

**MANAGEMENT OF  
CENTRAL NERVOUS SYSTEM  
INFECTIONS IN CHILDREN**

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# CLINICAL GUIDELINES ON CENTRAL NERVOUS SYSTEM INFECTIONS

## GUIDELINES ON MENINGITIS

### **Introduction**

These guidelines are aimed at achieving the best possible paediatric care for children with CNS infection within Sri Lanka. It should be utilized together with the clinical input and discretion of the managing paediatrician. Each patient should be individually evaluated and a decision made as to appropriate management in order to achieve the best clinical outcome. In the interests of patient care it is critical that contemporaneous, accurate and complete documentation is maintained during the course of patient management from arrival to discharge. Parental anxiety should not be discounted: it is often of significance even if the child does not appear especially unwell.

Suspected bacterial meningitis is a medical emergency. If untreated it is invariably fatal. Even with treatment, bacterial meningitis in childhood is associated with high morbidity and mortality. It is also important to treat meningitis promptly. Delay of treatment even for a few hours can make a huge difference to the final outcome.

It is anticipated that modifications may be required for local practice. Variations in management may also be required in individual cases. It is stressed that the guidelines are, by necessity, general in nature and are not intended as a substitute for clinical judgment. One has to be also mindful of evolving new knowledge that a document of this cannot fulfill.

### **Key points in the acute management of bacterial meningitis in children**

#### ***First principles***

- Early recognition and prompt management are the goals.

- Early consultation with a senior paediatric or senior emergency department staff member should occur in all cases of suspected meningitis. Any delay in making the correct decisions and the lost golden hours will have lasting consequences for the affected patient.

#### ***Clinical presentation***

- Not all patients will have fever, neck stiffness and altered mental status.
- The younger the patient, the more subtle the symptoms and signs and the higher should be the level of suspicion.
- Fever is not always present at presentation in acute bacterial meningitis. (50% of infants and 45% of older children in small case series.)
- Neck stiffness is more useful above 3 yrs of age and seen in 60-80% of cases.
- Clinical presentations can vary from being acute (hours to 1–2 days) to insidious (over a few days).
- Preceding upper respiratory tract infection is often present (~75 per cent).
- Seizures occur in 20–30 per cent.
- Papilloedema is rare in acute uncomplicated bacterial meningitis and when present it should be a reason to arrange for imaging without delay
- Bulging or tense anterior fontanelle is a useful sign in young infants who should be examined in the upright position when not crying.
- Prior antibiotics modify presentation and diagnostic yield, and should always be part of the history.

#### ***Initial management***

- The priorities are ensuring the adequacy of the Airway, Breathing, Circulation, Disability (level of consciousness) and Exposure (rash assessment and environmental control) i.e. ‘ABCDE’.
- The risks from inadequate cerebral circulation may be higher than the risks of cerebral oedema so volume expanders should be titrated against the patient’s perfusion.
- If venous access is significantly difficult, an intraosseous needle can be used.
- Seizures should be treated urgently.

- A bedside whole blood glucose reading (reflectance meter) e.g. ‘Dextrostix’, should be performed as part of the early assessment, especially in infants. If the level is less than 50mg/dl (and less than 40mg/dl in the neonate) action should be taken to correct it immediately. (x)
- Electrolyte abnormalities should also be addressed.

### ***Diagnosis***

- Ensuring the adequacy of the ABCDEs has priority over establishing a precise diagnosis.
- CSF examination provides the definitive diagnosis. Blood cultures may provide supportive evidence. Ideally, CSF via lumbar puncture (LP) and blood cultures should be taken prior to antibiotic therapy. Other investigations are helpful for acute management of a sick child, but not definitive in the diagnosis of meningitis.
- The initiation of appropriate antibiotic therapy assumes high priority. If the patient is too sick or unstable for immediate definitive investigations, then appropriate antibiotics should be commenced after taking blood for culture. (x)
- The LP should be performed when the patient is resuscitated and stable. (x)
- A cerebral computed tomogram (CT) scan is not part of the routine workup and is indicated only in specific situations (see text). It should only be done when the patient is stable.
- The limits of sensitivity of the CSF diagnostic tests, especially if pre-treated with parenteral antibiotics, should be recognized.
- CSF samples should be expeditiously transported to the laboratory and urgently analyzed. In case of delay in the transport of CSF, samples should not be refrigerated but kept at room temperature.

### ***Steroid therapy***

A recent systematic review supports the early use (just before or with first dose of antibiotics) of adjunctive steroid therapy provided children have not been pre-treated with antibiotics. The benefit is an approximate two-thirds reduction in severe hearing loss (Hib and non-Hib). The impact on long term cognitive function remains unanswered. There is insufficient information to be certain about the benefit of steroids in the 0–3 month age group given the different aetiological agents and unknown potential adverse effects of steroids in this age group. The benefit is also less clear in children who present late in the illness or in severe sepsis.

***Suggested criteria for steroid use in acute bacterial meningitis:***

- > three months of age
- Not pre-treated with parenteral antibiotics. Due to insufficient information, no clear recommendations can be given about steroids in the < 3 month age group and those presenting with advanced meningitis or severe sepsis.

***Suggested regimen:***

- Dexamethasone, 0.15 mg/kg/dose, IV, six-hourly for four days.
- Given as a 'push', followed by first dose of antibiotics for practical purposes.

***Antibiotic therapy***

Recommended empiric antibiotic therapy is:

- Neonates to three months: ampicillin plus cefotaxime (not ceftriaxone in neonates). If GBS is isolated high dose C Penicillin could be used alone (x)
- > three months: cefotaxime or ceftriaxone. (x)

