

GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF CRYPTOCOCCAL MENINGITIS AND DISSEMINATED CRYPTOCOCCOSIS IN HIV-INFECTED PATIENTS

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Acknowledgements:

Brian Eley and Helena Rabie for comments on management of paediatric cryptococcosis.

Pfizer supported the cost of the guideline writing committee and the poster supplied as an insert to this issue of the journal.



INTRODUCTION AND BACKGROUND

While the developed world has seen a substantial decline in incidence rates of CC after the advent of highly active antiretroviral treatment (HAART),¹⁻³ the enormity of the burden of AIDS on the African sub-continent and the anticipated delays in achieving full coverage of antiretroviral therapy (ART) programmes imply that CC will continue to cause mortality among our population for years to come. The prognosis of patients with cryptococcal meningitis was very poor prior to the availability of ART,⁴⁻⁶ but present survival rates in the context of ART co-administration are much improved.⁷⁻⁹ **Consequently it has become essential to improve the initial acute management of CC in order to maximise the patient's chances of initial survival and subsequent entry into the ART treatment programme.**

Existing international guidelines for the management of cryptococcosis¹⁰⁻¹⁴ are written for different geographical and clinical contexts and may be impracticable for implementation in sub-Saharan Africa given limited availability of drugs and other resources.

OBJECTIVE AND TARGET AUDIENCE OF GUIDELINES

The objective of these guidelines is:

- To set best practice standards for prevention, diagnosis, management and treatment of HIV-associated CC.
- To provide practical guidance for doctors working without specialist support who encounter CC in their routine practice.
- To identify gaps in the evidence base to guide further research.

A note on definitions:

Cryptococcal meningitis (CM) refers to meningo-encephalitis resulting from infection; disseminated cryptococcosis refers to infection of multiple body sites; and cryptococcosis (CC) refers to infection of any body site, with an organism from the genus *Cryptococcus*, including *Cryptococcus neoformans* and *C. gattii* (formerly *C. neoformans* var. *gattii*). Where the term 'cryptococcosis' (CC) is used in this document, it refers to either cryptococcal meningitis or disseminated cryptococcosis.

These guidelines do not provide guidance for the management of CC in HIV-negative persons, or pulmonary cryptococcosis, or cryptococcosis with limited organ involvement. Cryptococcosis rarely occurs in HIV-uninfected individuals and there are important differences in the management of these patients. HIV-positive patients with apparently limited organ involvement due to *C. neoformans* (e.g. cutaneous cryptococcosis) almost always have disseminated disease.

STRUCTURE OF THE GUIDELINES

- Part 1 comprises guidelines presented as a statement in a text box followed by explanatory notes.
- Part 2 (to be found on the HIV Society website, www.sahivsoc.org) presents a justification of or explanation for the guideline, quoting available evidence.

PART 1: GUIDELINES WITH EXPLANATORY NOTES

RECOMMENDATION 1: THE DIAGNOSIS OF CRYPTOCOCCOSIS

1. *When to consider the diagnosis*
Consider in all patients (whether known or not known to be HIV-seropositive) with the following: headache, unexplained fever, nausea and vomiting, neck stiffness, confusion, seizures, abnormal behaviour, new-onset psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness or coma.
2. *The role of lumbar puncture (LP) and computed tomography (CT) scan of the brain in the investigation of patients with suspected CM*
LP is necessary to establish an aetiological diagnosis of meningitis. Occasionally, patients with CM present with focal neurological signs: where possible, these patients should have a CT scan of the brain to ensure that LP is safe.
3. *The diagnosis of recurrent CC*
All patients with a history of a prior episode of CC and symptoms suggesting a recurrence should have an LP to confirm CC, to exclude concurrent pathology, to have an isolate for susceptibility testing and to identify and manage raised intracranial pressure.

WHEN TO CONSIDER THE DIAGNOSIS OF CC

Suspect cryptococcosis in all patients presenting with meningitis:

- Cryptococcosis is a common cause of meningitis in the AIDS era.
- Patients may not be aware of their HIV status and may be in a good state of health without features of HIV or AIDS at time of presentation with CC.

Clinical presentation of patients with cryptococcosis may include:

- Symptoms and signs related to raised intracranial pressure: headache, confusion, altered level of consciousness, 6th cranial nerve palsies with diplopia and visual impairment, papilloedema
- Fever of unknown origin
- Encephalitic symptoms including memory loss and new-onset psychiatric symptoms
- Cutaneous lesions (Fig. 1)
- Pulmonary involvement including cavitation, infiltration and consolidation.

Patients with CM may not have neck stiffness.



Fig. 1. Cryptococcal skin rash demonstrating the typical umbilicated nodules and papules. It is caused by haematogenous dissemination of the organism.

LUMBAR PUNCTURE AND CT BRAIN

LP is essential in order to establish an aetiological diagnosis of suspected meningitis. LP may also alleviate symptoms such as headache, altered level of consciousness and 6th nerve palsies which are a result of raised intracranial pressure.

