NATIONAL GUIDELINES FOR MANAGEMENT OF CENTRAL NERVOUS SYSTEM INFECTIONS IN CHILDREN

2023

SRI LANKA COLLEGE OF PAEDIATRICIANS

Patients are Safe within a Quality Service

Contributors

Sri Lanka College of Paediatricians

United Nations Children's Fund

Ministry of Health

Patients and Safe within a Quality Service

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Message from the President

Sri Lanka College of Paediatricians

The mission of the College is to facilitate the advancement of paediatric healthcare in the country, influence policy decisions, and support and sustain continuous professional development of child healthcare personnel while promoting collaboration among paediatricians.

In this context, our College had to step out of our main objective to develop guidelines for managing common paediatric conditions. In 2007, guidelines were developed in collaboration with the Ministry of Health. Since then, this would be the first update "Management of Central Nervous System Infections".

This endeavour attempts to improve and update the knowledge on managing CNS infections in childhood among all medical persons working with children and empower them to practice evidence-based management.

I want to thank all the members of the guideline committee who worked tirelessly to update this guideline, and I appreciate the effort made by all the authors to make this task a reality within a short time.

All relevant healthcare providers will use this book most effectively and provide a high standard in managing childhood CNS infections in Sri Lanka.

Professor Guwani Liyanage
President
Sri Lanka College of Paediatricians
2022/2023

Message from the
Director General of Health Services

As the Director General of Health Services in Sri Lanka, it is my honor to introduce this essential publication, “The National Guideline on the Management of CNS Infections in Children" that was developed by the Sri Lanka College of Paediatricians in collaboration with Ministry of Health. The development of this national guideline is a significant accomplishment that will undoubtedly revolutionize the management of central nervous system infections in children.

I extend my deepest gratitude to the authors, reviewers, editors, and the Directorate of Healthcare Quality and Safety and all the stakeholders in the Ministry of Health involved in the review process to publish this guideline as a national guideline. Your tireless efforts and commitment to excellence have resulted in a resource that will undoubtedly shape the future of paediatric healthcare and improve the lives of countless children.

Being an active professional body, the Sri Lanka College of Paediatricians has been liaising with the Ministry of Health in numerous activities. As the Director General of Health Services, I commend their commitment to excellence and contributions to the advancement of pediatric healthcare. May this guideline serve as a cornerstone for healthcare professionals, enabling them to provide the best possible care to children with CNS infections.

Dr Asela Gunawardana
The Director General of Health Services,
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Abbreviations

ABST - Antibiotics susceptibility test

ACT - Artemisinin based combination therapy

ADA - Adenosine deaminase

ADEM - Acute disseminated encephalomyelitis

ADH - Antidiuretic hormone

AFB - Acid-fast bacillus

AIDS - Acquired immunodeficiency syndrome

AIE - Autoimmune encephalitis

AIE- Autoimmune encephalitis

ARDS - Acute respiratory distress syndrome

ART - Anti-retroviral therapy

ASM- Antiseizure medications (ASM)

BDG - Beta D glucan

BW - Body weight

Ca - Calcium

CASPR - Contactin-associated protein like 2

CB NAAT - Cartridge-based nucleic acid amplification test

CDC - Centers for disease control and prevention

CM - Cerebral malaria

CMV - Cyto megalo virus

CNS - Central nervous system

CRP - Ç Reactive protein

CSF - Cerebro spinal fluid

CT - Computed tomography

DR - TB - Drug resistant tuberculosis

E. Coli - Escherichia coli

EBV - Epstein-Barr virus

EEG - Electroencephalogram

EIA - Enzyme immunoassay

ELIZA - Enzyme-linked immunoassay

EOD - Every other day

FBC - Full blood count

FDC - Fixed dose combination (Chapter 4 refer)

GA - Gestational age

GABA - Gamma-aminobutyric acid

GAD- 65- Glutamic acid decarboxylase

GCS - Glasgow coma scale

GM - Galactomannan

HHV 6 - Human herpes virus

HIV - Human immunodeficiency virus

HRP2 - Histidine-rich protein 2

HSV - Herpes simplex virus

ICP - Intra cranial pressure

ICU - Intensive care unit

IFN-γ - Interferon-gamma

IgM - Immunoglobulin M

IGRA - Interferon gamma release assay

IM - Intramuscular

IMCNS - Invasive mycoses of the central nervous system

IRIS - Immune reconstitution inflammatory syndrome

IV - Intravenous

IVI - Intravenous infusion

IVIG - Intravenous immune globulin

IVMP - Intravenous methylprednisolone

JE - Japanese encephalitis

K - Potassium

LGI1- Leucine-rich glioma inactivated 1

LP - Lumbar puncture

Mg - Magnesium

MIU - Milli-international units per litre

MMF- Mycophenolate mofetil (MMF)

MRI - Magnetic resonance imaging

MSF - Mediterranean spotted fever

NMDAR - Anti-N-Methyl-D-aspartate receptor

NMDAR- N-Methyl-D-Aspartic acid

NORSE - New-onset refractory status epilepticus

NSAIDs - Non-steroidal anti-inflammatory drugs

PCR - Polymerase chain reaction

Pf - Plasmodium falciparum

pLDH - Lactate dehydrogenase

PMN - polymorphonuclear leukocyte

PO - Per oral

PUO - Pyrexia of unknown origin

RBC - Red blood cells

RDT - Rapid diagnostic test

SGOT - Serum glutamic-oxaloacetic transaminase

SGPT - Serum glutamic-pyruvic transaminase

SIADH - Syndrome of inappropriate antidiuretic hormone secretion

SSPE - Subacute sclerosing panencephalitis

TB - Tuberculosis

TBM - Tuberculous meningitis

TE - Toxoplasma encephalitis

TST - Tuberculin skin tests

VAPP - Vaccine associated paralytic poliomyelitis

VGKC- Voltage gated potassium channel

VZV - Varicella zoster virus

1. MANAGEMENT OF CENTRAL NERVOUS SYSTEM INFECTIONS IN CHILDREN

1.1 Introduction to Guidelines

Central nervous system (CNS) infections include infections involving the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membrane. They probably are the commonest treatable cause of neurological morbidity in childhood and carry a high mortality in many instances. Hence this guideline is aimed at helping the clinician reduce the mortality and morbidity of CNS infections in children.

Clinical diagnosis of CNS infections is extremely difficult due to the wide spectrum of clinical characteristics which are of low sensitivity and specificity. Therefore, a high index of suspicion is a must to ensure that the diagnosis is not missed. The younger the child the more subtle are the clinical features making clinical diagnosis even more difficult.

A variety of organisms are implicated in CNS infections with bacterial and viral agents accounting for most cases. Rarely fungal and parasitic agents also present as CNS infections. The treatment urgency of bacterial meningitis and viral agents that are treatable with antivirals, often results in starting empirical antimicrobials on clinical suspicion. The nonspecific nature of the clinical diagnosis makes it essential to support the diagnosis with findings of investigations subsequently.

Age groups are considered as follows.