***Fluid Management***

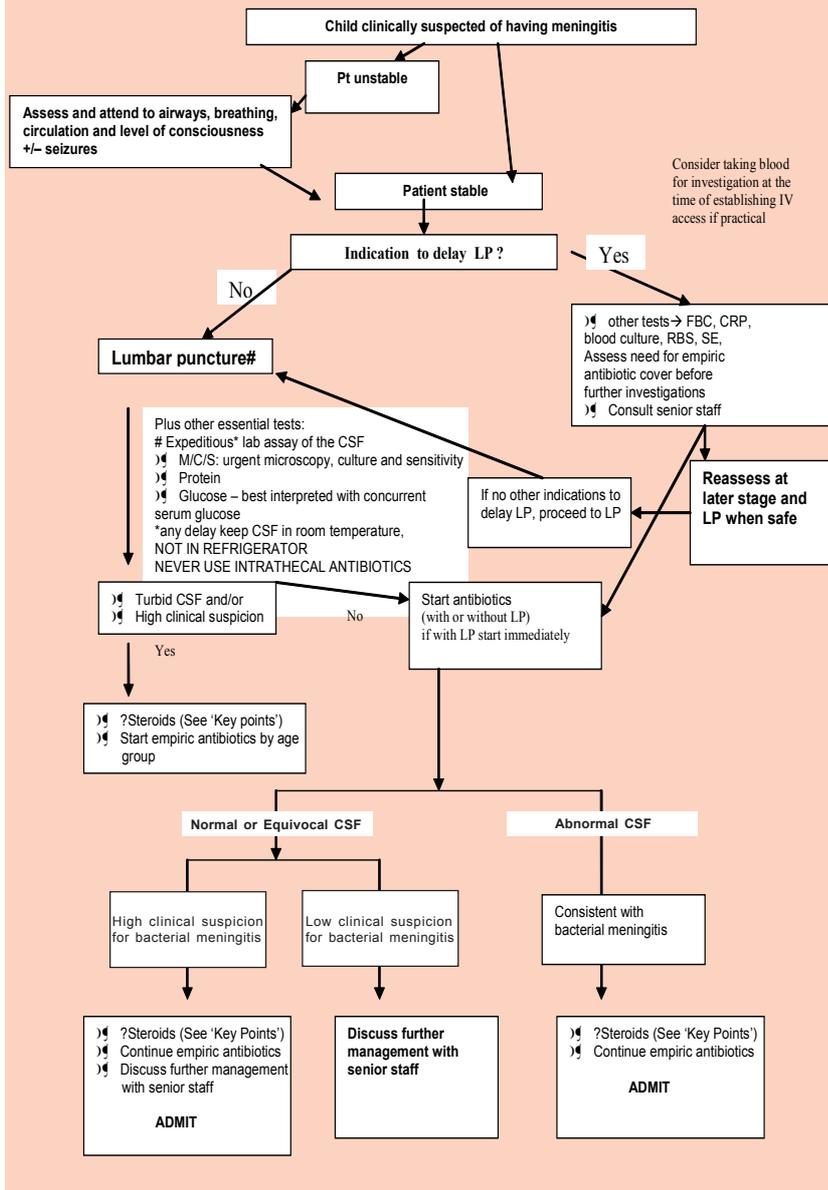
Patients with evidence of shock should be treated with a rapid infusion intravenous/interosseous crystalloid (Normal saline/Hartmann's solution) 20ml/kg. Fluid restriction (for SIADH) is not routinely recommended in the initial management but should be considered in specific circumstances; e.g. patients with recurrent seizures or when there is other evidence such as hyponatraemia.

***Further care***

Once the patient is resuscitated and stabilized, refining management and further investigations can be arranged under the direction of the responsible team.

The decision to transfer the patient or to continue to provide care locally will be determined by the local resources and the patient's needs.

### Algorithm: Acute management of suspected bacterial meningitis in children



### ***Clinical presentations***

While viral meningitis occurs more commonly than bacterial meningitis, it is often difficult to distinguish from bacterial meningitis. *Mycobacterium tuberculosis* (MTB) meningitis should also be considered in the differential diagnosis. MTB meningitis is rare and if suspected such patients are best managed by sending them to a specialized centre.

**However initial management of suspected meningitis should be done as for bacterial meningitis until proven otherwise.**

### ***Common presentations***

Clinical presentations of bacterial meningitis vary, depending on; age, duration of illness, the patient's response to infection, whether prior antibiotics have been used and the infecting organism. The presentations could be insidious (over a few days), acute and sometimes fulminant (a few hours).

**Overall, severity of the illness at presentation appears the most predictive of outcome.**

The history and examination of a child presenting with suspected meningitis is the same as any acutely unwell child, with attention paid to neurological signs and associated complications.

Apart from the clinical presentations, the history should include the following key elements:

- age (~90 per cent of bacterial meningitis occurs at age < five years)
- vaccination history
- recent use of antibiotics
- Drug allergies.

### **0–2 months**

The diagnosis may be more difficult in the very young as history and presentations can be non-specific. Features include:

- fever or hypothermia
- bulging fontanelle
- irritability
- high pitched cry
- lethargy
- altered mental state
- seizures
- apnoea
- poor feeding
- vomiting.

A high index of suspicion for meningitis must exist in sick, febrile or hypothermic newborns with or without the above features.

### **>2 months**

Symptoms become more CNS specific after this age. Acute presentations include:

- fever (not always present at presentation time ~50 % in infants and in ~45 % in older children in small case series)
- neck stiffness (60- 80%, more useful in children > 3 years)
- Kernig's sign (inability to completely extend the leg) in older children. Absence does not exclude meningitis
- Brudzinkin's sign (flexion at the hip and knee in response to forward flexion of the neck) in older children. Absence does not exclude meningitis
- irritability or lethargy
- altered mental state (highly variable)
- anorexia, nausea and/or vomiting (a common/non-specific symptom)
- photophobia (older children)
- seizures (about 20–30 per cent incidence)

**NB:** Papilloedema in uncomplicated early bacterial meningitis is rare. The presence of papilloedema suggests complications like venous sinus thrombosis, abscess, or subdural empyema, It is a reason to arrange imaging without delay

### **Children who have received prior antibiotics**

The clinical presentations and CSF findings in children who have received previous antibiotics may be modified. Some features include:

- less frequent presentations with temperature > 38.5°C
- less frequent alterations in mental status
- the relationship between polymorphonuclear cells and lymphocytes in CSF may be reversed.
- Culture and gram stain may be negative.

### ***Complications***

Patients may uncommonly present with early complications of sepsis or raised intracranial pressure:

- Septic shock
- Disseminated intravascular coagulopathy
- Cerebral abscess or subdural effusions
- Acute hydrocephalus
- Cranial nerve palsies
- Purpura fulminans
- Waterhouse-Friderichsen syndrome
- Cerebral herniation

### ***Minimizing delay in diagnosis***

To avoid a delay in the diagnosis of meningitis, the following important points must be noted.

- The early diagnosis of bacterial meningitis can be difficult even for experienced clinicians – a high index of suspicion should be maintained. If doubts exist about a diagnosis, consultation with a senior staff member is strongly advocated. Meningitis must be considered in any child with unexplained fever
- Meningitis needs to be considered in all children presenting with seizures in association with fever, particularly in children aged < 12 months, or the fever is prolonged in nature or refractory to management. Not all children presenting with fever and convulsions will have meningitis.
- The presence of an apparent explanation for fever eg. pharyngitis or otitis media does not rule out the possibility of meningitis. A preceding history of an upper respiratory tract infection may present in about 75 %.
- Maculopapular, petechial or purpuric rashes may sometimes be associated with *Neisseria meningitidis* meningitis/ septicemia. Petechiae and/or purpura have also (less commonly) been observed in *Haemophilus influenzae* type b or *Streptococcus pneumoniae* sepsis.
- Prior oral antibiotics for unexplained fever or other focus may confuse and delay diagnosis.

