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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 8
Toxicity Management

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		
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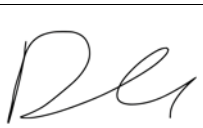
Author(s)	David Lawrence Lead Clinician		14/06/2018
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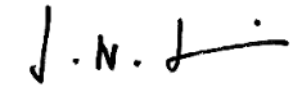
Approved by	Joseph Jarvis CI		14/06/2018

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version
1.1	14/06/2018	Addition of guidance for drug induced liver injury

Working Practice Document 8: Toxicity management

Purpose

This document outlines potassium and magnesium replacement for study patients receiving Ambisome or amphotericin B, the management of anaemia, the management of neutropenia, the management of renal and hepatic toxicity and the management of participants who become pregnant.

References

1. AMBITION Trial Protocol
2. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2
3. Oxford Handbook of Clinical Medicine, 8th Edition, Oxford University Press, April 2010
4. Joint Formulary Committee. *British National Formulary*. 66 ed. London: BMJ Group and Pharmaceutical Press; September 2013

Scope

This WPD applies to potassium and magnesium replacement for study patients receiving Ambisome or amphotericin B, the management of anaemia, the management of neutropenia, the management of renal and hepatic toxicity and the management of participants who become pregnant during the trial.

Materials

WPD 3: Patient enrolment and follow-up

SOP AE-SAE reporting

AMBITION Table to Grade the Severity of Adverse Events in Adults (DAIDs)

Working Practice Document 8: Toxicity management

1. Hypokalaemia

Ambisome or amphotericin B can cause hypokalaemia.

	Grade I	Grade II	Grade III	Grade IV
Potassium, serum, high	5.6 to < 6.0 *mmol/L*	6.0 to < 6.5 *mmol/L*	6.5 to < 7.0 *mmol/L*	≥ 7.0 *mmol/L*
Potassium, serum, low	3.0 to < 3.4 *mmol/L*	2.5 to < 3.0 *mmol/L*	2.0 to < 2.5 *mmol/L*	< *2.0 mmol/L*

Grade IV hypo or hyperkalaemia must be reported to the TMG within 24 hours.

All patients receiving Ambisome or amphotericin B as part of the study regimen will receive oral potassium supplementation on study enrolment, unless contraindicated (e.g. K+ >5.0 mmol/L).

Patient electrolytes will be measured routinely on study days 1, 3, 5, 7, 10, 12 and 14

Routine Potassium Supplementation:

- Intravenous 20mmol of KCl in I litre of normal saline should be infused over 2 hours on a daily basis prior to amphotericin administration
- Oral supplementation with 2 tablets of 600mg KCl twice daily: each tablet is equivalent to 8mmol of K+ equalling a daily supplement of 32mmol per day.

General Safety of Potassium Replacement:

- If hypokalemia is detected increase oral supplementation: a maximum of 24mmol (3 tablets) every 6 hours is permitted. Nausea can be a dose-limiting problem. Dosing should be based on serum potassium levels and renal function.
- For IV KCl the maximum infusion rate is 10mmol per one hour by peripheral IV (or 20mmol per hour by central IV). The ampoule should be diluted in at least 100mL of normal saline or 5% fluid.
- As much as 200mmol/day may be required for adequate replacement in the setting of amphotericin use, though this should be given in divided doses; both IV and PO methods of introduction should be utilized.
- If abnormal potassium levels are identified and treated then bloods must be repeated daily until levels have normalised

2. Hypomagnesaemia

Ambisome or amphotericin B can cause hypomagnesaemia.

	Grade I	Grade II	Grade III	Grade IV
Magnesium, serum, low mmol/L	0.60 to <0.70	0.45 to < 0.60	0.30 to <0.45	*<0.30*

Grade IV hypomagnesaemia must be reported to the TMG within 24 hours.

All patients receiving Ambisome or amphotericin B as part of the study regimen will receive oral magnesium supplementation on study enrolment, unless at sites where magnesium monitoring is available and oral replacement is contraindicated (e.g Mg >1.0 mmol/L).

Magnesium Replacement:

- All patients will receive oral magnesium supplementation: 2 tablets of Slow-Mag daily (535mg/tab or 10.66mmol/day) to prevent hypomagnesaemia.
- If patients exhibit persistently low serum potassium for ≥2 days (serum K^+ levels <3.0 mmol/L) despite adequate potassium replacement (>100 mmol K^+/day), request a measurement of serum magnesium (if available), as low magnesium may be responsible for the refractory hypokalaemia.
- If hypomagnesaemia is present oral supplementation can be increased to a maximum of 2 tablets four times a day (total 42mmol/day) but this will likely cause gastrointestinal disturbance.
- If a Grade III magnesium (<0.45 mmol/L) is found despite adequate oral magnesium replacement, IV Mg^{2+} replacement should be given as follows:
    a. Patients will receive 5g magnesium sulfate IV daily until serum magnesium levels normalize. (if magnesium level measurement is unavailable, normalising serum potassium levels can be used as a surrogate marker for adequacy of magnesium replacement.)
    b. $MgSO_4$ comes in vials containing 5g in 10mL solution (50%) which contains 40.5 mmoL of Mg^{2+} that must be mixed with 500 mL of IV normal saline to produce a 0.8% concentration. This may be a constituent of the routine 1 litre normal saline given pre-amphotericin, or an additional 500 mL.
    c. The $MgSO_4$ IV infusion rate should not exceed 150 mg/minute, thus 500 mL infused over >33 minutes is safe. In seizures, this 5g dose is routinely given within 3-4 minutes in a 10% concentration, thus ≤10% concentrations have a very wide safety tolerance.
    d. IV $MgSO_4$ may be administered concurrently with IV KCl replacement in the same IV fluid and through the same intravenous line.
    e. Alternatively, the 5g (50%) solution can also be injected intramuscularly into the buttock.

3. Anaemia

	Grade I	Grade II	Grade III	Grade IV
Haemoglobin (g/dl), Male	10.0 to 10.9	9.0 to < 10.0	7.0 to < 9.0	< 7.0
Haemoglobin (g/dl), Female	9.5 to 10.4	8.5 to < 9.5	6.5 to < 8.5	< 6.5

Grade IV anaemia must be reported to the TMG within 24 hours

If the haemoglobin <6g/dL or the patient is very symptomatic due to their anaemia (e.g. short of breath, fatigued, tachycardic), consider blood transfusion. The risk of sustained severe anaemia must be weighed by the study doctor against the risk of blood transfusion in resource poor settings on an individual patient basis. A clinical decision may be made to stop amphotericin B prematurely, but this should only be done after discussion with the PI. As a rule, if amphotericin B is held then the missed doses are not to be given after day 7.

If a patient requires a blood transfusion then bloods must be repeated the following day.

4. Neutropenia

Flucytosine can cause bone marrow depression leading to neutropenia.

	Grade I	Grade II	Grade III	Grade IV
Neutrophil Count, Low (cells/mm3; *cells/L*)	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*

Grade IV neutropenia must be reported to the TMG within 24 hours.

If a patient has a grade III or IV neutropenia then bloods must be repeated the following day.

If a patient has a *sustained* Grade III neutropenia (confirmed on following day), halve the dose of flucytosine. If grade IV Neutropenia, or the patient develops neutropenia-related complications, hold the flucytosine (5-FC) immediately. Consider re-introduction if the count the following day is grade III or better. If grade III re-introduce at half dose, if grade II or less then re-introduce at normal dose. Please discuss patient management further, as necessary, with the local PI. As a rule, if doses of flucytosine are held then they are not to be given at a later date.

Suggested strategy for suspected flucytosine induced neutropenia:

Grade III	Neutrophils < 600 x 10^6 /L)	Monitor FBC daily. If grade III is confirmed next day, halve dose of flucytosine (50%);
Grade IV	Neutrophils < 400 x 10^6 /L)	Stop flucytosine, until grade III level at which point resume at 50% dose

Recall that neutrophils <500 x10^6/L at baseline is an early withdrawal criteria for the patient.

If stopping flucytosine does not cause the neutropaenia to improve or reverse, consider stopping co-trimoxazole.

These are guidelines only and each case should be discussed with the site PI before changing doses of trial drugs

5. Thrombocytopoenia

Flucytosine can cause bone marrow depression leading to thrombocytopenia.

	Grade I	Grade II	Grade III	Grade IV
Platelet count, Low (cells/mm^3)	100,000 to <125,000	50,000-<100,000	25,000 to < 50,000	<25,000

Grade IV thrombocytopoenia must be reported to the TMG within 24 hours.

If a patient has a grade III or IV thrombocytopoenia then bloods must be repeated the following day.

If a patient has a *sustained* Grade III thrombocytopoenia (confirmed on following day), halve the dose of flucytosine. If grade IV thrombocytopoenia, or the patient develops thrombocytopoenia-related complications, hold the flucytosine (5-FC) immediately. Consider re-introduction if the count the following day is grade III or better. If grade III re-introduce at half dose, if grade II or less then re-introduce at normal dose. Please discuss patient management further, as necessary, with the local PI. As a rule, if doses of flucytosine are held then they are not to be given at a later date.

Suggested strategy for suspected flucytosine induced thrombocytopoenia:

Grade III	Platelets 25,000 to < 50,000 cells/mm^3	Monitor FBC daily. If grade III is confirmed next day, halve dose of flucytosine (50%);
Grade IV	Platelets < 25,000 cells/mm^3	Stop flucytosine, until grade III level at which point resume at 50% dose

Recall that platelets < 50,000 cells/mm^3 at baseline is an early withdrawal criteria for the patient.