Focal neurological signs in CM are relatively uncommon; where available, CT brain should be performed first in order to exclude the presence of space-occupying lesions. In resource-constrained settings where CT brain is not immediately available or likely to be significantly delayed, LP may be done without prior CT brain.

At LP, in suspected CC:

- Measure opening CSF pressure (normal <20 cm CSF) (see Fig. 2).
- Request the following investigations routinely: microscopy (cell count, Gram stain and India ink stain), chemistry (protein, glucose), bacterial culture, fungal culture.
- Cryptococcal antigen (CrAg) detection should be requested only if the India ink test is negative.

- Consider the following investigations: Adenine deaminase (ADA), smear and culture for *Mycobacterium tuberculosis* (requires at least 5 ml CSF), TPHA for syphilitic meningitis, *Toxoplasma gondii* IgG and IgM.
- Retain a tube of CSF at room temperature in event of laboratory error.
- If insufficient CSF is submitted, the laboratory will prioritise tests to be performed.
- Contact details for procurement of CSF manometer sets may be found in Appendix 2.



Fig. 2. Measurement of CSF opening pressure using manometer.

RECURRENT CC

A recurrent episode of CC is defined as:

1. Re-appearance of symptoms of cryptococcosis (headaches, neck stiffness and/or other neurological manifestation) after symptoms had fully resolved following treatment for the initial episode

WITH

2. Appropriate laboratory confirmation of the diagnosis – refer to recommendation 2 below.

In our context, recurrent CC may be a consequence of:

- Inadequate treatment of the first episode of cryptococcosis (through administration of fluconazole in the intensive phase, or insufficient dose/duration of fluconazole in the consolidation phase or failure to manage raised intracranial pressure appropriately)
- Failure to adhere to secondary prophylaxis (due to patient or health care service provider factors)
- In the context of ART, immune reconstitution inflammatory syndrome (IRIS)

Development of microbiological 'resistance' to fluconazole. Patients with suspected recurrence of CC require a lumbar puncture. Clinicians should not assume that symptoms are indicative of a recurrence. LP has the following advantages:

- The LP identifies the aetiological agent of meningitis and will provide a diagnosis of other infections if present.
- The LP provides the laboratory with an isolate for susceptibility testing if this is available.
- The LP establishes a diagnosis of raised intracranial pressure, and facilitates appropriate management thereof.

RECOMMENDATION 2: INITIAL TREATMENT OF CRYPTOCOCCOSIS

1. *Antifungal treatment of a first episode of CC*

Induction phase: Amphotericin B 1 mg/kg/dose ivi for 2 weeks (minimum 1 week).

Consolidation phase: Fluconazole 400 mg po daily for 8 weeks.

Secondary prophylaxis: Fluconazole 200 mg po daily for life or until CD4 >200 cells/ μ l for more than 6 months on ART (at least 12 months' fluconazole in total).
2. *Antifungal treatment of a subsequent episode* of CC that is thought to be due to fluconazole 'resistance':*

Induction phase: Amphotericin B 1 mg/kg/dose ivi for 2 -4 weeks or until CSF is sterile.

Consolidation phase: Fluconazole 800 mg po daily for 8 weeks with or without weekly amphotericin B 1 mg/kg.

Secondary prophylaxis:† Fluconazole 400 mg po daily for life (at least 12 months' fluconazole in total)

OR

Weekly amphotericin B 1 mg/kg/dose

OR

weekly amphotericin B 1 mg/kg/dose plus daily fluconazole 400 mg.

Secondary prophylaxis can be discontinued if CD4 count is >200/ μ l for 6 months on ART.
3. *Management of raised intracranial pressure (>20 cm CSF)*

Alleviate pressure initially by draining not more than 20 - 30 ml of CSF (to decrease opening pressure by 20 -

50%) at initial LP. Thereafter the need for pressure relief should be dictated by recurrence of symptoms of raised intracranial pressure. Patients may require daily LPs.

4. Pain and symptom management

Reduction of intracranial pressure alleviates headache and confusion. Residual pain may be managed with paracetamol and mild opiates (WHO level 1 and 2 analgesics¹⁵). Non-steroidal anti-inflammatory drugs should be avoided in patients receiving amphotericin B because concomitant administration may increase potential for nephrotoxicity.

*Patients who are not adherent to secondary prophylaxis may be treated with the regimen above for treatment of a first episode of CC.

[†]These combinations are not evidence-based.

ANTIFUNGAL TREATMENT OF A FIRST EPISODE OF CC

Infectious Diseases Society of America (IDSA) guidelines¹⁰ and other international guidelines recommend induction phase treatment with 0.7 - 1 mg/kg/dose amphotericin B AND 100 mg/kg/day 5-flucytosine; unfortunately the latter drug is not available in southern Africa.