- Apparent improvement with paracetamol is not helpful in excluding the diagnosis.
- Examination of any CSF samples taken is urgent. Thus, appropriate labeling of requests, facilitation of delivery of specimens and direct communication with the pathology laboratory is recommended. CSF FR(full report) examined after one hour is unreliable
- **In case of delay in sending the CSF, samples to be sent for culture should not be refrigerated but kept at room temperature.**  
(However, CSF samples sent for viral or mycobacterial studies or samples submitted only for bacterial antigen detection should be refrigerated)

### ***Initial management***

The assessment of any critically unwell child must always focus initially on resuscitation. The diagnostic test for meningitis is the lumbar puncture (LP). However, this test should not be undertaken until the patient has been resuscitated and stabilized. Assessing ABCDE, the ‘Airway, Breathing, Circulation, Disability (level of consciousness) and Environment (presence of rash, temperature control)’ is thus the first priority. Once the patient has been stabilized, then the examination should include general assessment looking for features of sepsis and meningitis.

### ***Resuscitation***

#### *Airway and Breathing*

Ensure that there is an open airway and adequate ventilation is established. Supplemental oxygen should always be administered. If ventilation or oxygenation is inadequate, then respiratory support should be commenced in the form of bag and mask technique, followed by endotracheal intubation.

#### *Circulation*

Fluid restriction is not an issue in the initial stabilization of children with meningitis. Patients with evidence of shock should be treated with a rapid infusion intravenous/interosseous crystalloid (Normal saline) 20ml/kg. Any considerations for fluid restriction (for syndrome of inappropriate anti-diuretic hormone, SIADH) should only be undertaken once the patient is no longer shocked.(see notes below on fluid therapy) (x)

### *Disability (level of consciousness)*

If there are signs of cerebral oedema (decreasing level of consciousness, bulging fontanelle, papilloedema, rising blood pressure with falling heart rate), mannitol (0.5–1.5g/kg = 2.5–7.5 mL/kg of 20% solution) should be given. It could be repeated if necessary 1–2 times after 4–8 hours. The bed should be elevated to 30° and ventilation controlled to maintain PaCO<sub>2</sub> between 30–35mmHg. (y)

### *Environment*

The presence of a rash may be indicative of meningococcal sepsis. Regulation of temperature is important in the acute management of children presenting with sepsis. (x)

### *Seizures*

Seizures should be treated immediately with a rapid injection of a benzodiazepine (eg midazolam, 0.15mg/kg, IV). Alternatively, IM midazolam (0.15mg/kg) or rectal diazepam(0.5mg/kg ) could be used. Considerations to a loading dose of phenytoin (20mg/kg over 20 minutes) should given if seizures continue. Phenytoin has the benefit of avoiding sedation, although phenobarbitone (20mg/kg) is more commonly used in neonates. Paraldehyde may also be used IM or rectally(mixed with olive oil or sunflower oil

### *Blood glucose, urea and electrolytes*

These must be checked early in the management and corrected if necessary. A bedside whole blood glucose (reflectance meter) e.g. ‘Dextrostix™’ should be performed in the early assessment, especially in infants.

### *Diagnostic tests*

The laboratory gold standard for establishing the diagnosis of bacterial meningitis is the isolation of the causative bacteria from the cerebrospinal fluid (CSF). However, laboratory diagnosis is often made using the combination of blood and/or CSF cultures along with Gram stain and chemical analysis of the CSF.

### *Investigations*

#### **1. Routine investigations for all patients with suspected bacterial meningitis**

- **Blood tests** - FBC, with differential WCC, blood film (A WCC of <10 x 10<sup>9</sup>/L does not exclude meningitis. Thrombocytopenia can occur in DIC)
  - Blood culture
  - CRP – (A trap to watch for is a low or normal CRP that may occur early in severe infection)
  - Blood urea, electrolytes, glucose, LFTs (Na to detect SIADH; renal and liver impairment can occur with sepsis)

- **CSF analysis- Full Report** - includes protein, cell count and gram stain (cells, specially polymorphs disintegrate fast; if not examined within one hour cell counts are unreliable)  
**Glucose** - to be interpreted with blood glucose measured simultaneously  
**Culture** - In case of delay, specimens should not be refrigerated but kept at room temperature

## 2. Possible additional tests based on clinical presentation

(as and when indicated )

- **Blood**
  - JE serology (IgM and IgG- IgG require convalescent serology too)
  - Herpes simplex serology
- **CSF**
  - Bacterial antigen detection
  - Mycobacterium tuberculosis- AFB, PCR and culture
  - Cryptococcal stain and antigen- immuno-compromised patients
  - Viral cultures – (only for enteroviruses at MRI – specimen should be taken within 1<sup>st</sup> 4 days of illness. Stool specimen should also be sent for enteroviral culture. Both specimens should be sent on ice)
  - Herpes simplex PCR
  - Antibodies
    - JE/HSV Ab (should be taken within 05 days of illness)
    - Mumps Ab (should be taken within 05 days of illness along with a blood/serum sample for Ab)
    - Measles Ab (should be taken within 05 days of illness along with a blood/serum sample for Ab)
- **Skin**
  - scrapings of skin lesions for microscopy + culture
  - When petechiae are seen gently derroof the lesion with a needle and roll the sterile swab over the base of the lesion and then on to a glass slide for microscopy and then another swab for culture
- **EEG**
  - for Herpes simplexencephalitis – focal changes specially in the temporal lobe

- CT brain - is of very limited use and is only indicated when there is doubt about other causes of meningism such as posterior fossa tumour or complications like abscess are clinically suspected. Any decision to perform a CT should not delay antibiotics. A CT scan cannot rule out raised intracranial pressure and a normal CT does not absolutely exclude subsequent risk of herniation.

### ***The Lumbar Puncture (LP)***

An LP for CSF analysis should be performed once the diagnosis of meningitis is suspected and after the patient is stabilised. If there are reasons to delay LP (see below) and bacterial meningitis is clinically suspected, antibiotics should be given prior to the LP. Early lumbar puncture rapidly confirms or excludes bacterial meningitis in most cases and should be performed when meningitis is suspected unless there is a specific contraindication. Antibiotics may sterilise the CSF within one hour in meningococcal meningitis and within four hours in pneumococcal meningitis. However, instituting antibiotics 1–2 hours prior to LP does not decrease the diagnostic sensitivity of the CSF culture if done in conjunction with blood cultures and CSF bacterial antigens. The decision to perform cranial computed tomogram (CT) before the LP is one factor contributing to delayed diagnosis. Although concerns about herniation following an LP exist, herniation is unlikely in children unless they have focal neurological findings or are comatose.

