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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 7
Study Drugs Administration

Title of study	High Dose AMBISOME© on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
Acronym	Ambition-cm – AMBIsome Therapy Induction OptimizatioN		
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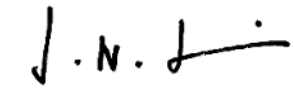
Approved by	Joseph Jarvis CI		20/07/2017

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version

Working Practice Document 7: Study Drugs administration

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Purpose

This document outlines the procedures for study drugs administration.

References

1. Joint Formulary Committee. *British National Formulary*. 66 ed. London: BMJ Group and Pharmaceutical Press; September 2013
2. AMBITION trial protocol
3. WPD 8 – Toxicity management
4. Nicolau DP, Crose H, Nightingale CH and Quintiliani R. Bioavaiability of fluconazole administered via a feeding tube in intensive care unit patients. *J Antimicrob Chemother* 1996;36(2):395-401

Scope

This WPD applies to the procedures for study drugs administration.

Materials

Trial Treatment

British National Formulary

Drug information inserts

NEWT guidance: http://www.newtguidelines.com/GeneralGuidance.html

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1. Ambisome

Rationale:

The aim of this policy is to ensure safe administration of Ambisome (liposomal Amphotericin B).

Procedure:

➢ **Prehydration:**

- Prehydration should ideally be given first thing in the morning.
- Give 1 litre of Normal Saline with 20mmol of KCl infused over 1-2 hours before the Ambisome infusion. This reduces the risk of renal toxicity and hypokalaemia.
- All patients will also be prescribed oral potassium and magnesium supplementation, with:
    - Two tablets twice daily of potassium chloride (Slow-K, 600mg, 8mmol K/tab)
        - Do not administer if most recent K+ >5.0 mmol/L
    - Two tablets once daily of magnesium chloride (Slow-Mag 535mg, 5.33mmol Mg/tab)

  for two days post discontinuation of Ambisome dosing with additional IV or oral supplementation if potassium or magnesium levels drop below normal ranges.
- Intravenous Ambisome is given as a single infusion on day 1.

➢ **Administration:**

Vials of AmBisome containing 50 mg of Amphotericin are prepared as Follows:

1. Add 12 ml of Sterile Water for Injection to each AmBisome vial, to yield a preparation containing 4 mg/ml amphotericin.

2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completely disperse the AmBisome. After reconstitution, the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Do not use if there is any evidence of precipitation of foreign matter.

3. The ultimate aim is to prepare a single, litre bag which contains the Ambisome with the remaining volume made up with dextrose, as per the table below. The first step is to, using

a sterile syringe, remove the equivalent volume of dextrose from the bag which will be replaced by the Ambisome.

4. Next, withdraw the reconstituted AmBisome into a sterile syringe. Using the 5-micron filter provided, instil the AmBisome preparation into the bag of dextrose and shaken to mix.

Example of the preparation of AmBisome solution for infusion at a dose of 10mg/kg/day in dextrose solution for infusion.

Weight (kg)	Number of vials	Total dose of AmBisome	Volume of reconstituted AmBisome (ml) at 4mg/ml	Additional dextrose (ml) to create a 1litre total infusion
40	8	400	100	900
40-45	9	450	112.5	887.5
45-50	10	500	125	875
50-55	11	550	137.5	862.5
55-60	12	600	150	850
60-65	13	650	162.5	837.5
65-70	14	700	175	825
70-75	15	750	187.5	812.5
75-80	16	800	200	800
80-85	17	850	212.5	787.5
85-90	18	900	225	775

- **The Ambisome should NEVER be mixed with Normal Saline or Half Normal Saline as it will precipitate**. The line that is used for Ambisome should not be used for administering any other drugs.

- Once mixed, the bag must be administered within 24 hours or discarded.

- It is not necessary to cover the bag or giving set as sunlight will not degrade the drug in the time taken to complete the infusion.

- The infusion must be given **over 2 hours and not faster** otherwise it can cause cardiac problems. Ambisome should ideally be administered in the morning.

Amphotericin B

Rationale:

The aim of this policy is to ensure safe administration of deoxycholate amphotericin B (Fungizone)

Procedure:

- **Prehydration:**

- Prehydration should ideally be given first thing in the morning.
- Give 1 litre of Normal Saline with 20mmol of KCl infused over 2 hours before the Amphotericin B infusion. This reduces the risk of renal toxicity and hypokalaemia.
- All patients will also be prescribed oral potassium and magnesium supplementation, with:
    - Two tablets twice daily of potassium chloride (Slow-K, 600mg, 8mmol K/tab)
        - Do not administer if most recent K+ >5.0 mmol/L
    - Two tablets once daily of magnesium chloride (Slow-Mag 535mg, 5.33mmol Mg/tab) for the duration of Amphotericin based therapy and two days post discontinuation, with additional IV or oral supplementation if potassium or magnesium levels drop below normal ranges.
- Intravenous Amphotericin B is prescribed according to the patient's weight at 1mg/kg/day therefore doses will usually range between 40mg and 80mg. It is given as a single infusion once daily.