In head-to-head trials, the combination 5-FC with amphotericin B 0.7 mg/kg/dose is superior to amphotericin B 0.7 mg/kg/dose alone¹⁶ in terms of early fungicidal activity. In the absence of 5-flucytosine, the writers believe that southern African patients should be treated with the higher dose of amphotericin B 1 mg/kg/dose. In South African adults amphotericin B 1 mg/kg/dose is well tolerated.¹⁷

Amphotericin B in the induction phase should be given for 2 weeks; however, 7 - 10 days may suffice.¹⁸

Where amphotericin B is unavailable or cannot be given safely, transfer the patient to a centre where amphotericin B is available. If this is not possible, substitute amphotericin B induction phase treatment with fluconazole 800 mg po daily for 4 weeks followed by fluconazole 400 mg daily for 8 weeks (continuation phase). Amphotericin B is superior to fluconazole at lower fluconazole doses.^{17,19,20} There are no studies comparing higher dose fluconazole with amphotericin B, but given that fluconazole is fungistatic, amphotericin B should always be the drug of first choice.

Give fluconazole intravenously in patients who are vomiting or comatose and unable to take it orally.

Refer for palliative care those patients who fail to respond to antifungal therapy and management of raised intracranial pressure, once other pathologies have been excluded.

ANTIFUNGAL TREATMENT OF A SUBSEQUENT EPISODE OF CC

Establish whether the patient was adherent to secondary prophylaxis. If not adherent, address the reasons, and treat as for the first episode of CC.

If the patient is on ART, this episode of CC may meet the definition for IRIS, in which case Recommendation 5 should be followed.

MANAGEMENT OF RAISED INTRACRANIAL PRESSURE

CSF opening pressure should be measured with every LP that is performed (Fig. 2). Patients with raised intracranial pressure experience considerable relief of symptoms following therapeutic LP.

Patients with persistent pressure symptoms that fail to respond to serial lumbar punctures may require lumbar drain insertion or shunting procedures. Neurosurgical consultation should be sought.

Patients with CM should not be treated with adjunctive steroids as this may adversely affect the prognosis.

RECOMMENDATION 3: ROLE OF THE LABORATORY IN THE DIAGNOSIS AND TREATMENT OF CC

1. The laboratory diagnosis of cryptococcosis

A case of cryptococcosis may be diagnosed definitively by culture or presumptively by tests indicating the presence of *Cryptococcus* species, including a positive India ink (Fig. 3) or cryptococcal antigen detection test on any specimen or mucicarmine-stained histopathological sections revealing the organism.

2. The role of antifungal susceptibility testing (AFST) in management of CC

AFST of *C. neoformans* against amphotericin B has no role in patient management.

AFST against fluconazole is not advised in first episodes of CC, but may have value in recurrent or unresponsive cases where testing is available.

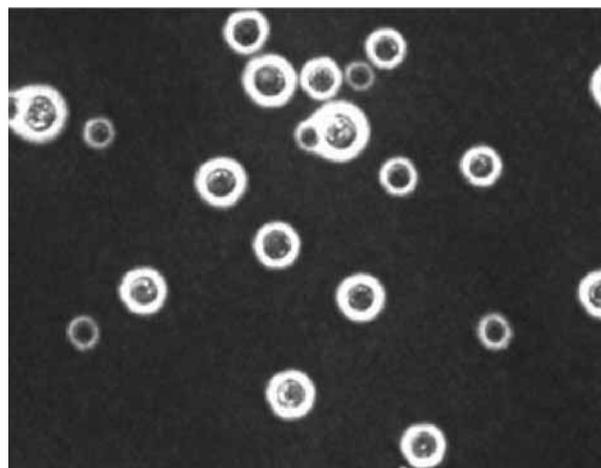


Fig. 3. India ink microscopy stain demonstrating encapsulated cryptococcal yeasts, some of them budding.

LABORATORY-BASED SURVEILLANCE FOR CC

South Africa has an active surveillance programme for CC. (Refer to Appendix 3.)

Laboratory diagnostic tests for CC

The India ink test has good sensitivity (80 - 98%)^{7,21} and specificity in ARV-naïve and fluconazole-naïve populations, but may have lower sensitivity in patients who are receiving fluconazole for other reasons (commonly mucocutaneous candidiasis), who present early in the course of disease and who have low fungal burden in the CSF. A negative India ink test does not exclude the diagnosis.

CrAg detection by latex agglutination has excellent sensitivity and specificity, but is expensive, especially when titres are performed. The test should be performed on neat and at least one titred specimen (preferably 1:8 dilution) in order to exclude false-negative results due to the 'prozone phenomenon'. Use this test only in the following circumstances:

- For all CSF when the India ink test is negative (unless an alternative diagnosis has been made e.g. bacterial meningitis)
- For non-CSF specimens such as blood or serum or urine if CSF is not obtainable.

Culture of *C. neoformans* is the gold standard for the diagnosis of CC. Culture may take up to 2 weeks to appear; therefore keep culture plates for 14 days before reporting specimens as negative (liaise with the laboratory service to ensure that this is done). Laboratories that offer antifungal susceptibility testing may wish to preserve cultures of *C. neoformans* from incident cases.

