Cryptococcal Meningitis

Organism: Cryptococcus neoformans

Microbiology

4 serotypes (A, B, C, D)

- A and D, AD Cryptococcus neoformans var neoformans-major cause
- B and C cryptococcus neoformans var gattii –infects immunocompetent host

Widespread in environment (soil contaminated with bird droppings)

Infection via inhalation
Round or oval yeast (saprophytic)
Encapsulated (30 um thick)
Polysaccharide capsule
Small particles (<5 microns): enter lung via inhalation

Clinical Features

Meningo-encephalitis is the most frequent manifestation of infection with cryptococcus
Insidious onset

Associated non-specific symptoms:
- Headache
- Fever
- Malaise
- Vomiting, nausea: 40%
- Meningism: uncommon
- Photophobia: uncommon
- Altered mental status: delirium, confusion, memory loss: 25%
- Seizures

Focal signs: cryptococcoma at site of dense neurologic conduction eg.internal capsule. The prescense of focal neurological signs or obtundation: CNS imaging before LP

If opening pressure >250 mm: drain CSF until < 200mm or 50% of opening pressure. In the absence of manometer measurements a maximum of 10 ml of CSF may be tapped.
May need daily LP until stable
Repeat LP at 2 weeks if there is a poor clinical response or if the patients clinical condition deteriorates. If CSF not sterile, continue with induction phase.

CSF examination:

Abnormal CSF (WBC, glucose, protein-mildly deranged)
CSF cell abnormalities may be modest or absent
Positive India ink (70-90%)
Cryptococcal antigen (CRAG)(93-99%) positive: titers are high: 1:1024

Gold standard for diagnosis of cyrptococcal meningitis: positive CSF culture (especially when CSF normal)
Serum Cryptococal antigen (CRAG) positive in > 90%
Recommended when LP cannot be done

Blood fungal culture positive in 66-80% with AIDS (33% non-AIDS)

Extra-neural crypto diagnosed by tissue exam

Radiological Investigations:

May have radiological evidence of simultaneous or recent cryptococcal pneumonia
CT Scan: exclude space-occupying lesion e.g., Toxoplasmosis, lymphoma
Cryptococcal meningitis: brain atrophy, ventricular enlargement, and rarely mass lesions

Most deaths secondary to cryptococcal meningitis occur in first 2 weeks of therapy. Many related to raised intra-cranial pressure.

Amphotericin B IV (0.7- 0.8-mg/kg/d +/- 5-flucytosine po: 14 days

NIAID MSG and ACTG trial: decreased mortality with amphotericin B 0.7mg/kg/day with or without 5-flucytosine for initial 2 weeks followed by 8 weeks of fluconazole/itraconazole
Then fluconazole 400mg daily: 8-10 weeks (consolidation phase)
Maintenance phase: lifelong suppression with fluconazole 200mg daily
Or itraconazole 200mg bd
Or amphotericin B (1mg/kg) IV: 1-2 times /wk

Consider stopping cryptococcal meningitis maintenance phase therapy if stable on HAART

NB : 5-flucytosine is NOT available in South Africa

Diflucan Partnership Programme

Amphotericin B: 14 days then fluconazole 400mg daily: 8-10 weeks

Alternatives:

Liposomal amphotericin B 4mg/day/IV : 14 days then fluconazole 400mg/daily: 8-10 weeks (expensive)

Reduction of raised intracranial pressure

LP to reduce raised intracranial pressure: reduces mortality and morbidity

Need to decrease opening pressure to 18cm

Improvement in headache, vomiting, neck stiffness, confusion, coma seen in 24hr
Mortality benefit in 30% is first 2 weeks

Cryptococcal meningitis is a fatal disease if left untreated
Even if treated, mortality is high (30%)

5-10% die within 2 weeks of diagnosis despite antifungal therapy

Indicators of poor prognosis:
Duration of symptoms (>2 weeks) before diagnosis
Altered mental state (coma)/localizing signs
High fungal burden
High CRAG titers: >1:1024
Positive India ink
Poor cellular response: <20 cells
Elevated intracranial pressure
Presence of extra neural cryptococcal disease
Cryptococcal positive on blood culture
Additional systemic bacterial infection (S. Aureus, Salmonella)
Hyponatraemia
Concomitant disease

ADMINISTRATION OF AMPHOTERICIN B

Amphotericin B is a colloidal suspension that must be prepared in an electrolyte free dextrose water to avoid precipitation.
There is no need to protect the drug suspension from light.

1. Preload the patient with 500ml of normal saline intravenously.
2. Recommended test dose: 1mg in 50ml dextrose water over 30 min.
   Monitor patient for 4 hours.
3. Full dose: 0.7mg/kg/day in 1liter dextrose water over 4-6 hours.
   Should not exceed 1.5mg/kg/dose.

Amphotericin B infusion often causes: chills/fever, anorexia, nausea and hypotension (rare)

Side effects of Amphotericin B

1. Hypokalaemia
2. Acidosis (may proceed to renal tubular acidosis)
3. Decreased erythropoietin: anemia
4. Hypomagnesaemia
5. Nephrotoxicity

The risk of renal injury may be reduced by pre and post hydration with 500ml saline and avoidance of other nephrotoxins e.g. aminoglycosides
Continuous infusion over 24 hours results in a decreased incidence of nephrotoxicity.
LUMBAR PUNCTURE

AIM: To diagnose infection or bleeding within the central nervous system.

LP: confirms the diagnosis of meningitis identifies the responsible organism and enables determination of antimicrobial sensitivity.

INDICATIONS:

(1) Suspected meningitis (any 2 of the following clinical features: fever, headache, altered mental status, neck stiffness)
(2) Investigation of febrile seizures
(3) Investigation of fever and delirium in the elderly

CONTRA-INDICATIONS:

(1) Raised intracranial pressure (bradycardia, hypertension, abnormal respiration): danger of uncal or cerebellar herniation that may precipitate cardiorespiratory arrest (coning)
(2) Focal neurological signs or seizures
(3) Cardiovascular compromise
(4) CT findings: lateral shift of midline structures
   Loss of suprachiasmic or basilar cisterns
   Obliteration of fourth ventricle
   Obliteration of superior cerebellar/quadrigeminal plate cisterns
   with sparing of ambient cisterns.
(5) Presence of localized infection at the puncture site
(6) Coagulopathy or a platelet count of less than 50 000 (purpura, petechiae)

COMPLICATIONS

(1) Bleeding: local hemorrhage due to injury to spinal and perivertebral veins
(2) Trauma to local structure: ligaments, periosteum, intervertebral discs
(3) Implantation of epidermal cells resulting in epidermoid tumors
(4) Localized infection: epidural abscess, discitis, osteomyelitis, meningitis, encephalitis
(5) Headache

INDICATIONS FOR CT PRIOR TO LP:

(1) Focal neurological signs
(2) Papillodema
(3) Significant alteration of level of consciousness
(4) Slowly progressive headache (days to weeks)
(5) Focal craniofacial infection e.g. Sinusitis, otitis (increased risk of cerebral abscess)

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