Definition

Infection of the brain and spinal column caused by *Cryptococcus neoformans*

Diagnosis

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of cerebrospinal fluid (CSF) opening pressure and rapid cryptococcal antigen assay is recommended

In settings with ready access to and no contraindication for lumbar puncture: Do a lumbar puncture to obtain CSF for CrAg ,India Ink and Gene Xpert and VDRL

CSF CRAG positive, India Ink Positive or culture growth confirmed (any one positive):

Contraindications include:
Significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs (excluding cranial nerve VI palsy) or recurrent seizures and, where possible, confirmed by computed tomography
Other contraindications include major spinal deformity and patient refusal after fully informed consent was sought.

Treatment and Management

	2-Week Induction therapy		Consolidation therapy	Maintenance (or secondary prophylaxis)
	1st week	2nd week	Week 3–10	After week 10
Preferred regimen	Amphotericin B deoxycholate (1.0 mg/kg/day) + flucytosine (100 mg/kg/day, QDS)	Fluconazole (1200 mg daily)	Fluconazole (800 mg daily)	Fluconazole (200 mg daily) Until patient is adherent to ART and antifungal maintenance treatment for at least 1 year and has either a CD4 count ≥100 cells/µl and a fully suppressed VL or a CD4 count ≥200 cells/µl
Alternative regimens: depending on drugs availability	Fluconazole (1200 mg daily) + flucytosine (100 mg/kg/day, QDS)			

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating HIV-associated cryptococcal meningitis among adults, adolescents and children

Treatment for pregnant women

Amphotericin B therapy can be given to pregnant women with meningeal and non-meningeal
disease. Exposure to flucytosine and fluconazole during pregnancy has been associated with an
increased risk of birth defects in animal studies and some uncontrolled human studies.

The use of flucytosine and fluconazole for treating cryptococcal disease in pregnant women should be
evaluated on an individual basis, considering the benefits and potential harm.

Prevention, monitoring and management of toxicity

Pre-emptive hydration and electrolyte supplementation

Adults and adolescents	1L of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B
	If available, magnesium supplementation should also be provided (two 250-mg tablets of magnesium trisilicate or glycerophosphate twice daily, or magnesium chloride 4 mEq twice daily).
Monitoring	
Serum potassium	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)

Prevention, monitoring and management of toxicity (cont)

Serum creatinine	Baseline and 2–3 times weekly (especially in the second week of amphotericin B administration)
Haemoglobin	Baseline and weekly
Management	
Hypokalaemia	If hypokalaemia is significant (K <3.3 mol/l), increase potassium supplementation to 40 mEq KCl by intravenous infusion and/or one to two 8-mEq KCl tablets orally three times daily. Monitor potassium daily.
Elevated creatinine	≥2 fold from the baseline value, increase pre-hydration to 1 L every eight hours and consider temporarily omitting a dose of amphotericin B. Once creatinine improves, restart amphotericin B at 0.7 mg/kg/day and consider alternate-day amphotericin B. If creatinine continues to rise, consider discontinuing amphotericin B and continuing with fluconazole at 1200 mg/day.

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Prevention, monitoring and management of toxicity (cont)

Severe anaemia	Transfusion should be undertaken if possible for severe amphotericin B–related anaemia

Fluconazole dose adjustment if significant renal impairment.
Anaemia may be a reason to discontinue amphotericin B prematurely in the second week of a planned two-week induction course of amphotericin B with fluconazole.
Monitor intake and output of fluid and daily weight, especially among children.
Flucytosine requires regular monitoring of full blood count

symptoms and signs of raised intracranial pressure

Symptoms
• Headache
• Nausea with or without vomiting
• Changes in vision or hearing (such as double vision, blindness or deafness)
Signs
• Change in mental status (ranging from confusion to lethargy to coma)
• Papilloedema
• Seizures
• Cranial nerve palsies (such as eye movement problems, particularly cranial nerve VI)
• Other focal neurological nervous system deficits

causes of persistent and recurrent symptoms

Persistent symptoms
• Raised intracranial pressure
• Treatment failure caused by suboptimal induction treatment
• Inadequate drug regimen, dose or duration
• Fluconazole drug resistance (rare)
• Other concomitant illness (such as viral, bacterial, or tuberculous meningitis)
Recurrent symptoms
• Raised intracranial pressure
• Treatment failure due to suboptimal induction, consolidation or maintenance treatment
• Inadequate drug regimen, dose or duration
• Failure to prescribe or to adhere to fluconazole consolidation or maintenance treatment
• Fluconazole drug resistance (rare)
• Cryptococcal immune reconstitution inflammatory syndrome (IRIS) following ART initiation
• Other concomitant illness (such as viral, bacterial or tuberculous meningitis)

managing cryptococcal IRIS

1. Continue ART.
2. Promptly manage raised intracranial pressure.
3. Optimize anti fungal therapy and consider restarting induction therapy
4. Short-course oral steroid therapy may be considered if there is continued deterioration
and/or the development of life-threatening complications (such as intracranial space--occupying
lesions with mass effect or extra-cranial disease impinging on vital structures) despite the above measures.

managing cryptococcal IRIS (cont)

Immediate ART initiation is not recommended for adults, adolescents and children living
with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of anti-fungal treatment.

Discontinuing fluconazole maintenance treatment

Is HIV viral load monitoring is available

If stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥100 cells/mm3 and a fully suppressed viral load

Is HIV viral load monitoring is not available

If stable on and adherent to ART and antifungal maintenance treatment for at least one year and has a CD4 cell count ≥200 cells/mm3

For children living with HIV who are 2–5 years old and have successfully treated cryptococcal
disease, discontinuing anti-fungal treatment maintenance is recommended if the child is stable on and adherent to ART and anti-fungal maintenance treatment for at least one year and has a CD4 cell count percentage greater than 25% or an absolute count
>750 cells/mm3.
Maintenance treatment for cryptococcal disease should not be discontinued for children younger
than two years.

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