Neonates – Up to 28 days

Infants – 1 month to 1 year

Children – 1 year to 16 years

The success of treatment depends on;

Early diagnosis and treatment

CNS infections, especially meningitis is a medical emergency as treatment delay of few hours can make the difference between mortality, poor neurological outcome and complete recovery.

Aetiological diagnosis

Identification of specific microbiological agent is a crucial part of management.

Appropriate supportive and adjunctive interventions

This is a very important aspect of management that could greatly influence the outcome. This could even be more important than antibacterial drugs in certain situations.

Early recognition and management of complications

Delay of recognition of complications remains to be a pitfall in management of CNS infections, adding to mortality and morbidity.

Ensuring sufficient treatment and follow up will help to optimize outcome.

Prevention

This includes prevention of disease in individual contacts using a prophylactic antibacterial as well as public health measures to prevent and mitigate outbreaks including strategies such as notification and immunization.

1.2 Diagnosis of CNS infections

1.2.1 Clinical diagnosis

Common clinical features of CNS infections in children include;

Classical triad	*Other common features*	*In severe/complicated cases*
Fever	Headache	Focal neurological deficits
Meningism (in meningitis)	Vomiting	Features of raised ICP
Altered mental status or behavior	Seizures	Features of septic shock
		Rash of meningococcal infection

Features seen in neonates and infants would additionally include;

Hyper/hypothermia	Poor feeding	Bulging anterior fontanel
Irritability/excessive crying	Lethargy	

- All three features of the classical triad for meningitis are present only in a minority of patients. In cases where none of the three features are present, the diagnosis of CNS infection is unlikely. The exception is cerebral abscess where all three features could be absent.

- Fever may be absent even in patients with bacterial infections.
- Classical triad may be absent if the child was treated with antibiotics before the hospital admission.

1.2.2 Investigations

Full blood count, C reactive protein - can give supportive evidence for diagnosis.
Serum electrolytes, blood sugar - necessary for evaluation for complications.

Blood culture
Blood cultures should be collected before starting antibiotics.
The required volume of blood, depending on the method used for blood culture, should be collected. Low volumes lead to false negative results.
Do not refrigerate the samples.
Always use universal aseptic precautions.

Cerebrospinal fluid (CSF) investigations

- Cell count and differential count
- CSF protein
- CSF sugar (with concomitant blood sugar)
- Microscopy – Gram stain, Ziehl-Neelsen stain (Only if samples are available), wet preparation, dark ground microscopy, India ink preparation based on suspected pathogens
- Culture* – pyogenic culture (TB culture, fungal culture if indicated)
- CSF antigen test – bacterial (cryptococcal antigen if indicated)
- If CNS tuberculosis suspected – GeneXpert MTB/RIF ultra PCR assay
- Other tests as appropriate – e.g. antibody detection, PCR for meningococci and pneumococci, PCR and culture for viruses, tests for parasitic infections

*** All attempts should be made to perform lumbar puncture before commencing antibiotics.**

CSF culture should preferably be collected before starting antibiotics if there are no contraindications for lumbar puncture.

If the volume of CSF collected for culture is more than 1ml, centrifuged deposit of the sample can be Gram stained and cultured, increasing the yield. During specimen collection last sample should be sent for microbiological testing.

Absolute contraindications for lumbar puncture

Signs of raised ICP

- Depressed level of consciousness (GCS< 13)
- Papilledema
- Unequal, dilated or poorly reactive pupils
- Absent oculocephalic (doll's eye reflex)
- Irregular breathing
- Decorticate or decerebrate posturing
- Slow pulse and/or rising blood pressure

Coagulopathy – coagulation tests outside normal range or platelets < $100x10^9$/litre

Skin sepsis at lumbar puncture site or spinal epidural abscess

Relative contraindications

Focal neurological signs – e.g. **cranial nerve palsy, Hemiplegia**/ Focal seizures

Recent seizures (within 30 minutes)

Rash suggestive of meningococcal septicemia (spreading purpura)

Circulatory or respiratory insufficiency

Table 1.1: Cerebrospinal fluid findings in normal children and neonates

	Appearance	**Opening pressure**	**Cells** Cells/µL	**Glucose** mg/dL	**Protein** mg/dL
Child> 1 month	Clear	<28cm H_20	<5,>75% lymphocytes (less than 2 polymorphs)	>50 or 75% of serum glucose	20-45
Neonate	Clear/ xanthochromic		<30 or 20 cells (up to 5 polymorphs)	>50 or 75% of blood glucose	100-120

Table 1.2: Cerebrospinal fluid findings in children and neonates with central nervous system infection

	Opening pressure	**Cells** cells/μL	**Glucose** mg/dL	**Protein** mg/dL	**Other**
Bacterial	Elevated (>28 cm H_2O)	>100-10,000 >90% PMN; partially treated cases may have as low as 1 WBC/μL	Low (<40 - 50% of serum glucose)	Elevated (>50) 100-500	Organisms seen in Gram stain Culture may isolate the organism
Partially treated bacterial infection	Normal or elevated	Mononuclear cells may predominate	Normal or decreased	Normal or increa-sed	Organisms may be seen in Gram stain Cultures maybe sterile. PCR for bacterial antigens may be positive
Viral	Normal or mildly elevate	10-1000 Lymphocyte predominant but PMN early	>60% serum glucose (may be low in HSV and mumps)	Mildly Elevated 50-200	Many Arboviruses are detected by serology.
Tuber-culosis	Usually elevate	10-500 PMN very early but lymphocyte predominant through most of the course	Low < 50 Drops further if not treated	Highly elevated 100-3000	Acid fast bacilli are rarely seen in smear. PCR may detect gene-tic material. Testing large volumes will help increase detection.
Fungal	Usually elevate	50-500 PMN very early but mononuclear cells predominant	Low <50 Drops further if not treated	Elevated 25-500	Budding yeast cells may be seen in Gram stain. Capsular yeast cells can be seen in India ink stain. Organisms may be grown in culture. (Sensitivity can be

		through most of the course Cryptococcus infections may have no cells			increased by performing above tests using the deposit of the centrifuged specimen). In cryptococcal infection serum and CSF antigen may be positive
AIE	Normal or elevated	Usually <100 cells with dominant Lymphocytes	Normal	Normal or elevated	CSF antibodies such as anti NMDAR anti-body maybe positive

ADEM = Acute disseminated encephalomyelitis, AIE = autoimmune encephalitis, NMDAR = *N*-methyl-D-aspartate receptor, PCR = polymerase chain reaction, PMN = polymorphonuclear

From Nelson Textbook of Pediatrics 21st Edition

For neonates refer National Guidelines for Newborn Care Volume II, page 51

Imaging

- Imaging findings are not specific but is helpful for excluding contraindications for lumbar puncture and could be helpful in differentiation between various infections.
- Imaging may not be necessary in all patients with CNS infections.
- Normal CT or MRI scans do not exclude CNS infections.

Please remember all patients with fever and seizures may not have meningitis

1.3 Algorithm for initial management of children with clinical features of CNS infection

AIM to start antibiotics within 1 hour of suspecting meningitis.