### ***Indications to delay the LP***

- Signs of raised intracranial pressure—altered pupillary responses, absent Doll’s eye reflex, decerebrate or decorticate posturing, abnormal respiratory pattern, papilloedema, hypertension and bradycardia
- Recent (within 30 minutes) or prolonged (over 30 minutes) convulsive seizures
- Focal or tonic seizures
- Other focal neurological signs—hemi/monoparesis, extensor plantar responses, ocular palsies
- Glasgow Coma Score < 13 or deteriorating level of consciousness
- Strong suspicion of meningococcal infection (typical purpuric rash in an ill child)
- State of shock
- Local superficial infection
- Coagulation disorder.

### ***Interpreting the CSF***

1. If there is difficulty in interpreting the LP, a clinical microbiologist, infectious disease physician or senior staff should be consulted.
2. No CSF test is fully reliable in distinguishing bacterial from non-bacterial meningitis. In rare instances (<3%), 'normal' CSF findings have been associated with culture proven bacterial meningitis. However, in most cases, clinical indicators of meningitis or sepsis will be present. (Very rarely initial LP could still be normal but with evidence in LP done subsequently. A repeat LP at 24–48 hours may be indicated when clinical indicators of meningitis are present but CSF examination is normal. This should be decided by a senior person in special circumstances)
3. Post-ictal CSF abnormalities (pleocytosis or raised protein) are rare, and should not be readily accepted as a cause for an abnormal CSF.

### ***Guide to distinguishing a traumatic tap from CSF pleocytosis***

A simple rule is that for every 500 RBC in the CSF, it is acceptable to have one WBC.

However this depends on the peripheral white and red cell counts. A more precise formula to estimate the WCC in CSF has been described.

1. The ratio of RBC to WBC in the periphery is generally 1000 RBC: 1–2 WBC x 10<sup>6</sup>/L.
2. Thus, number of WCs introduced into the CSF per L = 
$$\frac{\text{WBC}_{(\text{Peripheral})} \times \text{RBC}_{(\text{CSF})} \times 10^6/\text{L}}{\text{RBC}_{(\text{Peripheral})}}$$
3. Compare result with actual number of WCC in CSF.
4. 1000 x 10<sup>6</sup>/L RBC in CSF raises CSF protein by about 0.015g/L.

**Normal ranges and typical findings in patients with meningitis**

	Polymorphs (x 10 <sup>6</sup> /L)	Lymphocyte (x 10 <sup>6</sup> /L)	Protein (g/L)	Glucose mmol/L	Glucose (CSF:Blood ratio)
<b>Normal ≤1 month of age</b>	0	≤11	< 1.0	≥2.1	≥0.6
<b>Normal &gt; 1 month of age</b>	0	≤5	< 0.4	≥2.5	≥0.6
<b>Bacterial meningitis</b>	100–10,000 (but may be normal)	Usually < 100	> 1.0 (but may be normal)	Usually decreased	< 0.4 (but may be normal)
<b>Viral meningitis</b>	Usually <100	10–1000 (but may be normal)	0.4–1 (but may be normal)	Usually normal	Usually normal

**Normal Values**

	Cell count	Predominant cells	Protein (g/l)	Glucose (% of blood sugar)
Neonates	<30 /ml	neutrophils	0.4 – 1.2	2/3 <sup>rd</sup> (66%)
Children	<10/ml	lymphocytes	0.2 – 0.8	60%
Adults	<10/ml	lymphocytes	0.2 – 0.5	60%

**Cellular response and biochemical properties in meningitis**

	Bacterial meningitis	Viral meningitis	TB / cryptococcal meningitis
Cell count / mm <sup>3</sup>	100-3000	10-500	100-500
Differential count	Mainly neutrophils	Mainly lymphocytes	Mainly lymphocytes
Protein g/l	0.5-3.0	0.5-1.0	1.0-6.0
Glucose % Blood sugar expected range	<60% (0.0-2.2mmol/l)	Normal	<60% (0.0-2.2mmol/l)

**White cells in CSF**

1. The presence of polymorphonuclear (PMN) cells is always abnormal and if present, usually suggests bacterial meningitis. It may also occur in the early phase of viral meningitis, but lymphocytosis is more commonly seen.
2. In partially treated bacterial meningitis, the relationship between PMNs and lymphocytes may be reversed.
3. In tuberculous (TB) meningitis, the total WCC is usually < 500 x 10<sup>9</sup>/L and lymphocytes predominate (although PMNs may predominate in the early stages). Characteristically, the CSF glucose is low (< 50% of serum glucose) and CSF protein raised (often 1.0–3.0 g/L), but normal values do not exclude TB meningitis.

### ***CSF glucose concentration***

Blood glucose levels obtained at the time of the LP enables proper interpretation of the CSF glucose as changes in the CSF glucose level follow changes in the blood glucose by about 30 minutes. CSF glucose < 2.2 mmol/L is found in about 2/3rds of patients with bacterial meningitis. CSF: blood ratio <0.3 is found in 70%. However, a normal glucose does not exclude meningitis. While the CSF glucose seldom influences treatment decisions, the CSF glucose level was found useful in the following situations.

- Patients pre-treated with antibiotics
- CSF pleocytosis – to aid in differentiating between the most likely class of organism
- Patients > eight weeks of age
- Patients at risk of unusual organisms.

### ***CSF protein concentration***

About 90 % of patients with bacterial meningitis will have elevated protein levels. The protein levels may be elevated in a traumatic tap. There will be an approximate 0.01–0.015 g/L increase in protein levels for every 1000 RBCs in uncentrifuged CSF samples.

### ***Gram stain***

- This is the best single test for rapidly diagnosing bacterial meningitis and initiating appropriate therapy.
- The Gram stain will identify bacteria in 60–90 % of cases. Occasionally, the Gram stain will be positive despite the absence of pleocytosis.
- Gram stain yields are reduced if there has been prior treatment with antibiotics, but other CSF indices may still indicate a likely bacterial infection.

