**CNS INFECTIONS**

**Pyogenic (bacterial) meningitis**

**Definition:** is an inflammation of the arachnoid layer of the meninges and the fluid that circulates, in the ventricles and sub-arachnoid space (CSF), caused by bacterial infection

**Etiologic agents:** the causes of bacterial meningitis vary with age:

• ***Infants (< 1 year)***: *E. coli, group-B streptococcus, Listeria monocytogenous* are the commonest causative agents.

• **Young children/toddlers (age 1- 6 years)**: *Haemophilus influenza, Meningococcus* account for > 50 % of cases

• **Adolescents and Adults:***Meningococcus, Pneumococcus* are the commonest etiologies

• **In immunocompromised hosts and cancer patients**: *Listeria, Staphylococcus, Pseudomonas aeruginosa* etc.

**Rout of infection:**

• **Droplet infection through the upper airways:**E.g. In *Meningococcus meningitis,* with possibly epidemic spread

• **Haematogenous spread:**e.g. in Pneumococcus pneumonia

• **Contagious spread from adjacent sites:**e.g. in otitis media, sinusitis

• **Direct:**e.g. in open head injury

**Clinical presentation**

• **Incubation period:** the incubation period for Meningococcal meningitis may range from

1-10 days, but mostly the clinical manifestations occur within in 2-4 days

• Meningitis may manifest as an acute fulminant illness that progress rapidly in few hours or as a subacute infection that progressively worsens over several days.

• The classic clinical triad of meningitis is **fever, headache and nuchal rigidity (neck stiffness)**, which are seen in > 90 % of patients.

• Alteration in metal status can occur in > 75 % of patients and can vary from lethargy to coma.

• Nausea and vomiting are common symptoms.

• Avoiding light (photophobia) is seen in some patients.

• Seizure occurs as part of the initial presentation of bacterial meningitis, or during the course of the illness in 20-40 % of patients

• In Meningococcal meningitis of sudden onset with severe course, patients develop diffuse erythromatus maculopapular rash which rapidly becomes petechial, purpural or bullos lesions. The petichiae are found on the trunk, lower extremities, in the mucous membrane and the conjunctiva, and occasionally on the palms and soles.

• In older and debilitated patients the symptoms of meningitis may be subtle.

***Meningeal signs*** are clinical signs often sound in patients with meningitis

• ***Neck stiffness*** when head is flexed passively

• ***Kerning’s sign***: when one leg which is flexed at the hip and knee joints, is passively extended at the knee joint, the other leg flexes at the knee.

• ***Brudzinski’s sign:*** Upon passively flexing the head, one notices flexion of both legs at the knees

***Note:*** These classic meningeal signs may not be seen in infants, old persons and patients in coma.

**Complications:**

• Brain edema,

• Hydrocephalus

• Brain abscess,

• Septic vein thrombosis

• Hearing impairment

• Fulminant meningococcal sepsis: Waterhouse-Friedrichsen syndrome is a clinical condition resulting from hemorrhagic necrosis of the adrenal gland, with multi-organ failure. Patients are hypotensive or in shock. Disseminated intravascular coagulation (DIC) with skin and mucosal purpura and bleedings are commonly seen associated features.

**Diagnostic approach**

• History, physical examination,

• Search for possible source of infection (pneumonia , otitis media , sinusitis , head injury)

• CSF analysis

• Identify the organism from CSF and blood (culture, PCR etc.)

• Serologic antibody test : latex agglutination test

**Laboratory findings:**

**General signs of inflammation:**leukocytosis, CRP and ESR ↑

**CSF analysis:**

• Gross appearance and opening pressure: CSF looks turbid and the opening pressure is increased (due to raised intra cranial pressure )

• Cell count and differential: polymorphonuclear leukocytosis

• Biochemical tests: glucose is decreases and protein in the CSF is elevated

• Gram stain Culture and sensitivity

o Meningococcus are seen as gram negative intracellular diplococcic

**CSF analysis findings in different types of meningitis**

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|  | **Bacterial meningitis** | **Viral meningitis** | **Tuberculous**  **meningitis** |
| **Appearance** | **Turbid** | **Clear** | **Cob-web**  **appearance** |
| **Cell count/μl** | **Several thousand** | **Several hundreds** | **Several hundreds** |
| **Cell type** | **Granulocytes(PMNLs)** | **Lymphocytes** | **Lympho-, monocytes** |
| **Glucose** | **↓ (< 30 mg/dl)** | **Normal** | **↓ (< 30 mg/dl)** |
| **Protein** | **↑ (> 120 mg/dl)** | **Normal** | **↑ (> 120 mg/dl)** |
| **Lactate**  **dehydrogenase**  **( LDH)** | **> 3.5 mmol/L** | **< 3.5 mmol/l** | **> 3.5 mmol/l** |

**Differential diagnosis:**

• Virally caused meningoencephalitis (Coxsackie-, Echo-, Mumps-virus, HIV, measles,

CMV, VZV, HSV)

• Chronic meningitis: Tuberculous meningitis, Cryptococcal meningitis

• Subarachnoid hemorrhage

**TREATMENT:**

**A. Antibiotic Therapy**

**1. Empirical antibiotic therapy**:

Bacterial meningitis is a medical emergency and antibiotics should be initiated immediately before the results of the CSF gram stain and culture are known.