Immediate actions

- Screen for critical complications: Airway and breathing, circulation, raised intra cranial pressure
- Collect a blood culture before starting antibiotics
- Send blood for FBC, CRP, electrolytes, glucose, urea
- Perform lumbar puncture whenever possible (if no contraindications)

LP contraindicated: see above *page no-17

Defer lumbar puncture

- **Start steroids and antibiotics**
- **Manage as for raised ICP**
- Discuss and arrange ICU admission and urgent neuroimaging

(Do not delay antibiotics/steroids for imaging or intensive care admission)

LP not contraindicated

Perform lumbar puncture

- Collect at least 30 drops of CSF
- Arrange urgent transport to microbiology and request urgent microscopy and antigen testing when available and culture
- Protein and glucose
- Other tests (viral, fungal, TB etc.) depend on the clinical picture
- **Start steroids and antibiotics**

- **Dexamethasone** 0.15 mg/kg every 6 hours for 4 days (maximum per dose 10mg) by intravenous injection.
  - Only if older than 3 months
  - Best started 15-20 minutes before or with the first dose of antibacterial
  - No evidence of benefit if started later than 12 hours after 1st IV antibiotic dose
  - Do not use when suspecting meningococcal septicemia or TB meningitis (until anti -TB treatment started)
- **Anti microbials**

➢ <u>For children older than 3 months</u>: **ceftriaxone** 100 mg/kg once daily (max. 4 g/day) intravenously
  - 3 months to 9 years – intravenous infusion
  - Above 9 years – may be given as intravenous injection
  - When no IV access available deep intramuscular injection maybe used (1 g per site).

(Alternative : cefotaxime 50 mg/kg /dose 6 hourly intravenously : max 2g)

➢ <u>Child less than 3 months</u>: **cefotaxime** (50 mg/kg/dose 12 to 6 hourly) intravenously and ampicillin (100mg/kg/dose 12 to 6 hourly) or penicillin (100 mg/kg/dose 12 to 8 hourly) intravenously. (Alternative treatment for term non-icteric neonates is ceftriaxone 50mg/kg/once daily) intravenously).

- Add **vancomycin** 15 mg/kg 6-8 hourly (max 500 mg) as intravenous infusion in those critically ill, with trauma, surgery, shunt, immune deficiency or suspected antibiotic resistance.
- Add acyclovir 500mg/m^2 8 hourly as slow intravenous infusion <u>only if there is objective evidence of HSV or varicella infection – mouth ulcers, varicella rash, seizures with rapid deterioration of consciousness or behaviour)</u>

Avoid hypotension: Maintain normal mean arterial pressure (use inotropes when needed) as this is essential to maintain cerebral perfusion.
Continue to monitor for features of raised ICP and circulatory or ventilatory insufficiency as these can manifest at any time during resuscitation and treatment.

Fluid management

- Carry out appropriate volume resuscitation but do not use excessive fluid.
- Do not restrict fluids unless SIADH present.
- Always use isotonic (0.9% saline/5% dextrose) solutions.
- Use osmotherapy if signs of raised ICP present.
    - Hypertonic saline (3-5ml/kg) bolus or infusion can be given and repeated if serum sodium is < than 160mEq/dl or serum osmolality is less than 340 mOsm/kg.
    - Or Mannitol 0.25 -1.5 g/kg (1 month – 11 years) or 0.25-2g/kg (2- 17 years) as intravenous infusions over 30-60 minutes, if no hypovolemia or oliguria (dose can be repeated 1-2 times, after 4-8 hours).

CT scan

- Indicated when GCS ≤8 or focal neurological signs present in the absence of an explanation
- Clinically stabilize the child before CT scanning
- Do not delay treatment to undertake a CT scan.
- CT scan cannot reliably detect raised intracranial pressure. This should be assessed clinically.

Avoid

- Hypovolemia
- Hypoglycemia
- Hyperthermia
- Hyponatraemia
- Seizures
- Acidosis
- Anemia
- Coagulopathy
- Abnormal electrolytes

1.4 Common complications/disabilities seen at presentation

The following should be actively looked for and aggressively treated as they are not uncommon to be seen at presentation and will add to the mortality and morbidity

- Raised ICP
- Hydrocephalus
- Seizures
- Electrolyte imbalance
- Circulatory collapse due to sepsis

1.5 Prevention

All meningoencephalitis patients should be notified on suspicion using H544 form. Please note that proper diagnosis card should be given for meningoencephalitis with aetiological agent if available as this acts as the source for epidemiological data collection.

Notification and contact tracing with chemoprophylaxis and immunization where appropriate should be attempted.

1.6 References

1. Kliegman R. Nelson Textbook of Pediatrics. Edition 21. Philadelphia, PA: Elsevier, 2020.
2. Waghdhare S, Kalantri A, Joshi R, Kalantri S. Accuracy of physical signs for detecting meningitis: a hospital-based diagnostic accuracy study. Clinical Neurology and Neurosurgery. 2010 Nov 1;112(9):752-7.
3. Amarilyo G, Alper A, Ben-Tov A, Grisaru-Soen G. Diagnostic accuracy of clinical symptoms and signs in children with meningitis. Pediatric Emergency Care. 2011 Mar 1;27(3):196-9.
4. Sigfrid L, Perfect C, Rojek A, Longuere KS, Lipworth S, Harriss E, Lee J, Salam A, Carson G, Goossens H, Horby P. A systematic review of clinical guidelines on the management of acute, community-acquired CNS infections. BMC Medicine. 2019 Dec;17:1-7.
5. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clinical Microbiology and Infection. 2016 May 1;22:S37-62.
6. Waterfield T, Maney JA, Fairley D, Lyttle MD, McKenna JP, Roland D, Corr M, McFetridge L, Mitchell H, Woolfall K, Lynn F. Validating clinical practice guidelines for the management of children with non-blanching rashes in the UK (PiC): a prospective, multicentre cohort study. The Lancet Infectious Diseases. 2021 Apr 1;21(4):569-77.
7. Barkovich AJ. Pediatric neuroimaging. Lippincott Williams & Wilkins; 2005.

2. MANAGEMENT OF BACTERIAL MENINGITIS IN CHILDREN

2.1 Clinical presentation

Clinical presentation of bacterial meningitis varies depending on the age, duration of illness, pre-treatment antibiotics, infecting organism and the patient's response to infection.

The presentations could be insidious (evolving over a few days), acute or fulminant (occurring over a few hours) *(Refer chapter 1 page 17 for clinical presentations)*

2.2 Bacterial meningitis in neonates

The diagnosis may be difficult in the very young as history and presentation can be non-specific.

A high index of suspicion for meningitis is required in sick, febrile or hypothermic newborns with or without the suggestive clinical features.

Note: Herpes simplex virus (HSV) infection, although uncommon, can mimic bacterial meningitis in newborns.