Antifungal susceptibility testing of *C. neoformans*

Antifungal susceptibility testing requires specialised laboratory services and trained laboratory personnel, both of which are not often available to routine general hospital services. Clinicians should be wary of indiscriminate reporting of antifungal susceptibility testing results and should interpret these results with specialist consultation.

Clinically reliable and objective values for interpretation of susceptibility testing (MIC breakpoints) of *C. neoformans* against fluconazole have not been established; therefore although testing can be done, results may not be predictive of clinical response and outcome.

Microbiological resistance to fluconazole may be present when a recurrent isolate of *C. neoformans* has a higher MIC (at least 2 dilutions) than the incident isolate when the AFST has been done in parallel (i.e. at the same time), using E-test or CLSI M27-A2 methodology and where control strains have been included. Given that AFST can only be done in this manner after management of the patient's recurrent episode has commenced, AFST results are not expected to impact significantly on initial management of relapse episodes.

Susceptibility testing methodology of *C. neoformans* against amphotericin B is not sufficiently developed for applicability to the clinical setting.

RECOMMENDATION 4: SUPPLEMENTARY MANAGEMENT OF CC

1. *Counselling of patients diagnosed with CC*
All patients who are diagnosed with CC should be counselled (once fully conscious) regarding:
 - The need for compliance with fluconazole therapy (both consolidation and secondary prophylaxis)
 - The urgent need for HIV testing (if HIV status unknown) and lifelong ART.
2. *Concurrent opportunistic infections including tuberculosis in patients with CC*
Diagnose and treat concomitant opportunistic infections in patients with CC, particularly pulmonary and extrapulmonary tuberculosis, pneumocystis pneumonia (PCP), bacterial pneumonia, and chronic diarrhoea. All patients with CC should have a chest X-ray.

COUNSELLING OF PATIENTS DIAGNOSED WITH CRYPTOCOCCOSIS

Patients, their relatives and caregivers should be counselled regarding cryptococcosis:

- That the initial treatment phase will last 10 weeks, and
- That secondary prophylaxis will be required for an extended period of time.

Clear written instructions regarding the patient's medication schedule should be provided.

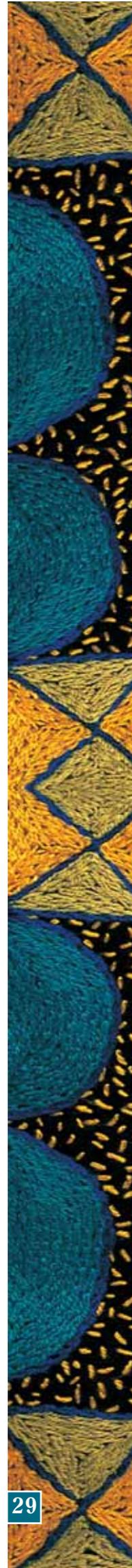
All patients who do not know their HIV status should be strongly advised to undergo testing as part of provider-initiated testing and counselling (PITC). A diagnosis of CC represents an opportunity for enrollment into HIV services. In the context of ART, patients with cryptococcosis have a reasonable prognosis for survival.

Sample drugs (fluconazole, antiretroviral drugs, co-trimoxazole) including the dispensed containers and pills are helpful aids for counselling the patient.

Patients who are confused should be counselled when their level of consciousness has improved, and ideally a family member or caregiver should be involved in the counselling.

CONCURRENT OPPORTUNISTIC INFECTIONS

Patients with CC are profoundly immunosuppressed and often have concurrent opportunistic infections including tuberculosis. Clinicians should ensure that patients who have symptoms suggestive of TB (fevers, cough, night sweats, loss of weight) are appropriately investigated as pulmonary cryptococcosis may mimic pulmonary TB. Microscopy and culture for tuberculosis of sputum and other clinical specimens should be performed where indicated.



PG 30 NEW AD - ABBOTT

PG 31 NEW AD - ABBOTT

RECOMMENDATION 5: THE ROLE OF ANTIRETROVIRAL THERAPY IN PATIENTS WITH CC

Role of ART

ART is the most effective intervention to treat AIDS, and is the most potent mechanism to prevent both primary and secondary recurrences of CC. Commence patients (according to relevant local guidelines) on ART a matter of urgency.

1. ART

All patients with HIV and CC require ART and co-trimoxazole prophylactic therapy. ART should be commenced 2 - 4 weeks after initiation of antifungal therapy using relevant national guidelines for drug regimens and monitoring.

2. Immune reconstitution inflammatory syndrome (IRIS) and CC

Management of a patient with suspected paradoxical IRIS requires the following:

- Continuation of ART
- Lumbar puncture to exclude additional pathology, to obtain an isolate for susceptibility testing to fluconazole and to measure intracranial pressure
- CT scan of the head when focal neurological signs are present
- Appropriate antifungal therapy
- Culture-positive cases should receive treatment according to Recommendation 2
- Culture-negative cases should continue with their consolidation phase treatment or secondary prophylaxis (clinicians should ensure adherence) as appropriate
- Oral steroid therapy with prednisone 1 mg/kg daily for at least a week if symptoms fail to respond after appropriate management of raised intracranial pressure and symptomatic treatment. Some patients require prolonged courses of steroids to control IRIS manifestations.