**Gram stain results of common bacteria causing community acquired bacterial meningitis**

<b>Organism</b>	<b>CSF Gram Stain</b>
<i>Group B streptococcus</i> .....	Gram positive cocci resembling streptococci
<i>Streptococcus pneumoniae</i> .....	Gram positive diplococci or GPC resembling streptococci
<i>Neisseria meningitides</i> .....	Gram negative diplococci or gram negative cocci
<i>Haemophilus influenzae</i> .....	Gram negative cocco-bacilli
<i>Enterobacteriaceae eg E coli</i> .....	Gram negative rods
<i>Listeria monocytogenes</i> .....	Gram positive rods
	Gram variable rods*

\*Discuss with microbiologist

**Antibiotic management**

*General*

**Age Group**      **Common organisms**      **Empiric antibiotic selection**

0–1 months      Group B streptococcus, *Escherichia coli*, *Listeria monocytogenes*      Ampicillin (or benzyl penicillin) + cefotaxime.

1- 2 months      Neonatal organisms, Haemophilus Pneumococcus, Meningococcus      \*NB: Ceftriaxone is contraindicated in neonates. Benzyl Penicillin + Cefotaxime/Ceftriaxone

> 2 months–5 years      Meningococcus, Haemophilus, Pneumococcus      **Empiric antibiotic selection** Cefotaxime or ceftriaxone

> 5 years      Pneumococcus, Meningococcus      Cefotaxime or ceftriaxone

Myelomeningocele, CSF shunts, post neurosurgery, penetrating trauma, basal skull fracture      Vancomycin + ceftazidime  
Vancomycin + cefotaxime

**Antibiotic doses**

1. Benzylpenicillin 60mg/kg (max 2.4g) IV 4-hourly
2. Ampicillin 50mg/kg (max 2g) IV 4-hourly
3. Cefotaxime 50mg/kg (max 2g) IV 6-hourly
4. Ceftazidime 50mg/kg (max 2g) IV 6-hourly
5. Ceftriaxone 100mg/kg (max 4g) IV Daily
6. Vancomycin 15mg/kg (max 500 mg) IV 6-hourly  
(not for routine use)

***Adjunctive therapy – Corticosteroids***

Systematic reviews/studies examining the efficacy and safety of early adjuvant corticosteroid therapy in children (and adults) with acute bacterial meningitis has recently become available. The studies have been heterogenous with respect to study protocol and study population. Several issues were not addressable. These include the role of steroids in children presenting with both meningitis and severe sepsis, the impact of steroids on long term cognitive function, and potential adverse impact of treating viral meningitis with steroids. However the current consensus opinion is that early steroids in acute bacterial meningitis caused by either Hib or non-Hib in children reduce the risk of severe hearing loss by about two thirds. Impact on neurological sequelae remains uncertain. Steroids do not increase mortality and is not associated with increased adverse events.

Based on the findings, it seems reasonable to use dexamethasone in acute bacterial meningitis in children > three months of age, provided that children have not been pre-treated with parenteral antibiotics. There is insufficient information about steroids in infants < three months of age and in those presenting with severe sepsis or delayed or advanced meningitis.

*If steroids are indicated:*

- Steroids should be given early. For practical reasons, steroids should be given at the time antibiotics are administered as a single push to minimise potential delay in antibiotic administration. The suggested dosing regimen is 0.15mg/kg, IV, every six hours for four days
- If steroids are used and resistant pneumococcus is found (or suspected), careful monitoring of patients during therapy for indications of failure of drug therapy should be done. Consideration should be given to a repeat LP to document a sterile CSF 48–72 hours after the start of therapy.

## ***Chemoprophylaxis***

### **1. Haemophilus influenzae**

1. Chemoprophylaxis is recommended for all household contacts , irrespective of age when at least one unvaccinated contact is younger than four years of age.
- 2 . When index case is under 2 years of age commence a full course of Hib vaccination as soon as possible after recovery regardless of any previous immunization. Unvaccinated contacts under 5 years of age should be immunized as soon as possible.

#### ***Drugs for prophylaxis***

##### *Rifampicin*

Neonate 10mg/kg	daily for 4days
Child 20mg/kg	daily for 4days
Adult 600mg/kg	daily for 4days

If Rifampicin is considered unsuitable

##### *Cefuroxone*

Child 50mg/kg	IM daily for 2 days
Adult 1g	IM daily for 2 days

### **2. Neisseria meningitidis**

1. Chemoprophylaxis is recommended for all household and day care contacts , irrespective of age.
- 2. Prophylaxis is not recommended for healthcare workers unless** direct contact with respiratory secretions of patients with suspected or proven *Neisseria meningitidis* has occurred.

##### *Rifampicin*

Neonate-1year 5mg/kg	12 for 2days
Child ( 1-12years) 10mg/kg	12hrly for 2days
Adult 600mg/kg	12 hrly for 2days

##### *Cefuroxime*

Child 125mg as single dose IM	
Adult 250mg as single dose IM (preferred option during pregnancy)	

##### *Ciprofloxacin*

500mg orally as single dose

Patients with meningococcal or Hib disease should be given rifampicin prior to discharge from hospital to assure elimination of the organism.

### ***Isolation***

Haemophilus influenzae – Patient becomes noncommunicable within 24-48 hrs after starting effective antibiotic therapy.<sup>1</sup>

Meningococcal meningitis – Isolation for 24 hrs after start of chemotherapy.<sup>1</sup>

## **GUIDELINES ON ENCEPHALITIS**

### ***Key Points***

- Suspected encephalitis is a paediatric emergency.
- Early recognition and prompt management and early consultation/ involvement of senior staff member is important as with meningitis
- Encephalitis is an acute inflammatory process that affects brain tissue and is almost always accompanied by inflammation of the adjacent meninges.
- Encephalitis presents as diffuse and/or focal neuropsychological dysfunction. From an epidemiologic and pathophysiologic perspective, encephalitis is distinct from meningitis, though on clinical evaluation the two often coexist with signs and symptoms of meningeal inflammation, such as photophobia, headache, or a stiff neck.
- Majority of encephalitis are viral though it could also be caused by bacterial infection
- Causative agents include arboviruses, enteroviruses, herpes simplex types 1 and 2, varicella zoster (VZV), rabies, etc. though 25%- 50% of cases do not have a specific pathogen isolated.
- Japanese encephalitis (JE) is the commonest form of clinical encephalitis known to occur in epidemic form.
- Herpes simplex encephalitis (HSE) is the most common non-epidemic encephalitis and account for 10% of all encephalitis world over.
- Most of the time viral encephalitis is asymptomatic or sub-clinical. Only a small % develops clinically overt disease. In JE only about 1 per 250 infections results in symptomatic disease.
- Encephalitis resulting from viral infection manifests as either acute viral encephalitis or post-infectious encephalomyelitis. A distinction between these two is important because management and prognosis are different. Acute viral encephalitis is caused by direct viral infection of neural cells

with associated perivascular inflammation and destruction of gray matter. Post-infectious encephalomyelitis (also known as acute disseminated encephalomyelitis-ADEM) follows infection with various viral or bacterial agents; the primary pathologic finding is demyelination of white matter. This illness often occurs 2 to 3 weeks following an initial infection such as a respiratory viral syndrome or a vaccination.