Table 2.1: Cerebrospinal fluid findings in the normal neonate

	Colour	**Leucocytes /mm3**	**Proteinm g/dL**	**Glucose mg/dL**
Normal neonate	Clear/xanthochromic	<30 or 20 cells up to 5 polymorphs normal	100-120	>50 or 75% of blood glucose

2.2.1 Common aetiological agents in neonatal meningitis

- Early onset (vertical)
  - Gram negative organisms – commonly *Escherichia coli* (*E. coli*)
  - Group B Streptococcus
  - *Listeria monocytogenes*

- Late onset (Nosocomial/community)
  Coliforms (*E. coli* and *Klebsiella*)
  Group B Streptococcus
  Staphylococcus aureus
  Pseudomonas aeruginosa
  Enterobacter species

2.2.2 Management of neonatal meningitis

- Initiate treatment as soon as bacterial meningitis is suspected.
- Blood culture should be obtained before antibacterials are administered.
- CSF studies could be deferred if the newborn is unwell.

Antibacterial therapy

In neonates with bacterial meningitis, antibiotics should be administered as soon as possible.

Blood culture should be obtained before antibacterials are administered.

All neonates on suspicion of bacterial meningitis	empirical antibiotic therapy with benzylpenicillin **or ampicillin together with cefotaxime** (Ceftriaxone is an alternative for term non icteric neonates)
If ***Listeria monocytogenes meningitis is suspected***	**ampicillin with or without gentamicin**
In immunocompromised neonates	empirical antibiotic therapy with **vancomycin together with meropenem**

Duration of antibiotic therapy in uncomplicated neonatal meningitis

Duration of therapy is determined by the pathogen responsible for meningitis and the patient's clinical course.

Group B streptococcal meningitis – intravenous penicillin 14 days and combined with gentamicin initially can stop gentamicin if repeat CSF is sterile

- Gram-negative bacilli – intravenous cefotaxime for at least 21 days.
- Listeria monocytogenes – intravenous ampicillin for 21 days in total, with or without gentamicin for the first 7 days.
- If no pathogen is isolated in blood or CSF cultures – intravenous antibiotic duration to be decided on clinical grounds and CSF findings.

Table 2.2: Antibiotic dosages for neonatal bacterial meningitis adjusted by age

Antibiotic	Route	Dose		
		Preterm	**Age 0-7 Days**	**Age >7 Days**
Penicillin G (Benzylpenicillin) 1 mega unit (MIU) = 600 mg	Slow intravenous injection/ intravenous infusion		50mg/kg 12 hourly	100mg/kg 8 hourly
Cefotaxime	IV, IM		50 mg/kg 12 hourly	50 mg/kg 8 hourly up to age 20 days 50mg/kg 6 hourly (age 21-28 days)
Gentamicin (Monitor drug levels if facilities available)	Slow intravenous injection/ intravenous infusion		5mg/kg 36 hourly	5mg/kg 24 hourly
Ampicillin	IV Infusion (for Listeria meningitis)		100mg/kg 12 hourly	100mg/kg 8 hourly (age 7-21 days) 100mg/kg 6 hourly (age 21-28 days)
Meropenem	IV infusion		40mg/kg 12 hourly	40mg/kg 8 hourly body weight up to 50kg (>50kg 2g 8 hourly)
Vancomycin (Monitor plasma levels if facilities available)	IV infusion	Up to 29 weeks corrected GA 15mg/kg 24 hourly 29-35 corrected GA 15mg/kg 12 hourly	15mg/kg 8 hourly	1month – 11 years 10-15mg/kg 6 hourly 12-17 years 15-20mg/kg 8-12 hourly

GA- Gestational age IV – Intravenous IM – Intramuscular

MIU – Million International Unit

Supportive therapy including timely investigations is as important as antibiotics and is similar to meningitis in older children

- Adequate cerebral perfusion in neonatal meningitis is of paramount importance. Therefore, maintaining hydration is an important step in the management.
- Fluids should not be restricted unless there is evidence of raised intracranial pressure and syndrome of inappropriate ADH secretion (SIADH).
- Neonates with meningitis are prone to develop hyponatremia because of the SIADH, these electrolyte changes also contribute to the development of seizures, especially during the first 72 hours of disease.
- Maintain normoglycemia. Both hypo and hyperglycemia could be harmful.
- Anti-seizure medication – seizures occur in neonatal meningitis mostly due to acute symptomatic aetiology, therefore it is adequate to treat for a minimum duration. i.e. 72 hours from last seizure.
  (Intravenous phenobarbitone is the usual first choice for treatment of neonatal seizures. There are suggestions from studies that overzealous usage would cause brain cell apoptosis hence prudent use is recommended.)
- Ultrasonography, computed tomography (CT) with contrast and magnetic resonance imaging (MRI) is not needed in all patients but may be indicated to delineate intracranial pathology in a complicated situation.

2.2.3 Acute complications of neonatal bacterial meningitis

- Cerebral oedema (vasogenic and cytotoxic)
- Increased intracranial pressure
- Ventriculitis/cerebritis
- Hydrocephalus
- Brain abscess
- Cerebral infarction
- Cerebral venous thrombosis
- Arterial stroke
- Subdural effusion or empyema

2.2.4 When to perform a repeat lumbar puncture in neonates

- Persistent or re-emergent fever
- Deterioration in clinical condition
- New clinical findings (especially neurological findings)
- Persistently abnormal inflammatory markers

2.2.5 Long term sequalae of neonatal meningitis

Severe neurological disability and milder motor and psychometric impairment may persist in neonatal meningitis. It has been shown that these neonates would benefit from early intervention programs with multi-disciplinary approach.

All newborns recovering from meningitis should undergo auditory evoked potential studies to screen for hearing impairment within 6-8 weeks of discharge.

2.3 Bacterial meningitis in infants and children

2.3.1 Introduction

Prompt administration of antibiotics to a patient with suspected bacterial meningitis is essential.

Initial antibiotic selection should provide coverage for the 3 most common pathogens:
Streptococcus pneumoniae
Neisseria meningitides
Haemophilus influenzae type b

Other organisms should be considered depends on the risk factors and clinical features.

2.3.2 Investigations

Blood culture should be collected prior to starting antibiotics
Perform early lumbar puncture as a primary investigation unless it is contraindicated.

Lumbar puncture (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.

If there are reasons to delay LP and bacterial meningitis is clinically suspected, antibiotics should be given without waiting for the LP after obtaining blood culture.

Antibiotics may sterilize 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 significantly decrease the diagnostic sensitivity of the CSF, 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.
- A normal CT brain does not exclude raised ICP and should not be the only factor to influence the decision to perform an LP.
- Although concerns about herniation of the brain following an LP exist, herniation is unlikely in children unless they have focal neurological findings or are comatose.
- Refer chapter 1 for contraindications for LP.

Interpretations of CSF findings

1. If there is difficulty in interpreting the CSF findings, a senior clinician, clinical microbiologist or infectious disease physician should be consulted.
2. No CSF test is fully reliable in distinguishing bacterial from non-bacterial meningitis
3. In most cases, clinical indicators of meningitis or sepsis will be present.
4. A repeat LP in 36–48 hours may be indicated when clinical indicators of meningitis are present but initial CSF examination is normal after consultation with paediatric neurologist.
5. Post-ictal CSF abnormalities (pleocytosis or raised protein) are rare and should not be readily accepted as a cause for an abnormal CSF.
6. Guide to distinguish 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.
   When red cell count is >10,000 cells/mm^3, the method will not be precise. Therefore, it is advisable in a traumatic tap to rely mostly on the Gram stain, bacterial antigen, culture/ABST and CSF sugar.