If stopping flucytosine does not cause the thrombocytopoenia to improve or reverse, consider stopping co-trimoxazole.

These are guidelines only and each case should be discussed with the site PI before changing doses of trial drugs.

6. Renal toxicity

	Grade I	Grade II	Grade III	Grade IV
Creatinine, High	>1.43 – 1.69 mg/dL >127 – 150 µmol/L (1.1 to 1.3 ULN*)	>1.69 - 2.47 mg/dL >150 – 216 µmol/L (<1.3 to 1.9 ULN)	>2.47 - 4.55 mg/dL >216 – 400 µmol/L (1.9 - 3.4 x ULN)	>4.55 mg/dL >400 µmol/L (≥ 3.5 x ULN)

*ULN = Upper Limit of Normal

Grade III and IV AEs will be generated by the Electronic Data Capture system when a patient has the creatinine levels stated in the table above. Absolute creatinine will be the guiding figure for AE reporting but be conscious of the need to calculate creatinine clearance particularly for adjusting the dose of drugs.

Grade IV nephrotoxicity must be reported to the TMG within 24 hours.

General Principles

- Ensure adequate hydration
- Assess need for nephrotoxic drugs e.g. ibuprofen and stop if possible
- Monitor electrolytes closely – acute renal failure can lead to life threatening hyperkalaemia

Dose adjustment for renal failure

Amphotericin-B-deoxycholate

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 < 220 µmol/l: 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 48 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.
- As a rule, if doses of amphotericin B are held then the missed doses are not to be given after day 7.
- AVOID other nephrotoxic agents such as aminoglycosides, NSAIDS if possible.

NB This is a guideline only and all dose adjustments should be discussed with the site PI.

Flucytosine

Dose adjustment for reduced creatinine clearance as follows:

Creatinine clearance ml/min	Individual dose mg/kg	Dose interval hour
>40	**25**	**6**
40-20	**25**	**12**
20-10	**25**	**24**
<10	**25**	**>24**

Fluconazole

If creatinine clearance reduces to < 50 ml/minute give same initial dose but reduce subsequent doses by 50%.

NB This is a guideline only and all dose adjustments should be discussed with the site PI.

7. Drug-induced liver injury

	Grade I	Grade II	**Grade III**	**Grade IV**
ALT (or SGPT), High	50 to < 100 IU/L 1.25 to < 2.5 x ULN	100 to <200 IU/L 2.5 to < 5.0 x ULN	200 - 400 IU/L 5.0 to < 10.0 x ULN	> 400 IU/L ≥ 10.0 x ULN

ULN = Upper Limit of Normal

Grade IV hepatotoxicity must be reported to the TMG within 24 hours.

Grade III and IV AEs will be generated by the Electronic Data Capture system when a patient has the ALT levels stated in the table above.

Diagnosis

- Nonspecific symptoms developing after introduction of a drug (such as nausea, anorexia, malaise, fatigue, right upper quadrant pain, or pruritus) may indicate drug toxicity and should prompt an evaluation for drug-induced liver injury.
- The diagnosis needs to include additional blood tests to assess the cause of hepatic injury including full liver function tests, coagulation screen and hepatitis serology.
- If there is suspicion of cholestasis, imaging to rule out biliary obstruction is also indicated.

General Principles

- The first treatment for drug-induced liver injury is the withdrawal of the toxicity-associated suspected drugs – e.g. TB treatment, co-trimoxazole, flucytosine or fluconazole could be held in the case of Grade IV hepatotoxicity.
- Monitor ALT level closely, until improvement.
- Consider reintroduction of drugs carefully when ALT level becomes 200 IU/L or less.
- Continue monitoring closely after reintroducing drugs.
- As a rule, if doses of flucytosine or high dose fluconazole are held then they are not to be given at a later date.

8. Management of participants who become pregnant during the trial

Although very unlikely, due to severity of disease, it is possible that a female participant may become pregnant while on consolidation therapy with fluconazole during the 8-week trial follow-up period.

- At the beginning of the trial all women should be informed that fluconazole is not-known to be safe in pregnancy and that it is advised she does not become pregnant during the one year fluconazole consolidation/maintenance therapy.

- If a woman does become pregnant the case should be discussed with the PI on a case-by-case basis.

- On termination from the trial at week 10 women should again be advised to avoid pregnancy until the end of fluconazole maintenance therapy. It should however be strongly reiterated that continuation of fluconazole therapy is vital to stop the meningitis recurring and stopping is not advised.

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.

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

Date	Name (Please print)	Signature