- No satisfactory specific treatment exists for most common acute viral encephalitides. Clinically distinguishing these from HSE and VZE which could be effectively treated with acyclovir is an important step in the management.

### ***Clinical presentation***

- Encephalitis frequently begins as an acute febrile illness or with nonspecific systemic features such as malaise, anorexia, vomiting, abdominal pain, myalgia, mild headache, chills, or low-grade fever. Additional features that may be noted during specific viral syndromes include pharyngitis, rash, diarrhea, cough, or other respiratory symptoms.
- The interval between the onset of nonspecific, systemic complaints and the appearance of overt neurologic symptoms or signs ranges from a few hours to several days and vary according to the cause and severity of the infection
- Early features of mild encephalitis consist of headache, malaise, somnolence, and mild cognitive or behavioral disturbances
- In more severe infections, alterations in the sensorium, drowsiness, confusion and restlessness which progress rapidly could be seen.
- Seizure are common and in JE convulsions occur in nearly 90% of patients.
- Findings from physical examination are not usually diagnostic. Focal neurological deficits (eg, opisthotonos, pareses, tremors, ataxia, hypotonia, diplopia), accentuated reflexes, and extensor plantar responses may be observed. Abnormal movements and, rarely, tremor may be seen. Increased intracranial pressure can also lead to papilloedema and VI cranial nerve palsy.
- Signs of meningeal irritation such as neck stiffness are common but comparatively less severe compared to the rapidly deteriorating level of consciousness,
- Focal features such as paralysis or aphasia increase the probability of HSE but focal features may be seen in other encephalitis too (eg EBV). However about 20% of HSE cases may be relatively mild and atypical without the typical focal features

- The presence of myelitis or poliomyelitis points away from HSE and towards the possibility of polio, enterovirus, or arbovirus infection.
- If the peripheral nervous system is involved then this raises the possibility of the encephalitis being ADEM or an infection with CMV, VZV or Epstein-Barr virus (EBV), which can all produce a combination of central and peripheral signs
- There is great clinical variability in the presentation of viral encephalitis and such clinical variability can be influenced by the age of the infected person, differences in host immune responses, or pathogenic variations in virus strains.

### ***Differential diagnosis of encephalitis***

Viral encephalitis usually consists of fever, headache, and clouding of consciousness together with seizures and focal neurology in some cases. However, the distinction between an infective viral encephalitis and a metabolic encephalopathy or ADEM may not always be straightforward

#### **Causes of viral encephalitis include,**

- Herpes simplex virus (HSV-1, HSV-2)
- Other herpes viruses: varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6)

#### **Adenoviruses**

- Influenza A
- Enteroviruses, poliovirus
- Measles, mumps and rubella viruses
- Rabies
- Arboviruses—for example, Japanese encephalitis, West Nile encephalitis virus, tick borne encephalitis viruses

#### **Common causes of encephalopathy include**

- Anoxic/ischaemic
- Metabolic
- Nutritional deficiency
- Toxic eg. lead
- Systemic infections
- Critical illness
- Malignant hypertension
- Mitochondrial cytopathy (Reye's and MELAS syndromes)
- Paraneoplastic
- Neuroleptic malignant syndrome
- Traumatic brain injury
- Epileptic (non-convulsive status)

***Differences between encephalopathy and viral encephalitis***

<b>CLINICAL FEATURES</b>	<b>ENCEPHALOPATHY</b>	<b>ENCEPHALITIS</b>
Fever	Uncommon	Common
Headache	Uncommon	Common
Depressed mental status	Steady deterioration	May fluctuate
Focal neurologic signs	Uncommon	Common
Types of seizures	Generalised	Generalised or focal
<i>Laboratory findings</i>		
Blood	Leucocytosis uncommon	Leucocytosis common
CSF	Pleocytosis uncommon	Pleocytosis common
EEG	Diffuse slowing	Diffuse slowing and focal abnormalities
MRI	Often normal	Focal abnormalities

***Viral encephalitis vs post – infectious encephalomyelitis***

ADEM, also known as postinfectious encephalomyelitis, usually follows either a vaccination within the preceding four weeks, or an infection which may be a childhood exanthema such as measles, rubella or chickenpox, or else a systemic infection characteristically affecting the respiratory or gastrointestinal systems

***Comparison between ADEM and viral encephalitis***

<b>Clinical features</b>	<b>ADEM</b>	<b>ENCEPHALITIS</b>
Age	Children	Any age
Recent vaccination	Common	Uncommon
Prodromal illness	Usual	Occasional
Fever	May occur	Common
Visual loss (one or both eyes)	May occur	Uncommon
Spinal cord signs	May occur	Rare
<b>Laboratory findings</b>		
Blood	Leucocytosis occasionally occurs	Leucocytosis common
MRI	Multiple focal areas of hyper intensity that are the same and may involve white matter of both hemispheres, basal ganglia, brainstem, cerebellum, and spinal cord	One or more diffuse areas of hyper intensity involves the grey matter of both cerebral cortices and its underlying white matter and, to a lesser extent, basal ganglia, brainstem, and cerebellum
CSF	Lymphocytic pleocytosis, elevated protein, normal glucose, and negative cultures. Red blood cells seen in acute haemorrhagic leucoencephalitis.	Lymphocytic pleocytosis, elevated protein, normal glucose, and negative cultures. Red blood cells may be seen in herpes simplex encephalitis.

## ***Investigations***

### *General*

1. Haematological - FBC – leucocytosis common in ADEM; relative lymphocytosis may occur in viral encephalitis ESR – when very high D/D include tuberculosis/malignancy
2. Biochemical – metabolic encephalopathy
3. Drug screen and urine analysis
4. Cold agglutinins – mycoplasma
5. Serology- Ab to arbovirus – take acute and convalescent samples for viral antibody titres - these are of little value in the acute management of the patient because of the delay in obtaining the results
6. Chest X ray

### ***Neurological***

**Electroencephalogram(EEG)** – should be obtained in all cases of suspected encephalitis if possible.

- In general except a few cases most viral encephalitis will have an “abnormal” EEG
- In viral encephalitis, EEG usually shows slowing of background rhythms or epileptiform discharges that can be focal or diffuse
- In patients with biopsy-proven HSE, 80% will show focal abnormalities on the EEG.

Focal EEG changes may be seen with other types of encephalitis too

- **EEG in HSE**

Slow waves, spikes, or spike-wave discharges, including periodic lateralizing epileptiform discharges that localize to the temporal regions increase the probability of HSE but their absence does not exclude HSE.