CSF antigens/PCR – Will be useful to confirm aetiology with a short turnaround time.

Gram stain

- This is the **best single test** for rapidly diagnosing bacterial meningitis and initiating appropriate therapy.
- The Gram stain may identify bacteria in 60–90 % of cases but in local setting yield is much lower.
- 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.

Gram stain results of common bacteria causing community-acquired bacterial meningitis.

CSF Gram Stain	Likely organism
Gram positive cocci in chains	Group B streptococcus
Gram positive diplococci	*Streptococcus pneumoniae*
Gram negative diplococci	*Neisseria meningitidis*
Gram negative cocco-bacilli	*Haemophilus influenzae*
Gram negative bacilli	Enterobacteriaceae e.g., *E coli*
Gram positive bacilli	*Listeria monocytogenes*

White cells in CSF

The presence of polymorphonuclear cells (PMN) is always abnormal and if present, may suggest bacterial meningitis. However, it may also occur in the early phase of viral meningitis, but lymphocytosis is more common. Therefore, if the other clinical and biochemical parameters are supportive of a viral meningitis, entertaining this diagnosis and re-affirmation with a senior paediatrician or paediatric neurologist is suggested.

e.g. West-Nile Virus the Cerebrospinal fluid (CSF) analysis may reveal elevated protein and increased leukocyte levels, with predominant neutrophils.

In partially treated bacterial meningitis, the relationship between PMNs and lymphocytes may be reversed.

CSF glucose

Blood glucose level obtained before the LP enables proper interpretation of the CSF glucose.

CSF glucose < 2.2 mmol/L is found in about 2/3rd of patients with bacterial meningitis. However, it may be lowered in TB meningitis, mumps meningitis and fungal meningitis.

CSF protein

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, although this is an unreliable calculation.

Table 2.3: Interpretation of CSF changes in meningitis

Condition	Leucocytes mm^3	Protein mg/dL	Glucose mg/dL	Remarks
Normal	<5>75% lymphocytes	20-45	>50 -75% of serum glucose	
Acute bacterial meningitis	10-10,000 or more. PMN predominate	100-500	Decreased <40-50% of serum glucose	Organisms may be seen in Gram stain. Culture may isolate the organism
Partially treated bacterial meningitis	5-10,000 Mononuclear cells may predominate if pretreated	Normal or increased	Normal or decreased	Organisms may be seen in Gram stain in a slide prepared within few hours. Pre-treatment may render cultures sterile. bacterial antigens may become positive
Viral meningitis or meningoencephalitis	Rarely >1000 cells PMNs seen early but mononuclear cells may predominate	50-200	Normal Maybe <40% of serum e.g. (15-20% in mumps)	

Suspect Tuberculous Meningitis (TBM) if CSF lymphocyte count is increased and if there is a history suggesting a risk of TBM.

2.3.3 Antibacterial therapy in infants and children with bacterial meningitis

Empirical therapy

For children > 3 months: ceftriaxone 100 mg/kg once daily (max. 4 g/day) intravenously (Alternative: cefotaxime 50 mg/kg per dose 6 hourly intravenously: max 2g).

When no IV access available deep intramuscular injection maybe used (1 g per site).

- Add **vancomycin** 15 mg/kg 6-8 hourly (max 500 mg) as intravenous infusion over 1 hour in those critically ill, with trauma, surgery, shunt, immune deficiency or suspected antibiotic resistance.

Vancomycin and cefotaxime/ceftriaxone combination provides adequate coverage for most penicillin-resistant pneumococci and beta-lactamase producing *Haemophillus influenzae* type b

Note

- **Patients with meningococcal or Hib disease should be given a chemoprophylactic agent such as rifampicin prior to discharge from hospital to ensure elimination of the organism if they were not treated with a third-generation cephalosporin.**
- In Hib, if the index case is below 2 years, a full course of Hib vaccination should be given as soon as possible after recovery, irrespective of previous vaccination.
- In suspected or diagnosed meningococcal meningitis – isolate the patient and adhere to droplet precautions to prevent transmission in the first 24 hours of antibiotic therapy.

Table 2.4: Dosages and dosing intervals for intravenous antimicrobials in infants and children with bacterial meningitis

Antibiotic	**Intravenous Dosage**	**Maximum Daily Dose**	**Dosing Interval**
Penicillin G (Benzylpenicillin)	400,000 MIU/kg/dose 1 MIU- 600 mg 50mg/kg /dose	24 MIU/14.4g	4-6 hourly
Cefotaxime	50 mg/kg/dose	12 g	6 hourly
Ceftriaxone	80- 100 mg/kg/dose or	4 g	once daily
	50 mg /kg/dose	4g	12 hourly
Ceftazidime	50 mg/kg/dose	6 g	8 hourly
Meropenem	40 mg/kg/dose	6 g	8 hourly
Vancomycin (monitor renal function / monitor serum levels when possible)	1 month – 11 years 10-15mg/kg per dose 12-17 years 15-20mg/kg per dose	2g/per dose	1 month – 11 years 6 hourly 12-17 years 8-12 hourly

Table 2.5: Duration of antimicrobial therapy in infants and older children

Organism	Choice of antibiotic	Duration
H. influenzae type b	cefotaxime/ceftriaxone	07-10 days
*S. pneumoniae**	cefotaxime/ceftriaxone	14 days
N. meningitidis	cefotaxime/ceftriaxone	05-07 days
Bacterial meningitis with no pathogen isolated	cefotaxime/ceftriaxone	10 days

* Should be guided by minimal inhibitory concentration (MIC) with the opinion of a microbiologist.

- If the response is not achieved within 72 hours or in case of rapid deterioration or reemergence of clinical features, recommend to consult paediatric neurologist and a microbiologist.

2.3.4 Acute/Ongoing management

1. Seizures in meningitis or encephalitis should be treated immediately.
2. Careful management of fluid and electrolyte balance is important in the treatment of meningitis. Over or under hydration are associated with adverse outcomes.
3. If patients have more than one of the signs of shock or hypovolemia (hypotension, poor peripheral perfusion, cold clammy extremities, and tachycardia with low volume pulses, high blood lactate or large base deficit) administer 20 mL per kg of 0.9% sodium chloride as a bolus and repeat if necessary.
4. Fluids used as normal maintenance should be iso-natraemic e.g. 0.9% sodium chloride with addition of glucose. Hyponatraemic/low osmolar solutions should **NOT** be used
5. Inotropes may be indicated if the patient shows persistent signs of hypoperfusion and should be managed in an intensive care setting.
6. Hyponatraemia occurs in about one-third of children with meningitis.
   Causes of hyponatraemia:
   - Increased ADH secretion (syndrome of inappropriate anti-diuretic hormone secretion)
   - Increased urine sodium losses (cerebral salt wasting)
   - Excessive electrolyte-free water intake or administration

Careful monitoring of sodium levels and vigilance regarding signs of over hydration are critical during treatment.

In all children with meningitis, regardless of the presence of intracranial hypertension, it is essential to ensure normal blood pressure and adequate circulation.

