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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 11
Management of patients with recurrent symptoms and possible Immune Reconstitution Inflammatory Syndrome (IRIS)

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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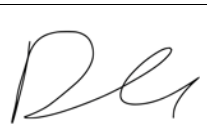
Author(s)	David Lawrence Lead Clinician		20/07/2017
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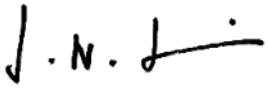
Approved by	Joseph Jarvis CI		20/07/2017

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

Working Practice Document 11: Management of patients with recurrent symptoms and possible Immune Reconstitution Inflammatory Syndrome (IRIS)

Purpose

This document describes the process of managing patients with recurrent symptoms and possible IRIS

References

1. Longley N, Harrison TS, Jarvis JN. Cryptococcal immune reconstitution inflammatory syndrome. Curr Opin Infect Dis. 2013 Feb;26(1):26-34

2. Wiesner DL, Boulware DR, Cryptococcus-Related Immune Reconstitution Inflammatory Syndrome (IRIS): Pathogenesis and Its Clinical Implications. Curr Fungal Infect Rep. 2011 Dec 1;5(4):252-261.

3. Haddow LJ et al; Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. International Network for the Study of HIV-associated IRIS (INSHI). Lancet Infect Dis. 2010 Nov;10(11):791-802.

4. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis 2010; 50:291.

Scope

This WPD applies to the process of managing patients with recurrent symptoms and possible IRIS

Materials

WPD 12: Lumbar Puncture

WPD 10: Management of raised intracranial pressure

Study patients will be provided with the contact numbers of the study team and encouraged to present to medical attention early in case of recurrence of symptoms such as headache.

Patients with recurrence of symptoms will be assessed at the earliest opportunity by the study team. If the team is alerted out of hours regarding a recurrence of symptoms in a study patient, the patient should be preferentially assessed at the site hospital.

Possible reasons for symptomatic re-presentation include:

1. **IRIS**:

Case definition for paradoxical cryptococcal IRIS in HIV patients:

- Antecedent requirements:

- Taking antiretroviral therapy (ART)
- Cryptococcal disease diagnosed before ART by positive culture or typical clinical features plus positive India ink staining or CrAg detection
- Initial clinical response to antifungal therapy with partial or complete resolution of symptoms or signs, fever, or other lesions, or reduction in CSF cryptococcal antigen concentration or quantitative culture

Clinical criteria:

- Event occurs within 12 months of ART initiation, reintroduction, or regimen switching after previous failure
- Clinical disease worsening with one of the following inflammatory manifestations of cryptococcosis:
    - Meningitis
    - Lymphadenopathy
    - Intracranial space-occupying lesion or lesions
    - Multifocal disease
    - Cutaneous or soft-tissue lesions
    - Pneumonitis or pulmonary nodules

2. **Non-adherence to Fluconazole**

This can be assessed by patient history and pill count.

This is indicated by an increase in quantitative culture or antigen titre, or any positive cryptococcal culture after 3 months of antifungal therapy.

3. **Fluconazole resistance**

Isolates from patients with culture positive relapse will be saved for susceptibility testing, where applicable. Secondary resistance is rare with highly active induction regimes as used in the trial.

4. **Alternative non cryptococcal diagnosis.**

Commonest diagnoses to consider: TB meningitis and bacterial meningitis.

Assessment

1. **History**

   a. Duration and nature of symptoms such as headache, visual loss, diplopia

   b. Adherence to fluconazole

   c. Previous use of fluconazole

   d. ARV history including possible adherence issues

   e. Previous problems with raised intracranial pressure

   f. Full systemic enquiry

2. **Examination**

- A full examination of the patient should be undertaken, including examination for other possible opportunistic diseases such as tuberculosis or lymphoma.
- In particular neurological examination should determine the presence or not of meningism, focal neurological signs, signs of raised CSF pressure.

At this stage fill in the Recurrence of symptoms eCRF

3. **Laboratory tests**

- Routine blood tests including FBC and U&Es are to be taken.
- If the patient is on ARV therapy, CD4 and viral load tests may be performed, if not done recently.

4. Imaging

- Patients who are obtunded or have focal neurological signs should have CT brain imaging, if possible with contrast.
- A routine CXR on readmitted study patients is warranted.

5. Lumbar puncture

- In study patients with recurrence of headache in whom the study doctor suspects a diagnosis of cryptococcal meningitis relapse or IRIS, a lumbar puncture (LP) will be performed, unless contraindicated.
- The CSF opening pressure (OP) will be measured and a therapeutic tap performed if the OP ≥ 25 cm H_2O [Refer to WPD10: Management of raised intracranial pressure].
- CSF from suspected cryptococcal meningitis relapse or IRIS will be sent for the following laboratory tests:
    - Routine biochemistry-including CSF glucose and protein
    - Routine microbiology-including WCC, RBC, WCC differential, microscopy and culture
    - Prolonged fungal culture (2 weeks incubation)
    - TB culture
    - Ideally a paired serum glucose sample should be sent alongside the CSF samples. Serum RPR testing may be indicated.
    - The CSF will be plated and saved in cases of suspected relapse or IRIS patients. The quantitative culture may be very useful in distinguishing IRIS versus non adherence/resistance to fluconazole.

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Management approach:

There is no well-established guidance regarding the management of patients presenting with recurring symptoms or a possible diagnosis of IRIS.

Individual patient management should be discussed on a case by case basis with the local and international PI. The following points serve as guidance only.

a) **ARVs**: Continue

b) **Raised CSF pressure**: Manage according to WPD10 (Management of raised intracranial pressure)

c) **Antifungal drugs**: Pending results of investigation, depending on clinical status, patients may be restarted on Amphotericin B (if nonadherence or fluconazole resistance suspected, or atypical for IRIS); in some cases (if typical for IRIS and patient clinically stable) fluconazole may be continued.

d) If CSF culture positive, especially if CFU count increased, give Amphotericin B at least until CSF culture negative and then switch to secondary prophylaxis. Consider fluconazole MIC testing if available.

e) If CSF culture negative, or CFU decreasing, and no alternative diagnosis, and features of IRIS (above), the diagnosis is most likely IRIS:

- Continue ARVs & fluconazole
- Manage CSF pressure as necessary
- If patient condition severe or deteriorating, despite above, consider corticosteroids (Prednisolone 60mg PO or dexamethasone 4mg tds as a guide, to be tapered over 2-3 weeks).
- **This should be prescribed only after discussion with the PI.**

Following discharge, patients with cryptococcal meningitis relapse or IRIS must be monitored closely.

A routine follow-up visit should take place a week following discharge.

Further visits will be determined by the patient's clinical condition and the need to carefully taper steroids (over 2-3 weeks) in symptomatic cryptococcal meningitis IRIS patients.

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 WPD and understand the material contained in it)

Date	Name (Please print)	Signature