➢ **Administration:**

Amphotericin B comes in 50mg vials of yellow powder. Each vial needs to be **reconstituted with 10ml of Water for Injection**. The dose is then drawn up according to the table below.

Prescribed dose	Amount drawn up from vial(s)	Number of vials required
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

NB A single vial could provide enough drug for more than one day. Efforts should be made to avoid wasting amphotericin B therefore remaining amphotericin can be stored in the fridge and used for the same patient the next day, providing the next dose is given within 24 hours and no doses are omitted.

- The dose must then be injected into a **1000ml bag of 5% Dextrose or 10% Dextrose** and shaken to mix.
- **The Amphotericin B should NEVER be mixed with Normal Saline or Half Normal Saline as it will precipitate**. The line that is used for Amphotericin-B should not be used for administering any other drugs.
- Once mixed, the bag must be administered within 24 hours or discarded.
- It is not necessary to cover the bag or giving set as sunlight will not degrade the drug in the time taken to complete the infusion.
- The infusion must be given **over 4 hours and not faster** otherwise it can cause cardiac problems. Amphotericin B should ideally be administered in the morning.

1. Flucytosine / Fluconazole

Route of administration of fluconazole and flucytosine of patients unable to take oral medication due to impaired swallow, confusion or reduced consciousness:

- Fluconazole capsules can be given down nasogastric tube (bioavailability >97%)
- Flucytosine tablets can be crushed and given down a nasogastric tube

Numerous clinical trials have given FLU and 5FC down NG tubes before. including, but not limited to:

Van Der Horst C, Saag M, Gretchen A et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *NEJM* 1997; 337:15-21.

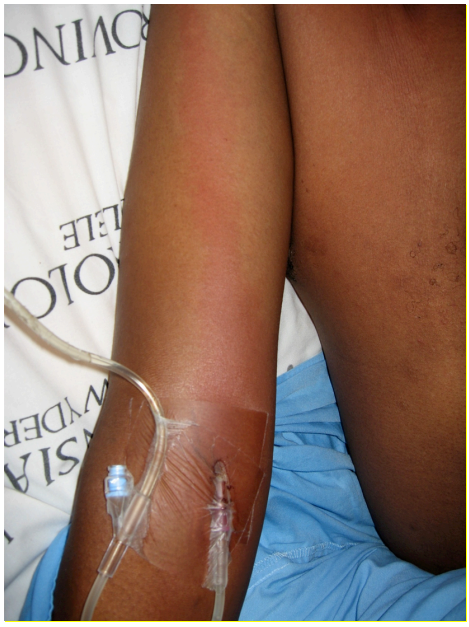
Nussbaum JC, Jackson A, Namarika D et al. Combination flucytosine and high dose fluconazole is superior to fluconazole monotherapy for cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis* 2010; 50(3):338-344

Please refer to the NEWT guidelines when preparing capsule and/or tablets for nasogastric administration.

THROMBOPHLEBITIS

Infusion lines must be checked daily for signs of thrombophlebitis

Picture 1. Thrombophlebitis from a cannula in the right antecubital fossa



Thrombophlebitis is a common side effect of Ambisome or Amphotericin B therapy.

The peripheral line must be flushed with 5% dextrose for injection before and after administration of Ambisome or Amphotericin B.

Peripheral lines must be checked for symptoms and signs of thrombophlebitis on a daily basis. If in doubt, the peripheral line should be re-sited.

If symptoms and signs of thrombophlebitis are present, the peripheral line must be removed immediately and a new peripheral line re-sited. The site of thrombophlebitis should be swabbed and the swab sent to the microbiology laboratory for microscopy, culture and sensitivities. If blood culture microbiology facilities are available, blood cultures should be sent for microscopy, culture and sensitivities.

If the patient has severe thrombophlebitis, is haemodynamically unstable or has a proven line-related bacteraemia, antibiotic therapy is warranted. Take blood cultures if febrile. An appropriate initial antibiotic in the case of severe thrombophlebitis would be flucloxacillin. In areas where there are high levels of MRSA then vancomycin may be preferable. Individual patient management and antibiotic choice should be discussed with the local PI.

Thrombophlebitis requiring antibiotic therapy constitutes a medically important event that should be reported to the Trial Managament Group (TMG) as a SAE.