Monitor

- Vital signs – heart rate, blood pressure, Glasgow coma scale (GCS), Focal neurological signs, signs of raised ICP (Cushing's triad-bradycardia, high blood pressure respiratory insufficiency)
- Electrolytes, urea, creatinine, blood glucose and drug levels (if feasible)

Steroids should be given early.

To minimize delay in administration of antibiotics the first steroid dose should be given immediately prior to antibiotics.

Intravenous dexamethasone 0.15mg/kg 6 hourly as intravenous injection is given for 4 days.

2.3.5 Adjuvant therapy – Corticosteroids

- Early adjuvant corticosteroid therapy in children with acute bacterial meningitis has reduced the 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.

There is insufficient information about steroids in infants less than three months of age and in patients with severe sepsis or delayed or advanced meningitis.

2.3.6 Long-term management

- Offer children and infants following bacterial meningitis with a severe or profound deafness an urgent assessment for cochlear implants as soon as they are fit to undergo testing

- A Paediatric/Paedatric Neurology follow up should be continued after acute episode and the following complications need to be addressed.
  - Psychosocial problems
  - Neurological and developmental problems
  - Behavioral changes
  - Learning disability
  - Orthopedic complications (damage to bones and joints)
  - Skin complications (including scarring from necrosis)

} Meningococcal septicemia

2.4 Prevention

2.4.1 Notification

All meningoencephalitis patients should be notified on suspicion using H544 form. Please note that diagnosis card should be given as meningoencephalitis with aetiological agent if available as this acts as the source for epidemiological data.

2.4.2 Immunization

Routine childhood immunizations have been shown to effectively decrease the incidence of certain types of meningitis.

Vaccines are available for pneumococcal, meningococcal*, Haemophilus influenzae b.*

2.4.3 Post exposure prophylaxis

Chemoprophylaxis has been shown to reduce mortality and morbidity in bacterial meningitis

Table 2.6: Chemoprophylaxis for bacterial meningitis

Causative Organism	Drug Name	Age of Contact	Dosage
Haemophilus influenzae	Rifampicin*	>12 years and adults	600 mg orally once daily for 4 days
		3 months-12 years	20 mg/kg orally once daily for 4 days; not to exceed 600 mg/dose
		1-3 months	10 mg/kg orally once daily for 4 days
	Ceftriaxone [when Rifampicin contraindicated]	< 12 years	50 mg/Kg (max 1g) IM once daily for 2 days
		> 12 years	1g IM once daily for 2 days
Neisseria meningitides	Rifampicin*contra indicated if allergy to Rifampin or other Rifamycins	>12 years	600 mg orally 12 hourly for 2 days
		1-12 years	10 mg/kg orally 12 hourly for 2 days; not to exceed 600 mg/dose
		< 1 year	5 mg/kg orally 12 hourly for 2 days
	Ceftriaxone	>12 years	250 mg Intramuscular single dose
		1-12 years	125 mg Intramuscular single dose
	Ciprofloxacin (Unlicensed indication when there is no alternative)	12-18 years	500 mg orally single dose
		5-11 years	250mg orally single dose
		Full term neonates to 4 years	30mg/kg orally single dose (maximum 125mg)

Haemophilus influenzae type b

The risk of invasive Hib disease is increased among unimmunized household contacts younger than 4 years.

Recommendations for rifampicin chemoprophylaxis for contacts of index cases of invasive Hib disease include the following:

- All household contacts with at least one contact younger than 4 years who is unimmunized or partially immunized; those with a child younger than 12 months who has not received the primary series; and those with an immunocompromised child (even if older than 4 years), regardless of immunization status.
- Nursery and childcare center contacts regardless of age, when 2 or more cases of invasive disease have occurred within 60 days.
- The index case if younger than 2 years or with a susceptible household contact and treated with ampicillin or chloramphenicol.

Neisseria meningitides

Candidates for chemoprophylaxis against meningococcal disease include the following:

- All household contacts
- Childcare or nursery school contacts during the 7 days before illness onset
- Contacts directly exposed to index case secretions through kissing, sharing toothbrushes or eating utensils, or other markers of close social contact during the 7 days before illness onset
- Persons who had mouth-to-mouth resuscitation or unprotected contact during endotracheal intubation in the 7 days before illness onset
- Contacts who frequently slept or ate in the same dwelling as the index patient during the 7 days before illness onset
- Passenger seated directly next to an index patient on a prolonged travel lasting >8 hours

Streptococcus pneumoniae

Routine chemo prophylactic measures for invasive disease secondary to *S. pneumoniae* are limited to people with specific medical conditions.

2.4 References

1. Kliegman R. Nelson Textbook of Pediatrics. Edition 21. Philadelphia, PA: Elsevier, 2020.
2. Stevens JP, Eames M, Kent A, Halket S, Holt D, Harvey D. Long term outcome of neonatal meningitis. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2003 May 1; 88(3): F179-84.
3. Coetzee M, Mbowane NT, De Witt TW. Neonatal sepsis: Highlighting the principles of diagnosis and management. South African Journal of Child Health. 2017 Jul 12; 11(2): 99-103.
4. https://www.rch.org.au/clinicalguide/guideline_index/Meningitis_Guideline
5. BNF children (bnfc) 2018-2019
6. Nelson JD, American Academy of Pediatrics. 2023 Nelson's Pediatric Antimicrobial Therapy.

3. MANAGEMENT OF SUSPECTED ACUTE VIRAL ENCEPHALITIS IN CHILDREN

3.1 Introduction

Acute encephalitis syndrome is a medical and neurological emergency, requiring immediate consideration of key issues including immediate life support, identification of cause, and when available, and institution of specific therapy. Residual neurological morbidity remains at a significant level following viral encephalitis.

These guidelines are formulated to help in the management of commonly encountered viral encephalitis and do not cover viral encephalitis in the neonatal period and in immunocompromised children, rabies encephalitis, and chronic viral encephalitis such as sub-acute sclerosing panencephalitis (SSPE).

The aetiological agents are varied, and paediatricians treating such children could face difficulties as diagnostic testing may not be available for some of the agents at times.

3.2 Aetiological agents of clinically important viral encephalitis in Sri Lanka

- Japanese encephalitis virus (JE)
    - May be epidemic or sporadic
    - High case fatality rate (20-30%) and frequent residual neuropsychiatric damage (50-70%)
- Herpes simplex virus 1 (HSV-1)
    - The most common cause of sporadic fatal viral encephalitis, in western countries
    - Scant epidemiological data available makes this an apparently uncommon agent in Sri Lanka.
    - In untreated patients, mortality is high (70%), which is decreased to 15-20% in treated patients (risk of sequelae of around 11%).
- Varicella zoster virus (VZV) – Usually present with classical rash but may present without the typical rash
- Enteroviruses
- Dengue virus – Incidence is reasonably high in Sri Lanka

- Measles virus
- Mumps virus
- Chikungunya
- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- Human immunodeficiency virus (HIV)
- Human herpes virus 6 (HHV-6)
- Influenza
- Vaccine associated paralytic poliomyelitis (VAPP)
- Rabies
- Emerging other viral agents – Human parvovirus, West Nile virus, Zika virus, Nipah virus

3.3 Clinical features

Clinical features will overlap with those of other CNS infections. The **suspicion of viral aetiology is high when there are seizures and rapid deterioration in behaviour /cognition / personality or consciousness**.