PREVENTION OF CC

ART should be initiated after patients have been screened for the presence of opportunistic infections by clinical history and examination, with or without laboratory investigations as indicated. Screening for CC by performing serum CrAg testing in patients with low CD4 counts and evidence of systemic illness prior to commencement of ART may have a role in preventing the development of CC soon after ART initiation²²⁻²⁴ (see below). Primary prevention of CC with fluconazole may have a limited role in patients with CD4 counts below 100 cells/ μ l where delays in access to ART are anticipated.²⁵

INITIATION OF ART IN ARV-NAÏVE CLIENTS WITH CC

All HIV-positive patients who develop CC are eligible for co-trimoxazole preventive therapy (CPT) and ART.

Evidence for the optimal timing of ART initiation is not available: we believe ART is most appropriately started 2 - 4 weeks after treatment for CC has commenced. Although no prospective evidence exists in this regard, given these patients' advanced immunosuppression, delaying ART introduction beyond 4 weeks to reduce the risk of IRIS may increase the risk of mortality. The long in-hospital stay associated with amphotericin B therapy should facilitate pre-ART counselling, identification of a treatment supporter and early referral to an ART centre.

Patients who are initiated on ART should be counselled regarding the risk of development of IRIS.

If a patient is referred to another facility for ART, the need for fluconazole maintenance therapy should be communicated.

Antiretroviral regimens including nucleoside and non-nucleoside reverse transcriptase inhibitors are appropriate. Caution should be observed when using nevirapine-containing ART regimens as fluconazole increases nevirapine levels and may result in hepatotoxicity with fluconazole co-administration.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Patients who are receiving ART may develop IRIS related to infection with *Cryptococcus* species in the following scenarios:

- 'Unmasking' IRIS occurs in patients not known to have CC who are commenced on ART and develop an incident episode of CC within the first 3 months of ART. These episodes of CC usually meet the definition for a diagnosis of CC (Recommendation 3) and should receive antifungal therapy according to Recommendation 2. Patients who are eligible for ART should have opportunistic infections excluded; serum CrAg testing may identify patients at risk for 'unmasking' IRIS.
- 'Paradoxical' IRIS occurs in patients who have a diagnosis of CC before starting ART and have responded to antifungal therapy. The most common presentation of paradoxical IRIS is recurrent meningitis associated with raised intracranial pressure, but other manifestations like enlarging cryptococcomas, encephalitis and lymphadenitis are described. Recommendation 5 advises on paradoxical IRIS.

RECOMMENDATION 6: CC IN SPECIAL POPULATIONS

1. Cryptococcosis in the pregnant patient

No alterations in the management of cryptococcosis are required for treatment of cryptococcosis in pregnancy.

Although fluconazole is teratogenic, the high mortality of the condition necessitates optimal management of the mother.

2. *Fluconazole prophylaxis in women of child-bearing age*

Fluconazole is teratogenic. Women of childbearing age and potential who require fluconazole in the course of treatment for other conditions should be counselled regarding the need for appropriate contraception.

3. *Cryptococcosis in paediatric patients*

Cryptococcosis in children should be suspected, diagnosed and treated according to guidelines for adults with the following exceptions as listed below:

Antifungal treatment of CC in paediatric patients

Induction phase: Amphotericin B 1 mg/kg/dose ivi for 2 weeks (relapse episodes should be treated for 4 - 8 weeks, preferably until CSF fungal culture is negative). Adequate hydration during amphotericin B treatment should be maintained.

Consolidation phase: Fluconazole 12 - 15 mg/kg once daily for a further 8 weeks (the maximum dose should not exceed 400 mg).

Secondary prophylaxis: Fluconazole 6 - 10 mg/kg once daily for life. In children over the age of 2 years who have evidence of sustained immune reconstitution on ART (2 - 6 years old: CD4 percent > 25%, more than 6 years old: CD4 count >200 cells/ μ l) and who are asymptomatic with their last episode of cryptococcosis having been more than 12 months previously, secondary prophylaxis can be stopped.

Management of raised intracranial pressure

Recommendations for management of intracranial pressure in adults apply to children (i.e. repeated lumbar punctures).

For refractory raised intracranial pressure, referral to or discussion with a specialist centre is advised.

CRYPTOCOCCOSIS IN CHILDREN

Cryptococcosis in children is uncommon, but does occur with a bimodal distribution, firstly in neonates and young infants where the mode of acquisition is possibly vertical, and secondly in school-going and adolescent children who acquired HIV infection in early childhood or infancy. The latter group presents very similarly to adult CC.

RECOMMENDATION 7: DRUG INFORMATION, TOXICITIES AND INTERACTIONS IN PATIENTS TREATED FOR CC

1. *Drug information*

Refer to text below, and Appendix: Amphotericin B information sheet for clinical staff

2. *Additive drug toxicities, interactions and required alterations of dose in patients receiving fluconazole together with other anti-infective agents*

Fluconazole is an enzyme inhibitor and may cause levels of concomitantly administered drugs to increase.