RIGORS

If patients experience Ambisome or Amphotericin B therapy-induced rigors then follow these steps:

- Assess the patient and monitor observations
- Halve rate of infusion and give paracetamol (500mg if <50kg, 1000mg if ≥50kg)

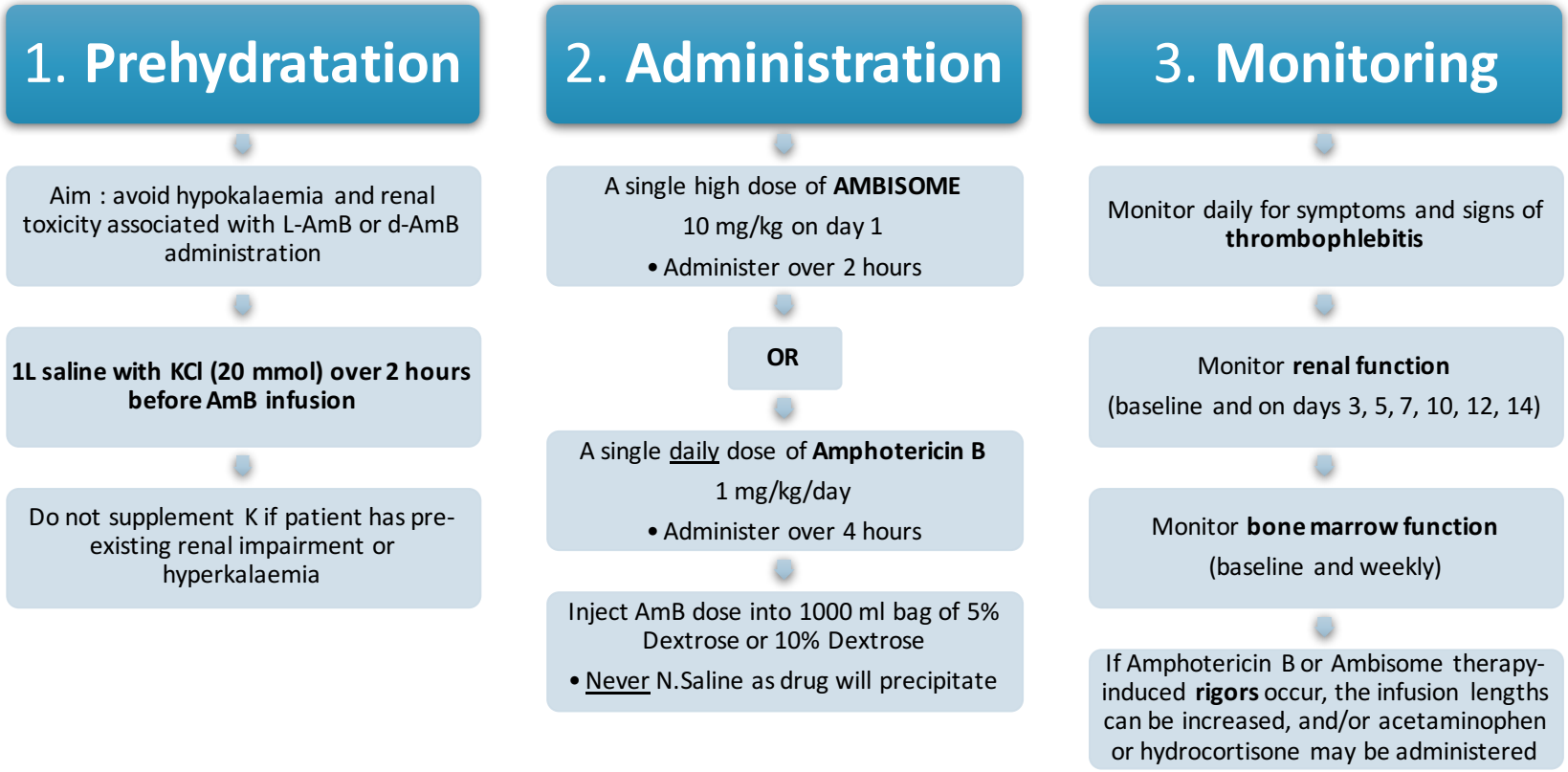
If the rigors continue:

- Stop the infusion
- Assess the patient and monitor observations
- Consider hydrocortisone (200mg IM or IV)
- Restart the infusion after one hour at the same, halved rate of infusion

If the rigors continue:

- Stop the infusion indefinitely
- Assess the patient and monitor observations
- Give hydrocortisone (200mg IM or IV) if not already administered
- Contact the local PI or a senior clinician

SUMMARY


1. Prehydratation
Aim : avoid hypokalaemia and renal toxicity associated with L-AmB or d-AmB administration
1L saline with KCl (20 mmol) over 2 hours before AmB infusion
Do not supplement K if patient has pre-existing renal impairment or hyperkalaemia
2. Administration
A single high dose of AMBISOME
10 mg/kg on day 1
• Administer over 2 hours
OR
A single daily dose of Amphotericin B
1 mg/kg/day
• Administer over 4 hours
Inject AmB dose into 1000 ml bag of 5% Dextrose or 10% Dextrose
• Never N.Saline as drug will precipitate
3. Monitoring
Monitor daily for symptoms and signs of thrombophlebitis
Monitor renal function
(baseline and on days 3, 5, 7, 10, 12, 14)
Monitor bone marrow function
(baseline and weekly)
If Amphotericin B or Ambisome therapy-induced rigors occur, the infusion lengths can be increased, and/or acetaminophen or hydrocortisone may be administered

Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the training log located in the Investigator Site File (ISF)

New staff are trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

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Staff signatures: (signing below indicate that you have read this SOP and understand the material contained in it)

Date	Name (Please print)	Signature