Other features that may increase the suspicion of a viral aetiology.

- Prodromal symptoms – flu-like illness, diarrhoea
  - Rash, vesicles, past history of chicken pox
  - Any epidemic of acute encephalitis in neighborhood e.g. Japanese Encephalitis
  - History of animal contact, insect bite, dog bite
- Clinical pointers to specific viral aetiologies,
  - Skin rashes – dengue, measles, varicella, coxsackie, enterovirus, HSV (herpes labialis)
  - Parotid swelling and orchitis – mumps
  - Fronto-temporal lobe dysfunctions (personality changes, confusion and disorientation) – HSV
  - Brainstem dysfunction – enterovirus, mumps, and rabies
  - Dystonia or extrapyramidal movements – Japanese Encephalitis, Dengue encephalitis
  - Myocarditis – entero virus, coxsackie

3.4 Diagnosis

3.4.1 Biological materials

Usual CSF findings in viral encephalitis include lymphocytic pleocytosis, mild to moderately elevated proteins, and normal CSF sugar. The CSF can be tested for viral genome (PCR), antigens, antibodies against the virus and complete virus (viral culture).

Other biological materials that can be tested include blood, urine, stool, airway secretions, wound secretions and brain tissue.

Guidelines for collection, storage and transport of samples

Available tests and the sample collection regarding viral encephalitis is given in the MRI web site. Department of virology, sample send out guidelines

Please visit *https://www.mri.gov.lk*

Blood

- Collect within 4 days after the onset of illness for isolation of virus and genome and antigen detection and at least 5 days after the onset of illness for detection of IgM antibodies.
- A second, convalescent sample should be collected at least 10-14 days after the first sample for serology.
- Take clotted blood sample. Separate serum after clot retraction.
- Serum should be transported as soon as possible and should be transported in a cold box with **ice packs within 48 hours**. It can be stored at for a maximum period of **7 days at +2°C to +8°C.**
- **If delay is anticipated (more than 72 hours), sera must be frozen at -20°C and transported to the laboratory on frozen ice packs**.
- Repeated freezing and thawing can have detrimental effects on the stability of IgM antibodies.

Cerebrospinal fluid

- Send for cell count, virology-PCR (low sensitivity if CSF tested late), culture and serology, bacteriology and biochemistry
- CSF should be sent as soon as possible because sensitivity decreases if CSF tested late.
- May be stored **at +2°C to +8°C** in case of delays of less than 72 hours in processing for virus culture or viral PCR
- If greater delays are likely (more than 72 hours), CSF should be frozen at -20°C.

Swabs (naso-pharyngeal, throat, vesicle)

Dacron/ Nylon swabs with plastic shaft should be used and put into virus transport medium (VTM). Swabs may be utilized for range of virus cultures and PCR.

Urine

10-20 mL of urine should be collected into sterile containers without preservatives. Store at -+4°C for less than 48hrs.

Stool

Stool should be collected for enterovirus culture into clean containers; store at +4°C for less than 48hrs.

Brain biopsy

Brain specimens should be collected unfixed into a sterile container with VTM or normal saline for PCR. Brain smears can also be used for viral antigen detection by immunofluorescent antibody staining, and for electron microscopy with negative staining.

3.4.2 Neuroimaging

CT scan which is often the only available modality in an emergency situation may give valuable information such as presence of bleed, cerebral edema, temporal lobe hypo-densities in herpes simplex encephalitis and thalamic abnormalities in JE.

When MRI is available it could give additional valuable information including aetiological pointers such as,

- Herpes simplex encephalitis: Abnormal signal intensity in medial temporal lobe, cingulate gyrus, and orbital surface of frontal lobes.
- Japanese B encephalitis: Abnormal signal intensity in thalami (87-94%), substantia nigra, and basal ganglia.

MRI will also be useful to exclude other causes of fever and rapid clinical decline such as ADEM and AIE.

3.4.3 EEG

Usually shows non-specific slowing in viral encephalitis. The presence of periodic lateralized epileptiform discharges (PLEDs) is characteristic but not diagnostic of herpes simplex encephalitis, but their absence does not rule out the diagnosis.

3.5 Management

3.5.1: Rapid assessment and stabilization – please refer to page 34

3.5.2: Antiviral treatment

Aciclovir can be started if sporadic viral encephalitis is suspected. Decision for continuation would depend on clinical evolution microbiological and serological findings as well as EEG and imaging data. As sample collection/transport can affect accuracy of test results negative testing alone will not completely rule out viral aetiology.

For HSV: Aciclovir

<3 months: 20 mg /kg every 8 hourly as intravenous infusion for 21 days

3 months - 12 years: 500mg/m^2 8 hourly as intravenous infusion for 21 days (Maximum dose – 750mg per dose usually)

>12 years: 10mg/kg 8 hourly as intravenous infusion for 21 days (Maximum dose – 750mg per dose usually)

Confirmed HSV encephalitis in neonates – Refer to paediatric neurologist for further management as chronic suppressive therapy with antivirals are usually indicated.

For VZV : Aciclovir

<3 months: 10-20 mg/kg every 8 hourly as intravenous infusion for 10-14 days

3 months – 12 years: 500mg/m^2 8 hourly as intravenous infusion for 10-14 days

>12 years: 10mg/kg 8 hourly as intravenous infusion for 10 -14 days (Maximum dose – 750mg per dose usually)

- Treatment continues longer if immunocompromised or in severe infection.
- When IV acyclovir high doses used, good hydration is mandatory to avoid nephrotoxicity
- Acyclovir should be given as a slow infusion using the largest available venous access

Following maybe considered with expert advice (microbiologist, virologist, paediatric neurologist etc.) Plan the dosing schedule with the consultation of the relevant expert and recent reliable paediatric formulary

- Ganciclovir plus foscarnet : CMV, HHV 6 in immune compromised children
- Oseltamivir : Influenza virus
- Ribavarin : Measles virus, Nipah virus
- Highly active antiretroviral therapy (HAART): HIV
- Valacyclovir/acyclovir/ganciclovir-B virus transmitted by monkey bites

Rabies virus – Rabies immunization Protocol for anti rabies post exposure therapy (PET 2019) for mainstay of management General circular number – 01-50/2019

3.5.3 Supportive Care: For symptomatic management – please refer page 23

***Corticosteroids*:**

The role of corticosteroids in the treatment of viral encephalitis is not established.

Corticosteroids may be considered along with acyclovir in patients with marked cerebral oedema, brain shift or raised intracranial pressure or possibility of ADEM or autoimmune encephalitis. (Methylprednisolone intravenously 30 mg /kg daily for 3-5 days).

However, it is preferable to consult with a paediatric neurologist before commencement of steroids.

Anti seizure medications

Anti-seizure medications should be used for acute seizure cessation. There is no benefit in long term treatment unless in specific contexts. This should be done in consultation with a paediatric neurologist.