Antibiotics should be given intravenously, at higher doses

• In adults without underlying disease: Ceftriaxone 2 gm IV BID plus Ampicilline 2 gm IV

QID for 2 weeks.

• Crystalline Penicillin 3-4 million IU, IV every 4 hours plus Choramphnicole 1gm IV QID are alternative antibiotics for a resource limited setting .

• Patients with ENT infection or head injury: Ceftriaxone 2 gm IV BID and Vancomycin 1 gm IV BID + treatment of the underlying cause.

• If suspected hospital-acquired infection: Ceftriaxone 2 gm IV BID plus Vancomycin 1 gm IV BID plus Gentamycin (80 mg TID)

• In immunodeficient patients: Ceftriaxone 2 gm IV BID plus Vancomycin 1 gm IV BID plus Ampicillin (2g IV QID)

**2. Specific antibiotic therapy:** is given when the specific etiologic agent is identified through gram stain or culture

• **N. meningitidis**:Even though Ceftriaxone or Cefotaxim provide adequate empirical coverage, Penicillin G remains the drug of choice for *N. Meningitides*

Crystalline Penicillin 3-4 million IU, IV every 4 hours for 7 -10 days may be adequate.

• **Pneumococcal meningitis**: Antibiotic therapy in initiated with Cephalosporins plus Vancomycine

Ceftriaxone 2 gm IV BID and Vancomycin 1 gm IV BID for 2 weeks

• **H. influenza**: Ceftriaxone 2 gm IV BID for 1- 14 days may be enough Choramphnicole 1gm IV QID may be an alternative antibiotic, for patients who may not afford Ceftriaxone.

**B. Symptomatic and adjunctive Therapy**

• **Steroids:**

o **Dexamethason**when initiated before antibiotic therapy reduces the number of unfavourable outcomes, including death and neurologic complications. It is mainly advantageous in children, predominantly with meningitis due to *H.Influenza and S. Pneumoniae.*

***Dose****:* Dexamethason10 mg IV 15-20 minutes before the first dose of antibiotics and 4 mg IV QID for 4 days

• **Treat increased intracranial pressure:**

o Elevation of the patients head to 30-45o

o Intubation and hyperventilation ( till PaCO2 is lowered to 25-30 mmHg )

o Mannitol IV infusion

• **Regulate water and electrolyte balance,**

• **Thromboembolism prophylaxis**

• **Patients with meningococcal meningitis should be isolated**.

**Chemoprophylaxis*:*** In case of *N. Meningitides,* all close contact to the patient should be given chemoprophylaxis with:-

• Rifampicin 600 mg PO BID for 2 days in adults and 10mg/kg PO BID for children > 1 yr.

• Ciprofloxacin 750 mg PO stat can be given as an alternative for adults.

**CRYPTOCCOCAL MENINGITIS**

The genus Cryptococcus contains at least 39 species of yeast, but few are able to cause disease in humans.

Most human infections are due to C. neoformans.

Infection with the fungus Cryptococcus (either C. neoformans or C. gattii) is called cryptococcosis.

Cryptococcosis is a global invasive mycosis associated with significant morbidity and mortality.

Cryptococcosis usually affects the lungs or the central nervous system (the brain and spinal cord), but it can also affect other parts of the body.

Brain infections due to the fungus Cryptococcus are called cryptococcal meningitis.

Meningitis is the most common manifestation of cryptococcal infection.

The lung is the second most common organ to develop clinical disease, usually pneumonia, which can occur in the immunocompetent

The skin is the third most common organ to be affected by cryptococcal infection

**Who is at risk?**

Most cases of C. neoformans infection occur in people who have weakened immune systems, such as people who:

• Have advanced HIV/AIDS,

• Have had an organ transplant

• Sarcoidosis;

• Lymphoproliferative disorder;

• Hypogammaglobulinaemia;

• Systemic lupus erythematosus;

• Cirrhosis;

• Peritoneal dialysis

• Are taking corticosteroids, medications to treat rheumatoid arthritis, or other medications that weaken the immune system.

**Clinical presentation**

* Headache
* Fever
* Neck pain; neck rigidity
* Nausea and vomiting, lethargy, personality change, memory loss
* Sensitivity to light
* Confusion or changes in behavior

The duration of symptoms before presentation is likely to be longer in non-AIDS patients

**DIAGNOSIS**

Definitive diagnosis of cryptococcal meningitis requires lumbar puncture with demonstration of yeasts with India ink stain, positive cryptococcal antigen testing or culture of the organism.

