Guidelines for the Prevention, Diagnosis and Management of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients

The diagnosis of cryptococcosis (CC)
- Consider the diagnosis of CC if a patient presents with any of: headache, unexplained fever, nausea/vomiting, neck stiffness, confusion, seizures, abnormal behaviour, new onset psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness or coma.
- Lumbar puncture is necessary for an antenatal diagnosis. If focal neurological signs are present, perform a CT brain (where available) to exclude LP site.
- Recurrent CC:
  - Repeat LP must be done to confirm CC, to exclude concurrent pathology, to have an isolate for susceptibility testing and to identify and manage raised intracranial pressure.

Treatment of CC
- Antifungal treatment of a first episode of CC:
  - Induction phase: Amphotericin B 1mg/kg/dose iv for 2 weeks (minimum 1 week)
  - Consolidation phase: Fluconazole 400mg po daily for 8 weeks
  - Secondary prophylaxis: Fluconazole 200mg po daily for life or until CD4 > 200cells/mm³ for more than 6 months on ART (at least 12 months fluconazole in total)
- If fluconazole “resistance” suspected:
  - Fluconazole “resistance” may be present when CC recurs despite adequate initial treatment of CC and compliance with secondary prophylaxis
  - Induction phase: Amphotericin B 1mg/kg/dose iv for 2-4 weeks or until CSF is sterile
  - Consolidation phase: Fluconazole 400mg po daily for 8 weeks with or without weekly amphotericin B 1mg/kg.
  - Secondary prophylaxis: Fluconazole 400mg po daily
  - OR Weekly amphotericin B 1mg/kg/dose
  - OR Weekly amphotericin B 1mg/kg/dose plus 400mg fluconazole daily. Secondary prophylaxis can be discontinued if CD4 count is > 200cells/mm³ for 6 months on ART (and at least 12 months fluconazole in total)
- Management of raised intracranial pressure (>20 cm CSF)
  - Initially drain not more than 20-30ml of CSF. Repeat the LP to control intracranial pressure if pressure symptoms recur (headache, neck stiffness, altered level of consciousness, 6th cranial nerve palsy).
- Pain and symptom management
  - Reduction of intracranial pressure alleviates headache and confusion. Residual pain may be managed with paracetamol and mild opiates
  - Avoid non-steroidal anti-inflammatory drugs.

The role of the laboratory in the diagnosis and treatment of CC
- Cryptococcosis is diagnosed by culture of Cryptococcus species, or a positive India ink test or a positive cryptococcal antigen detection test on any specimen or by histology.
- Antifungal susceptibility testing for CC
  - Antifungal susceptibility testing (AFST) against fluconazole advised in recurrent or unresponsive cases where testing is available using Etest® (bioMérieux) or M27-A2 methodology. AFST is not recommended for amphotericin B.

DRUG INFORMATION: Amphotericin B
- Dose and administration
  - Prefracte patients before every amphotericin B dose with 1 litre NS containing 20mmol (1 ampoule) KCl.
  - Then administer amphotericin B 1mg/kg in 1l of 5% dextrose water in controlled infusion over four hours.
- Prevention and management of side effects
  - Prevent nephrotoxicity and electrolyte abnormalities by:
    - prehydration,
    - avoiding nephrotoxic drugs (NSAIDs, antimycotics including streptomycin).
  - Routine administration of oral potassium and magnesium supplements.
  - Prevent phlebitis by rotation of the drip site every 2-3 days, and by flushing after infusion.
  - Prevent febrile reactions by administration of paracetamol 1g, 30 minutes prior to amphotericin infusion.
  - Monitor serum creatinine three weekly.
    - If serum creatinine increases by 2-fold or more, omit a dose of amphotericin B and/or increase prehydration to 1 litre/hr.
    - If serum creatinine fails to decrease after the above intervention, stop amphotericin B therapy and use fluconazole.

The role of antiretroviral therapy (ART) in patients with CC
- Role of ART
  - ART naive patients who develop CC should be treated with antifungal agents as above, and then commenced on ART as a matter of urgency. Commence ART 2-4 weeks after initiation of antifungal therapy.
  - Immune reconstitution inflammatory syndrome (IRIS) IRIS may occur when a patient who has a history of adequately treated CC is started on ART and develops a recurrence of the meningitis. Management of a patient with suspected IRIS requires the following:
    - Continuation of ART
    - Repeat LP to exclude additional pathology, to obtain an isolate for susceptibility testing to fluconazole and to measure intra-cranial pressure.
    - Raised intracranial pressure should be treated with serial LPs
    - CT scan if focal neurology is present.
    - Appropriate antifungal therapy.
  - Culture-positive cases should receive treatment according to Recommendation 2.
  - Predictors: 1mg/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.

CC in special populations
- Cryptococcosis in pregnant women and children
  - No alterations in the management of cryptococcosis are required in pregnancy, due to high mortality associated with CC. Fluconazole is teratogenic; therefore women of child bearing potential who require fluconazole should use effective contraception.
- Cryptococcosis in paediatric patients
  - Antifungal treatment of CC in children
    - Induction phase: Amphotericin B 1mg/kg/dose iv for 2 weeks (retapave episodes should be treated for 4-6 weeks, preferably until CSF fungal culture is negative). Adequate hydration during amphotericin B treatment should be maintained.
    - Consolidation phase: Fluconazole 12-15mg/kg once daily for a further 8 weeks (The maximum dose should not exceed 400mg)
    - Secondary prophylaxis: Fluconazole 6-10mg/kg once daily for life. Secondary prophylaxis can be stopped in children over the age of 2 years who are asymptomatic with their last episode of cryptococcosis having been more than 12 months previously and who have evidence of sustained immune reconstitution on ART as follows: 2-6 years old: CD4 percent > 25%, more than 6 years old: CD4 count > 350 cells/mm³
  - Management of raised intra-cranial pressure in children
    - Recommendations for management of intracranial pressure in adults apply to children (i.e. repeated lumbar punctures).
    - For refractory raised intracranial pressure, referral to a specialist centre is advised.

Drug information, toxicities and interactions in patients treated for CC
- Clinicians should be aware of overlapping toxicities particularly hepatotoxicity that occurs with the concurrent use of TB therapy (pyrazinamide, isoniazid and rifampicin) and nevirapine.
- Fluconazole levels are reduced by concurrent rifampicin therapy. Clinicians should be aware of overlapping toxicities particularly hepatotoxicity in patients treated for CC.

Supplementary management of CC
- Counseling of patients diagnosed with CC
  - All patients CC should be counseled (once fully conscious) regarding:
    - The need for compliance with fluconazole therapy
    - The urgent need for HIV testing (if HIV status unknown)
    - Co-terminus prophylaxis and ART if HIV positive

Contact Details: HIV CLINICIANS SOCIETY
Contact the NICD (011-386-7341), www.nicd.ac.za for information about the surveillance programme.