Contrary to the diffuse slow waves seen in other encephalitides, tracings in HSE cases are usually very asymmetrical and often show clear foci of spikes on an abnormally slow background. Low amplitude in one or more regions especially over the temporal lobes is not unusual.

Periodic complexes 1-3 seconds apart are frequent in the same area but are often transient. Periodic complexes occur most commonly between 2<sup>nd</sup> & 15<sup>th</sup> day of the disease and are rare after day 15. They are not specific and may occur with others like EBV or mycoplasma too.

- In severe cases of viral encephalitis, irrespective of aetiology, the EEG may demonstrate a burst suppression pattern or severe depression of background activity that may progress to electrocerebral silence

### *Imaging studies*

- CNS imaging studies should be done to exclude space occupying lesions like tumour or abscess and to identify abnormalities that are indicative of HSV encephalitis.
- MRI is the imaging of choice in suspected cases of viral encephalitis, although CT scanning may be used where MRI facilities are not available.
- **CT brain –**
  - Changes takes 3-4 days to appear even in HSE; - i.e. CT normal early in the illness
  - In HSE, 2/3<sup>rd</sup> have CT abnormalities; characteristically shows reduced attenuation in one or both temporal lobes or areas of hyperintensity.
- **MRI brain**
  - MRI is sensitive even in the early stages of HSE although rarely it may be normal

- The typical MRI features in HSE are areas of focal oedema in the temporal lobes and orbital surface of the frontal lobes as well as the insular cortex and angular gyrus
- Some other types of encephalitis like JE are also associated with particular MRI abnormalities
- Midline shift may be present in cases with significant cerebral oedema
- T2 MRI alone shows many changes

Though these neuroimaging techniques demonstrate significant changes, they are too non-specific to be used for aetiological diagnosis

Abnormalities seen in patients with postinfectious encephalomyelitis include areas of demyelination (often symmetric) of spinal cord, white matter, and basal ganglia.

#### ***Lumbar puncture and CSF analysis***

- Provided cranial imaging has excluded any contraindications such as a space occupying lesion or severe cerebral oedema and brain shift, a CSF analysis by lumbar puncture should be carried out in all cases of suspected encephalitis.
- The CSF in viral encephalitis typically shows a lymphocytic pleocytosis, elevated protein content, and normal or mildly depressed glucose content. However, these parameters vary considerably, and some patients may have an entirely normal CSF examination early in their disease. Patients with certain viral disorders, can have a CSF profile that resembles that of bacterial disease.
- The total leukocyte count usually ranges from 10 to 1000 cells/mm<sup>3</sup>, but counts as high as 8000 cells/mm<sup>3</sup> can be observed. Some patients lack CSF pleocytosis early in their illness; approximately 5%-10% of patients with biopsy-proven HSV encephalitis have normal cell counts on the initial CSF examination
- Although the CSF usually shows a lymphocytosis, neutrophils frequently predominate in the early stages of viral encephalitis. Other leukocytes, including monocytes (histiocytes), plasmacytoid cells (activated B cells), and eosinophils, can be detected.
- The typical features of HSE are a lymphocyte cell of 10–200/mm<sup>3</sup> and an increased protein of 0.6–6 g/l

- In most cases of viral encephalitis, the protein content is normal or mildly elevated, usually less than 100mg/dL but occasionally greater than 500mg/dL.
- CSF glucose is usually normal and when low it is important to exclude tuberculous meningoencephalitis
- Xanthochromia of CSF may be present in HSE it is of no specific diagnostic value
- Virus-induced abnormalities of the CSF can persist for extended periods.
- CSF for polymerase chain reaction (PCR) is very useful and detects viral DNA or RNA in CSF. It has greater than 95% sensitivity and 100% specificity for HSE DNA within the 1<sup>st</sup> week of illness. False negatives are most likely in 1<sup>st</sup> 24-48 hrs and after 10-14 days.
- PCR remains positive up to 5 days after initiation of treatment in HSE.
- CSF should be cultured for bacteria, viruses, fungi, and mycobacteria.
- Oligoclonal bands are sometimes present in the CSF of patients with post-infectious encephalomyelitis.

#### ***Management of encephalitis***

- As mentioned in the guidelines on meningitis initial management consist of ensuring the adequacy of the Airway, Breathing, Circulation, etc.
- Initial resuscitation also include treatment of shock, correction of hypoglycaemia if present and control of seizures.
- After initial resuscitation management include general and specific measures.

#### ***General & supportive care***

- The general management is essentially supportive and in severe cases patients should be managed in a high dependency medical environment or an intensive care unit(ICU).

While in the ward/ICU, monitoring of a suspected encephalitis patient should include

- Glasgow Coma scale score.(GCS)
- Seizure type and frequency.
- Clinical signs of intracranial hypertension.
- Blood pressure (continuous/hourly):
- Urine output every four hours: maintained at 0.5 ml/kg/hour.
- Calculated serum osmolality: every 24 hours (preferably every 12 hours).

■ Se Osmolality mosm/kg= 2(Na+K in mEq) + Glucose (mmol/L)+ Urea (mmol/L)

- Continuous oxygen saturation monitoring, if not possible at least hourly monitoring.
- Central venous pressure(CVP) for severe coma.

#### ***Control of increased intracranial pressure (ICP)***

- The control of increased intracranial pressure(ICP) and cerebral oedema is essential. The most important aspect of managing intracranial hypertension is early identification and initiation of appropriate therapeutic measures. Most therapeutic measures fail if instituted late, as irreversible cerebral damage often occurs before these agents start their action.
- The control of ICP include
  - Avoidance of situations that increase ICP
  - Therapeutic measures to reduce ICP

#### ***Control of factors aggravating ICP***

*Positioning of head.*- Keep head in midline position with a tilt up at 15°–30°(x)

*Temperature control.* – Fever worsens ICP by increase cerebral metabolism. As physical measures like sponging cause shivering, which can aggravate intracranial hypertension, they should always be used in conjunction with antipyretics.

*Sedation-* Pain and arousal cause raised ICP by increasing cerebral blood flow. Sedatives are useful to prevent worsening of intracranial hypertension by this mechanism. Conventionally, sedatives were avoided, due to fear of “clouding the neurological examination”. This is not a justifiable reason to avoid proper control of intracranial pressure through sedation. Sedation can be with diazepam 0.1-0.3 mg/kg/dose or phenobarbitone 3–5 mg/kg/day in two divided doses (y)

*Seizure control.-* Seizures increase intracranial pressure by increasing cerebral metabolism and cerebral blood flow and by Valsalva. Hence anticonvulsants should be administered prophylactically or therapeutically. PHENYTOIN: Loading dose 15-20 mg/kg to be infused at a rate of 1.0 mg/kg/min. (x)

Maintenance dose - 5-8 mg/kg/d. If the seizures persist, then another loading dose of phenobarbitone 10-20mg/kg can be given. DIAZEPAM INFUSION: If the seizures still persists, then diazepam infusion to be started at a rate of not more than 5 mg/min followed by infusion at rate of 0.1-0.4 mg/kg/hr. Diluents to be used - sterile water, normal saline. If the seizures are yet to be controlled, then any of the following options can be tried.