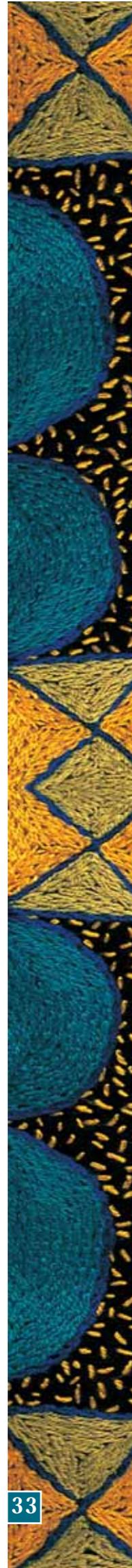
Concurrent medication (with fluconazole)	Drug interaction/additive toxicity	Required alteration
Pyrazinamide, isoniazid	Drug-induced hepatitis	None (clinical and laboratory monitoring is indicated)
Rifampicin	Reduced levels of fluconazole Drug-induced hepatitis	Consider increasing the secondary fluconazole prophylaxis dose by 50%. Clinical and laboratory monitoring is indicated regarding the potential for hepatotoxicity
Nevirapine	Drug-induced hepatitis	None (clinical monitoring with laboratory investigation if indicated). Some clinicians would not exceed a fluconazole dose of 400 mg daily.

*See caveat below.

DRUG INTERACTIONS

Administration of fluconazole in patients on concurrent intensive phase TB treatment appears to be a risk factor for drug-induced hepatitis.²⁶ Patients should be monitored both clinically and with laboratory testing.

Because of rifampicin induction of fluconazole metabolism, some clinicians consider increasing the dose of fluconazole by 50% during continuation phase and secondary prophylaxis.



Co-administration of fluconazole with nevirapine increases nevirapine levels and consequently the potential for hepatotoxicity.

DRUG INFORMATION

Amphotericin B (see also detailed information sheet for clinical staff in Appendix 1)

1. Dosage and administration

- a) Controlled infusion over 4 hours of amphotericin B at 1 mg/kg in 1 litre of 5% dextrose water should be given AFTER prehydration with 1 litre normal saline containing 20 mmol KCl (1 ampoule). A 'test dose', previously common practice, need not be given if the daily dose is run slowly over the first half hour of administration.

2. Prevention and management of side-effects

- a) Major side-effects include renal impairment due to renal tubular toxicity, usually in the second week of therapy, hypokalaemia, hypomagnesaemia and renal tubular acidosis, anaemia, febrile reactions and chemical phlebitis.
- b) Nephrotoxicity and electrolyte abnormalities may be prevented by avoiding amphotericin B in patients with renal impairment, by prehydration, by avoiding concurrent use of other nephrotoxins (non-steroidal anti-inflammatory agents (NSIADs), aminoglycosides including streptomycin) and by routine administration of potassium and magnesium supplements.
- c) Phlebitis may be prevented by rotation of the drip site every 2 - 3 days and by flushing of lines after the amphotericin B infusion is complete.
- d) Febrile reactions may be prevented when subsequent doses of amphotericin B are given by administration of paracetamol 1 g 30 minutes prior to dose. Severe febrile reactions may require hydrocortisone 25 mg ivi at the start of the infusion.
- e) If nephrotoxicity occurs, manage as follows:
 - i) If creatinine increases by 2-fold or more, omit a dose and/or increase prehydration to 1 litre 8-hourly
 - ii) If creatinine fails to decrease after the above intervention, stop amphotericin B therapy and use fluconazole.

Fluconazole

1. Dosage and administration.

Fluconazole has excellent bioavailability when administered orally; intravenous administration is rarely required. CSF penetration is >80% of serum levels.

2. Prevention and management of side-effects

Fluconazole is well tolerated. Patients with renal impairment require dose adjustment according to glomerular filtration rate (GFR):

■ GFR 10 - 50 ml/min, reduce dose by up to 50%

■ GFR <10 ml/min, give 25% of dose.

Calculate GFR using formula as follows:

$$\frac{140 - \text{age} \times \text{ideal weight}}{0.82 \times \text{serum creatinine}}$$

Women: multiply total by 0.85

Side-effects include nausea and vomiting, abdominal pain, rash and drug-induced hepatitis. Clinical monitoring for symptoms of hepatitis (nausea and vomiting, abdominal pain and jaundice) should be performed, with laboratory testing (alanine transaminase, ALT) if these symptoms occur.

Fluconazole may be teratogenic: Women of child-bearing potential should be advised regarding the need for effective contraception while on the drug.

Fluconazole is an enzyme inhibitor and may increase levels of certain drugs. Clinically relevant drug interactions requiring interventions are listed in Recommendation 7 above.

Flucytosine

Flucytosine is not available in southern Africa. Flucytosine is included in international guidelines¹⁰ for the management of CC in the context of induction phase and co-administration with amphotericin B.

