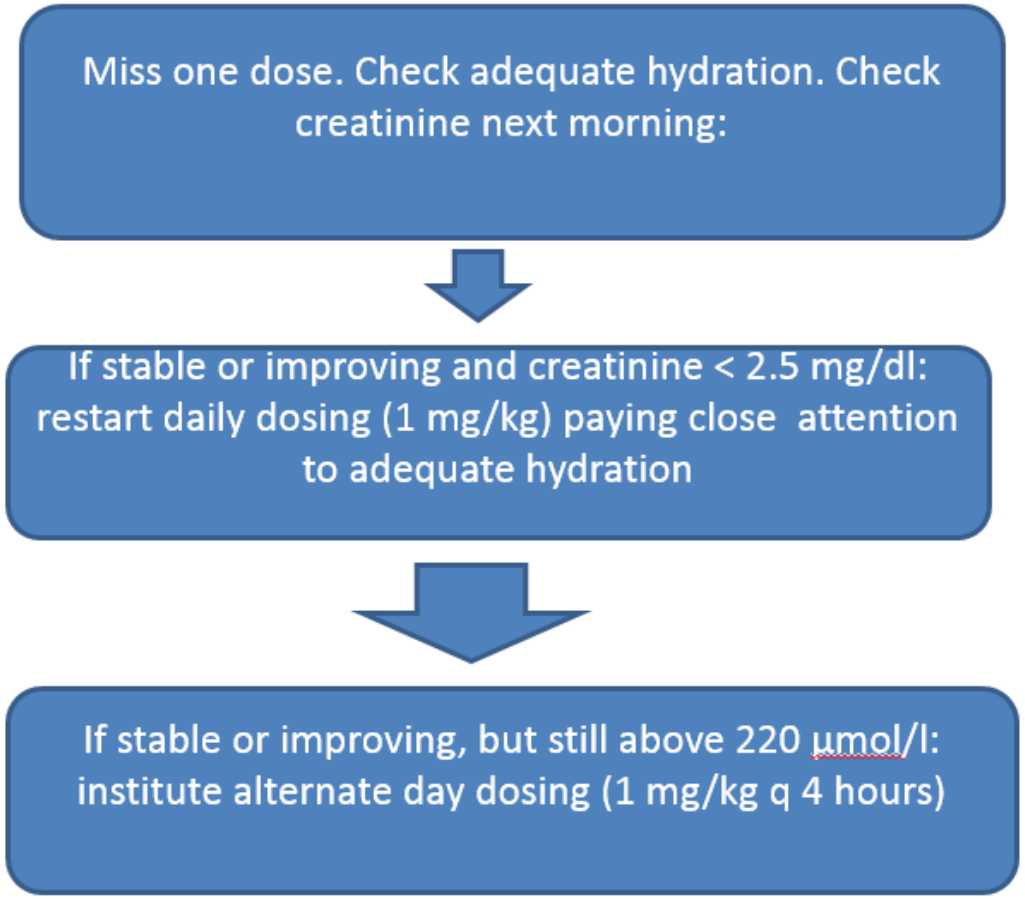
- Monitor full blood count (minimum baseline & weekly) & renal function (minimum baseline & twice weekly).

- 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):



- 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

Authors and affiliations

- St George's University of London

Mr Muirgen Stack – Education lead

Dr Angela Loyse – Academic lead

Prof Tom Harrison

Prof Anne-Marie Reid (previous Dean of Education)

Ms Sarah Burton

Dr Tihana Bicanic

Dr Sile Molloy

Ms Ida Kolte

- Institut Pasteur, France

Ms Aude Sturny-Leclère - Laboratory lead

Dr Timothée Boyer-Chammard – Clinical lead

Prof Olivier Lortholary

- National Institute Communicable Diseases, South Africa

Dr Nelesh Govender

- UNC Project Lilongwe, Malawi

Dr Cecilia Kanyama

- National Institute for Medical Research, Tanzania

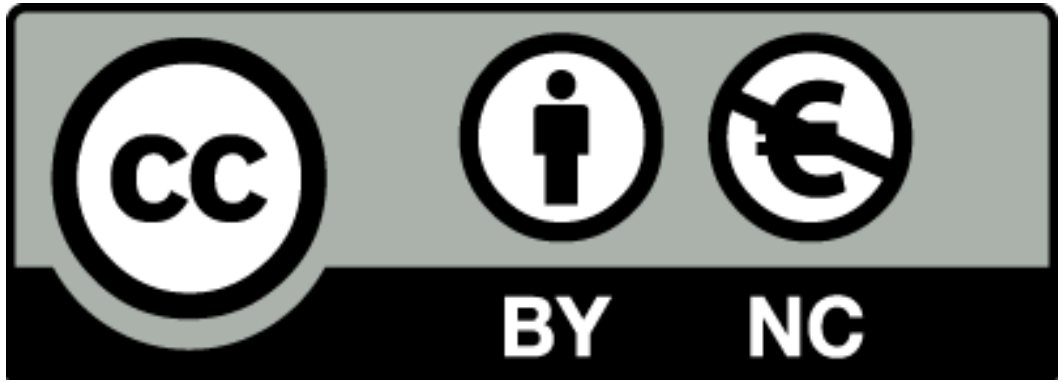
Dr Sayoki Mfinanga

Hôpital Central Yaoundé, Cameroon/ANRS

Dr Charles Kouanfack

Copyright, disclaimer and citation

- This work is licensed under the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0).
- All figures are reproduced with permission where possible.
- The information within this workshop is for guidance only and does not replace local and international guidelines.



Suggested Citation:

DREAMM Clinical Training: HIV–associated Cryptococcal Meningitis. DREAMM Project 2018, St George's University of London, UK. figshare. Available at DOI: 10.24376/rd.sgul.7398596