**Investigations**

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.

At LP, in suspected CC:

Measure opening CSF pressure (normal <20 cm CSF)

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.

* CSF examination generally reveals a mild mononuclear leucocytosis (50–500 cells/μL).
* The CSF protein is rarely greater than 500–1000 mg/Dl and it may be normal, especially in HIV patients.

**IMAGING**

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. CT brain scan is normal in 50% of patients with cryptococcal meningitis. The most common abnormal finding is hydrocephalus

Magnetic resonance imaging is more likely to demonstrate abnormalities than CT Scanning.

**ANTIFUNGAL TREATMENT**

Induction phase: Amphotericin B 1 mg/kg/dose iv 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; Until CD4 >200

**WHO RECOMMENDED TREATMENT**

**Induction**

The following is recommended as the preferred induction regimen:

• For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/ day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults), is the preferred option for treating cryptococcal meningitis among people living with HIV

The following induction regimens are recommended as alternative options depending on drug availability:

• Two weeks of fluconazole (1200 mg daily for adults) + flucytosine (100 mg/kg/day, divided into four doses per day).

• Two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults)

**Consolidation**

Fluconazole (800 mg daily for adults) is recommended for the consolidation phase (for eight weeks following the induction phase)

Fluconazole (200 mg daily for adults) is recommended for the **maintenance phase.**

**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.

For people with persistent symptoms of raised intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

**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 analgesics). Non-steroidal anti-inflammatory drugs should be avoided in patients receiving amphotericin B because concomitant administration may increase potential for nephrotoxicity.

**Note:** a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management should be provided to minimize treatment toxicity during induction phase with amphotericin B containing regimens and flucytosine

**TB MENINGITIS**

CNS tuberculosis accounts for 5-15% of all extra pulmonary tb with the higher incidence in children

It is five times more frequent in HIV infected persons than HIV negative

It is more likely to present with atypical symptoms and to progress rapidly in HIV infected than HIV negative

Caused by Mycobateria tuberculosis and rarely by non-tuberculous – M.bovis, M. africanum, M. avium-intracellulare

**Clinical features**

Prodromal period (2-4wks)

Malaise, anorexia, fever fatigue myalgias and headaches

TBM photophobia, fever, headache nausea and neck stiffness with variable alteration in mental status

**Clinical staging**

Stage I: Conscious and rational, fever, no neurological deficits non-specific signs and systems

Stage II: Conscious with altered, meningism and minor neurol. deficits

Stage III: Seizures, abnormal movement, coma and severe neurol. deficits

Neurol. deficits (stiff neck, hemiparesis, paraparesis, papilloedema, stupor and cranial nerve palsy)

**DIAGNOSIS AND MANAGEMENT**

**VIRAL ENCEPHALITIS**

**Definition:** Inflammation of the brain parenchyma, with or without involvement of the meninges, caused by virus. The spinal cord and/or nerve roots may also involve rarely.

**Signs and symptoms:**

• Acute febrile illness with evidence of meningeal involvement (meningeal signs)

• Altered level of consciousness (ranging from lethargy to coma)

• Abnormal mental state (hallucinations, agitation, personality change, behavioral disorder, psychosis)

• Evidence of either focal or diffuse neurologic signs or symptoms.

• Focal or generalized seizures occur in > 50 % of cases.

• Most common focal findings are aphasia, ataxia, hemiparesis (with hyperactive tendon reflexes), involuntary movements and cranial nerve deficits.

**Organisms: Viruses causing encephalitis**

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| **Common** | **Less common** | **Rare** |
| Arboviruses,  enteroviruses, HSV-1,  mumps | CMV, EBV, HIV,  measles, VZV | Adenoviruses, CTFV,  influenza A, LCMV,  parainfluenza, rabies,  rubella |

**Laboratory findings**

* **CSF examination:**check for increased intracranial pressure first. Characteristic profile is undistinguishable from viral meningitis and consists of lympocytic pleocytosis, elevated protein, normal glucose level
* CSF PCR, if available
* CSF culture, usually negative (esp. in HSV-1 infections)
* Serologic studies and antigen detection, if available
* MRI, CT, and EEG: if available, done to exclude alternative diagnoses, and assist in differentiation between focal and diffuse encephalitic process (e.g. 90 % of patients with

HSV-1 infection have abnormalities in the temporal lobe on MRI).

* **Brain biopsy:**reserved for patients with unclear diagnosis, lack of response to therapy and who have abnormalities on imaging techniques.

**TREATMENT**

**Supportive therapy (usually in ICU):**

• Check vital signs, restrict fluid, and give antipyretics.

• Treat seizures and/or give prophylactic therapy (high risk for seizures!).

**Medication:**

• Acyclovir 10 mg/kg TID for at least 14 days (adult dose).

• Gancyclovir (5 mg/kg BID) or Foscarnet (60 mg/kg TID) are especially recommended for CMV infections.