**MIDAZOLAM INFUSION:** Loading dose of 0.05-0.2 mg/kg stat followed by infusion at a rate of 1-5 µg/kg/min

*Appropriate fluid and electrolyte therapy -* Hypovolaemia often accompanies viral encephalitis due to decreased intake and increased loss (vomiting, sweating). Hence any initial dehydration should be corrected first. Continued fluid therapy should be with N/2 saline 2/3<sup>rd</sup> to 3/4<sup>th</sup> of the maintenance with allowance for temperature, hyperventilation, and urine output. With increased temperature fluid requirement is increased and if the urine output is more than 50% of the total input, then add the excess fluid to the maintenance

### ***Therapeutic measures to reduce ICP***

*Hyperventilation-* Can be done with bag and mask ventilation or after intubation. To decrease further rise in ICP during intubation either 4% lignocaine as local spray /adequate sedation is needed. When hyperventilation is used for the management of raised ICP, then aim is to achieve a  $Paco_2$  of 25mmHg. Intracranial pressure begins to diminish 10–30 seconds after inception of hyperventilation, reaches a peak in 30 minutes, and returns to the original value in less than hour. The level of  $PCO_2$  should be raised to 30-35mmHg after 1hour. Prolonged hyperventilation may worsen the outcome.

Hence, hyperventilation should be gradually withdrawn (rapid withdrawal causes rebound intracranial hypertension) after a period of 30–60 minutes so as to raise PCO<sub>2</sub> with institution of other modes of therapy simultaneously.

*Mannitol*- Response to mannitol depends on original intracranial pressure, dose given over the previous three hours (the lesser, the better effect), and rate of administration. Rapid administration is more effective in reducing intracranial pressure, but the action has a much shorter duration. A slower infusion rate produces a lesser degree of decrease that lasts longer. With mannitol significant side effects can occur if used inappropriately. Chronic continuous therapy should be avoided as the brain adapts to the sustained hyperosmolality and produces rebound cerebral oedema after withdrawal of anticerebral oedema measures). Initial bolus to be given over 30 min, DOSE: 2.5- 5ml/kg of 20% solution (0.5-1 g/kg) Repeat mannitol to be given only if serum osmolality is  $\leq 300$  mOsm/kg (to calculate osmolality-see above) and could be given every 4-6 hourly, at a dose of 2.5ml/kg, given over 30 minutes.

*Furosemide (furosemide)* alone causes a slow reduction in intracranial pressure, but when combined with mannitol, the fall in intracranial pressure is rapid and is sustained for a considerably longer period than when either agent is used alone. Dose: 1mg/kg/dose every 12<sup>th</sup> hrly can be given (potassium levels & blood pressure to be monitored while giving diuretics.)

*Thiopentone*: To be used only when the above measures fail, but can be combined with hyperventilation. Dosage: loading dose of 5 mg/kg given over 30 - 60 min with a maintenance dose of 1 mg/kg/hr as infusion. Maximum maintenance dose is 5 mg/kg/hr. Whenever the maintenance dose is increased by 1 mg/kg/hr, a loading dose of 5 mg/kg to be given. Caution:hypotension

### ***Specific measures & treatment***

1. Until a bacterial cause of CNS inflammation is excluded, parenteral antibiotics should be given. Treatment with a third-generation cephalosporin, such as cefotaxime sodium + c. penicillin or ceftriaxone sodium is recommended.
2. *Antiviral therapy*- If antiviral therapy is not given to patients with HSE the mortality is over 70% and this can be brought down to 20% if treated early using I.V Acyclovir. If HSE is a possibility then acyclovir, 10 mg/kg I.V three times daily, should be started as soon as possible. When the diagnosis is confirmed by CSF PCR, (HSE PCR is available in the private sector at present) and/or where there are characteristic MRI changes, acyclovir should be continued for 14 days. Acyclovir should only be

stopped where there is a definite alternative diagnosis made. The situation of still suspected HSE in the presence of a negative CSF PCR and MRI acyclovir for 10 days is still justified. Acyclovir is a very safe and relatively non-toxic however during IV acyclovir therapy renal function should be closely monitored because of the rare development of renal impairment. The risk of renal toxicity is reduced by adequately hydrating the patient (eg, 1 mL fluid per day for each 1 mg/d of acyclovir) Because of its high pH, IV acyclovir may cause phlebitis and local inflammation if extravasation occurs

### ***Prognosis***

Supportive care and rehabilitation are important after the patient recovers. Because some sequelae of encephalitis may be subtle, neurodevelopmental and audiologic evaluations should be part of routine follow-up.

Most patients completely recover from viral encephalitis; however, prognosis depends on the cause and severity of the illness and the patient's age. If the clinical illness is severe and substantial parenchymal involvement is evident, prognosis is poor. Potential deficits include intellectual, motor, psychiatric, epileptic, visual, and auditory abnormalities. The prognosis of HSE is better in younger patients, and those having a disease duration of four days or less and a Glasgow coma score of 6 or less at the time of acyclovir initiation.

#### **Cerebral malaria**

- Detailed clinical guidelines on cerebral malaria is not included in this document. The presentation is varied and may suggest other conditions, such as meningitis, encephalitis, or epilepsy. Thus, cerebral malaria should be considered in the differential diagnosis of a febrile neurological illness if a history of residence or travel through a malarious area exists.
- Seizures and coma are common in a child with malaria, (sometimes without cerebral malaria) and prolonged postictal state should raise suspicion of this dangerous entity. Cerebral malaria can be rapidly fatal, prompt diagnosis and immediate treatment is important.
- Quinine is still the DOC for severe and complicated malaria though resistance could be a problem. 15-20 mg/kg IV diluted in IV infusion fluid to 1 mg/mL; infuse over at least 4 h; followed by 10 mg/kg/dose q8-12h if continuation beyond 48 h is needed; reduce dose to 5 mg/kg q8h; switch to PO therapy as soon as possible

### ***Tuberculous Meningitis(TBM)***

This document does not include clinical guidelines for the management of TBMTBM continues to be an important disease and should be considered in the differential diagnosis in any patient presenting with fever and a change in sensorium. Tuberculous meningitis may present in acute, subacute, or chronic form.

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