New antifungal agents and their role in the management of cryptococcosis

1. Echinocandins (caspofungin/micafungin) have no activity against *C. neoformans*.²⁷
2. Voriconazole has excellent activity against *C. neoformans*,^{28,29} but is not available in the public sector in southern Africa and is expensive.

APPENDIX 1: INTRAVENOUS AMPHOTERICIN B: INFORMATION SHEET FOR CLINICAL STAFF

Dosage and administration

Intravenous amphotericin B is prescribed for once-daily administration according to the patient's weight (dose = 1 mg/kg). Total doses will usually range between 25 mg and 80 mg.

Prehydrate patients with 1 litre of normal saline containing 1 ampoule (20 mmol) of KCl infused over 2 hours before the amphotericin B infusion. This reduces the risk of renal toxicity and hypokalaemia, both side-effects of amphotericin B.

Amphotericin B comes in a vial that contains 50 mg of powder. Each vial is reconstituted with 10 ml of sterile water. The appropriate dose is then drawn up according to the table on p. 35.

The total dose must then be injected into a 1-litre bag of 5% dextrose or 10% dextrose and shaken to mix. Once mixed, the bag must be administered within 24 hours or discarded. Protection of the infusion from light (with brown bag) is not necessary provided it is administered within 24 hours of preparation. **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. The infusion must be given over 4 hours and not faster otherwise it can cause cardiac problems. Once the infusion is complete the line should be flushed with 100 ml normal saline.

Prescribed dose	Total volume drawn up from vial(s)	No. of vials required
25 mg	5 ml	1
30 mg	6 ml	1
35 mg	7 ml	1
40 mg	8 ml	1
45 mg	9 ml	1
50 mg	10 ml	1
55 mg	11 ml	2
60 mg	12 ml	2
65 mg	13 ml	2
70 mg	14 ml	2
75 mg	15 ml	2
80 mg	16 ml	2

Side-effects: how to avoid and manage them

Nephrotoxicity and electrolyte abnormalities may be prevented by prehydration with normal saline containing potassium (as above). Nephrotoxicity usually occurs in the second week of therapy with amphotericin B; baseline and twice-weekly monitoring of creatinine, potassium and magnesium is appropriate. If creatinine doubles, consider omitting a dose of amphotericin B or increasing prehydration to 1 litre 8-hourly. If creatinine remains elevated, stop amphotericin and use fluconazole. Oral potassium and magnesium supplementation may be given pre-emptively to prevent electrolyte abnormalities.

Phlebitis is **very common** in patients receiving amphotericin B and increases the risk of localised cellulitis as well as potentially fatal septicaemia. To minimise risk of phlebitis, flush lines with 100 ml normal saline after amphotericin B infusion is complete. **DO NOT** leave the empty bag of amphotericin B hanging overnight attached to the patient's drip. Remove the drip if the patient spikes a fever having been previously afebrile, or at first sign of redness or patient discomfort at site. Rotate drips routinely every 2 – 3 days.

Anaemia may occur in patients receiving amphotericin; however be sure to exclude other treatable causes. Monitor haemoglobin weekly.

Febrile reactions may occur; during the first infusion run the drip at a slow rate over first half hour and observe the patient closely. If febrile reactions occur, treat with paracetamol 1 g 30 minutes before infusion or if severe, hydrocortisone 25 mg ivi at the start of subsequent infusions.

APPENDIX 2: CONTACT DETAILS FOR ORDERING MANOMETRY SETS IN SOUTHERN AFRICA

Zenith Surgical cc		
<i>Telephone and e-mail</i>	<i>Postal address:</i>	<i>Street address:</i>
Tel: 011 991-7011	PO Box 1264	14 6th Avenue
Fax: 011 472-1270	Fontainebleau	Maraisburg
zenithsurgical@tiscali.co.za	2032	Roodepoort Johannesburg

APPENDIX 3: CONTACT DETAILS FOR GERMS-SA SURVEILLANCE FOR CC

Surveillance for CC is performed by the GERMS-SA laboratory network that is co-ordinated by the National Institute for Communicable Diseases (NICD). All cases (India ink or CrAg or culture positive cases) and all cultures of *Cryptococcus* species should be referred to the NICD. Dr Nelesh Govender (neleshg@nicd.ac.za; 011 386-6000) may be contacted for assistance pertaining to submission of isolates and cases.

REFERENCES

- Mirza SA, Phelan M, Rimland D, *et al*. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis* 2003; 36(6): 789-794.
- Friedman GD, Jeffrey FW, Udaltsova NV, Hurley LB. Cryptococcosis: the 1981-2000 epidemic. *Mycoses* 2005; 48(2): 122-125.

