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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 9
Management of deteriorating patients

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		
ISRCTN No.:	ISRCTN72509687		
WPD Current version	Version 1.0, 20/07/2017		
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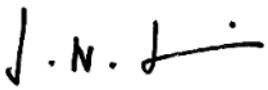
Approved by	Joseph Jarvis CI		20/07/2017

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

Working Practice Document 9: Management of deteriorating patients

Purpose

This document outlines the management of deteriorating patients.

References

1. AMBITION Trial Protocol
2. Oxford Handbook of Clinical Medicine, 8th Edition, Oxford University Press, April 2010
3. Joint Formulary Committee. *British National Formulary*. 66 ed. London: BMJ Group and Pharmaceutical Press; September 2013

Scope

This WPD applies to the management of some of the likelier causes for the deterioration of patients.

Materials

WPD 7, 8, & 11: Study drugs administration, Toxicity management, Management of patients with recurrent symptoms and possible IRIS

Deteriorating patients should be discussed as soon as possible with the local PI and, as required, with the TMG.

This WPD does not aim to replace basic medical care of the patient that will be provided on a case-by-case basis by the responsible clinicians, study Doctor and local PI.

The following recommendations serve as INITIAL GUIDANCE ONLY for the management of patients who are deteriorating. Local guidelines for managing clinical syndromes vary.

1. Reduction of GCS

- If imaging is readily available and can be obtained without delay, patient to receive brain scanning followed by LP with opening pressure (OP) measurement.

- In the absence of imaging facilities, the existing balance of evidence favours urgent lumbar puncture and measurement of OP.

- Blood tests including FBC, U&E, LFTs, and glucose should be performed.

- A full septic screen (CXR, urine dipstick and culture, blood culture if available) should be performed if raised intracranial pressure is not the obvious cause of the reduction in GCS.

- Review the drug chart for any concomitant medication which may reduce GCS

- The patient's induction antifungal regimen should continue unchanged. Any changes should be discussed first with the local PI.

- The need for broad spectrum antibiotics is to be decided by the study Dr and local PI.

2. <u>New onset of fever despite therapy for cryptococcal meningitis</u>

Cause of fever should be investigated with the following;

- Full clinical examination
- FBC and U&E
- Blood cultures if available
- Inspection of IV-line site
- Urine dipstick for nitrites, leucocytes and microscopy/culture if available
- Chest X ray if respiratory symptoms
- Sputum for AFBs and microscopy/culture if coughing
- Stool microscopy and culture if appropriate and available
- Decision to start antimicrobials rests with the study doctors though in suspected sepsis this should not be unduly delayed.
- Remember that nosocomial sepsis occurs in roughly 15% of patients receiving amphotericin based therapy for cryptococcal meningitis. Antibiotic choice should be made in light of local antimicrobial resistance patterns.

3. <u>New onset of shortness of breath</u>

- Full clinical examination with a focus on chest examination
- FBC and U&E

- Chest X Ray
- Sputum for AFB and culture if coughing
- ECG, if available
- Oxygen saturation measurement, if available
- Arterial blood gas, if available

4. Seizures

- ABC – Airways, breathing and circulation
- Check random blood glucose
- Treat in line with local site seizure protocol.
- An example is as follows:
    - 10mg (2mls) of diazepam in 8 ml of 5% Glucose or 0.9% saline
    - Given by slow IV or rectally if no IV access
    - Repeat if convulsion persists beyond 5 minutes
- If second dose diazepam fails, treat as status epilepticus
    - Oxygen supplementation
    - Phenobarbital 10-15mg/kg at max 100mg/minute. Maximum dose 1 gram.
    - Once the seizures have stopped, reduce the infusion rate

5. Recurrence of CM symptoms and possible IRIS

Please refer to the recurrence of symptoms WPD

6. **Drug toxicity & thrombophlebitis**

   Please refer to individual WPDs on toxicity management and Amphotericin B and Ambisome administration

Antituberculous therapy and antiretroviral therapy will be provided by local clinics.

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 WPD and understand the material contained in it)

Date	Name (Please print)	Signature