- Dromer F, Mathoulin S, Dupont B, Laporte A. Epidemiology of cryptococcosis in France: a 9-year survey (1985-1993). French Cryptococcosis Study Group. *Clin Infect Dis* 1996; 23(1): 82-90.
- Heyderman RS, Gangaizo IT, Hakim JG, *et al*. Cryptococcal meningitis in human immunodeficiency virus-infected patients in Harare, Zimbabwe. *Clin Infect Dis* 1998; 26(2): 284-289.
- Bogaerts J, Rouvroy D, Taelman H, *et al*. AIDS-associated cryptococcal meningitis in Rwanda (1983-1992): epidemiologic and diagnostic features. *J Infect* 1999; 39(1): 32-37.
- Moosa MY, Coovadia YM. Cryptococcal meningitis in Durban, South Africa: a comparison of clinical features, laboratory findings, and outcome for human immunodeficiency virus (HIV)-positive and HIV-negative patients. *Clin Infect Dis* 1997; 24(2): 131-134.
- Schaars CF, Meintjes GA, Morroni C, Post FA, Maartens G. Outcome of AIDS-associated cryptococcal meningitis initially treated with 200 mg/day or 400 mg/day of fluconazole. *BMC Infect Dis* 2006; 6: 118.
- Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O. Epidemiology of HIV-associated cryptococcosis in France (1985-2001): comparison of the pre- and post-HAART eras. *AIDS* 2004; 18(3): 555-562.
- Manosuthi W, Sungkanuparph S, Thongyen S, *et al*. Antifungal susceptibilities of *Cryptococcus neoformans* cerebrospinal fluid isolates and clinical outcomes of cryptococcal meningitis in HIV-infected patients with/without fluconazole prophylaxis. *J Med Assoc Thai* 2006; 89(6): 795-802.
- Saag MS, Graybill RJ, Larsen RA, *et al*. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* 2000; 30(4): 710-718.
- Bohme A, Ruhnke M, Buchheidt D, *et al*. Treatment of fungal infections in hematology and oncology – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2003; 82 Suppl 2: S133-S140.
- Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons – 2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med* 2002; 137(5 Pt 2): 435-478.
- Berenguer J, Laguna F, Lopez-Aldeguer J, Moreno S. Prevention of opportunistic infections in adult and adolescent patients infected with the human immunodeficiency virus in the era of highly active antiretroviral therapy. Recommendations of the Grupo de Estudio del SIDA (GESIDA/Plan Nacional sobre el SIDA). *Enferm Infecc Microbiol Clin* 2000; 18(9): 457-468.
- Mofenson LM, Oleske J, Serchuck L, Van DR, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2004; 53(RR-14): 1-92.
- Gabriel S. *Cancer Pain Relief: A Guide to Opioid Availability*. 2nd ed. Geneva: World Health Organisation, 1996.
- Brouwer AE, Rajanuwong A, Chierakul W, *et al*. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* 2004; 363: 1764-1767.
- Bicanic T, Meintjes G, Wood R, *et al*. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis* 2007; 45(1): 76-80.
- Tansuphaswadikul S, Nantawat W, Phonrat B, Boonpok N, Mctm AG, Pitisuttithum P. Comparison of one week with two week regimens of amphotericin B both followed by fluconazole in the treatment of cryptococcal meningitis among AIDS patients. *J Med Assoc Thai* 2006; 89(10): 1677-1685.
- Saag MS, Powderly WG, Cloud GA, *et al*. Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. *N Engl J Med* 1992; 326(2): 83-89.
- Larsen RA, Leal MA, Chan LS. Fluconazole compared with amphotericin B plus flucytosine for cryptococcal meningitis in AIDS. A randomized trial. *Ann Intern Med* 1990; 113(3): 183-187.
- McCarthy KM, Morgan J, Wannemuehler KA, *et al*. Population-based surveillance for cryptococcosis in an antiretroviral-naïve South African province with a high HIV seroprevalence. *AIDS* 2006; 20(17): 2199-2206.
- Micol R, Lortholary O, Sar B, *et al*. Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. *J Acquir Immune Defic Syndr* 2007; 45: 555-559.
- French N, Gray K, Watera C, *et al*. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS* 2002; 16(7): 1031-1038.
- Desmet P, Kayembe KD, De VC. The value of cryptococcal serum antigen screening among HIV-positive/AIDS patients in Kinshasa, Zaire. *AIDS* 1989; 3(2): 77-78.
- Chang LW, Phipps WT, Kennedy GE, Rutherford GW. Antifungal interventions for the primary prevention of cryptococcal disease in adults with HIV. *Cochrane Database Syst Rev* 2005; 3: CD004773.
- Pukenyte E, Lescuré FX, Rey D, *et al*. Incidence of and risk factors for severe liver toxicity in HIV-infected patients on anti-tuberculosis treatment. *Int J Tuberc Lung Dis* 2007; 11(1): 78-84.
- Cappelletty D, Eiselstein-McKittick K. The echinocandins. *Pharmacotherapy* 2007; 27(3): 369-388.
- Pfaller MA, Zhang J, Messer SA, *et al*. *In vitro* activities of voriconazole, fluconazole, and itraconazole against 566 clinical isolates of *Cryptococcus neoformans* from the United States and Africa. *Antimicrob Agents Chemother* 1999; 43(1): 169-171.
- Scott LJ, Simpson D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* 2007; 67(2): 269-298.