Treatment of cerebral oedema – Please refer chapter 1 page 23

3.5.4 Treatment of complications and rehabilitation

Symptomatic management does not differ from other CNS infections.

3.6 Preventive strategies

- Notification – All meningoencephalitis patients should be notified on suspicion using H544 form. Please be note that proper diagnosis card should be given for meningoencephalitis with aetiological agent if available as this acts as the source for epidemiological data collection.
- Outbreak management strategies.
- Immunization for JE, VZV (please refer to national immunization guidelines. (http://www.epid.gov.lk/web/images/stories/Immunization_Guide_2012.pdf)

3.7 References

1. Sharma S, Mishra D, Aneja S, Kumar R, Jain A, Vashishtha VM, Expert Group on Encephalitis, Indian Academy of Pediatrics. Consensus guidelines on evaluation and management of suspected acute viral encephalitis in children in India. Indian Pediatrics. 2012 Nov;49:897-910
2. Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, Klapper PE, Vincent A, Lim M, Carrol E, Solomon T. Management of suspected viral encephalitis in children–Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. Journal of Infection. 2012 May 1;64(5):449-77
3. World Health Organization. Acute Encephalitis Syndrome. Japanese encephalitis surveillance standards. January 2006. From WHO-recommended standards for surveillance of selected vaccine-preventable diseases. WHO/V&B/03.01 [cited 2016 Oct 14]. http://apps. who. int/iris/bitstream/10665/68334/1/WHO_V-B_03. 01_ eng. pdf; 2009
4. Karmarkar SA, Aneja S, Khare S, Saini A, Seth A, Chauhan BK. A study of acute febrile encephalopathy with special reference to viral etiology. The Indian Journal of Pediatrics. 2008 Aug;75:801-5
5. Kumar R, Tripathi S, Tambe JJ, Arora V, Srivastava A, Nag VL. Dengue encephalopathy in children in Northern India: clinical features and comparison with non dengue. Journal of the Neurological Sciences. 2008 Jun 15;269(1-2):41-8.
6. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. The Lancet Infectious Diseases. 2010 Dec 1;10(12):835-44.
7. Tyler KL. Emerging viral infections of the central nervous system: part 2. Archives of Neurology. 2009 Sep 1;66(9):1065-74.
8. Glaser CA, Honarmand S, Anderson LJ, Schnurr DP, Forghani B, Cossen CK, Schuster FL, Christie LJ, Tureen JH. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clinical Infectious Diseases. 2006 Dec 15;43(12): 1565-77
9. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. Current opinion in Neurology. 2010 Jun 1; 23(3):305-11.

10. Johnstone JA, Ross CA, Dunn M. Meningitis and encephalitis associated with mumps infection. A 10-year survey. Arch Dis Child. 1972 Aug;47(254):647-51.
11. Sankhyan N, Vykunta Raju KN, Sharma S, Gulati S. Management of raised intracranial pressure. The Indian Journal of Pediatrics. 2010 Dec;77:1409-16.
12. Suarez JI. Hypertonic saline for cerebral edema and elevated intracranial pressure. Cleveland Clinic Journal of Medicine. 2004 Jan 1;71:S9-13.
13. Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, Morishima T, Hirayanagi K. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. Journal of Neurology, Neurosurgery and Psychiatry. 2005 Nov 1;76(11):1544-9.
14. Hoke Jr CH, Vaughn DW, Nisalak A, Intralawan P, Poolsuppasit S, Jongsawas V, Titsyakorn U, Johnson RT. Effect of high-dose dexamethasone on the outcome of acute encephalitis due to Japanese encephalitis virus. Journal of Infectious Diseases. 1992 Apr 1;165(4):631-7.
15. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PE. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. European Journal of Neurology. 2010 Aug;17(8):999-e57.
16. Malavige GN, Lohitharajah J, Arambepola C, Wanigasinghe J, Gamage R, Gunaratne P, Ratnayake P, Chang T. Viral aetiologies of acute encephalitis in a hospital-based South Asian population.
17. Lohitharajah J, Malavige GN, Chua AJ, Ng ML, Arambepola C, Chang T. Emergence of human west nile virus infection in Sri Lanka. BMC Infectious Diseases. 2015 Dec;15(1):1-6.
18. Lohitharajah J, Malavige GN, Arembepola C, Wanigasinghe J, Gamage R, Gunaratne P, Ratnayake P, Chang T. Viral aetiologies of acute encephalitis in a hospital-based population in Sri Lanka. International Journal of Infectious Diseases. 2016 Apr 1;45:444.
19. Jouan Y, Grammatico-Guillon L, Espitalier F, Cazals X, François P, Guillon A. Long-term outcome of severe herpes simplex encephalitis: a population-based observational study. Critical Care. 2015 Dec;19:1-9.
20. BNF-C updated June 2020.

4. MANAGEMENT OF TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN

4.1 Introduction

Early diagnosis of Tuberculosis of CNS is important because of its significant morbidity and mortality if not treated early.

Forms of central nervous system infection due to *Mycobacterium tuberculosis* include meningitis, a diffused form of tuberculosis accounting for majority of CNS-TB, tuberculoma and spinal arachnoiditis.

Infection with *M. tuberculosis* is caused by close contact of the child with a bacteriologically positive TB patient, usually an adult from the same household. Risk factors for tuberculous meningitis (TBM) include age <5 years, severe acute malnutrition, primary immune deficiencies and HIV infection.

4.2 Clinical presentation

Tuberculous meningitis

Children with TBM may present as pyrexia of unknown origin (PUO) which often begins with a prodrome of constitutional symptoms such as lassitude, malaise, night sweats, and intermittent headache, to be followed by vague CNS symptoms such as behavioural changes, irritability, drowsiness, headache, vomiting and seizures.

Suspected pyogenic meningitis with subacute onset and/or with features of raised intracranial pressure not responding to antibiotic treatment, should prompt one to think of TBM.

Physical examination may reveal a global encephalopathy with or without focal deficits including cranial nerve palsies and motor deficits, hydrocephalus, and movement disorders.

Features that may help distinguish TB meningitis from bacterial meningitis include subacute presentation and presence of neurologic signs especially cranial nerve palsies most frequently involving cranial nerves II and VI.

An active search for extra neural tuberculosis will facilitate early diagnosis.

Tuberculoma

Tuberculoma may occur with or without evidence of TB meningitis. It is often seen in older children.

Patients may present with focal seizures if the lesions are in a supra-tentorial cortical location.

In posterior fossa lesions, there may be symptoms and signs of raised intracranial pressure, with multiple localizing signs and hydrocephalus.

Tuberculous spinal arachnoiditis

The signs and symptoms related to spinal cord and roots range from upper motor to lower motor or mixed pattern of involvement. Common findings are weakness, pain, and paraesthesia often in the lower limbs. Urinary complaints and constipation maybe seen. Neurological examination may yield changes in reflexes, changes, sensory function, and decreased power.

4.3 Complications of TB meningitis

Complications are common in CNS TB if there is a delay in presentation and/or starting treatment. Therefore, it is important to be aware of complications as they may even see at presentation.

- Hydrocephalus – presenting often with symptoms and signs of raised intracranial pressure (ICP).
- Infarctions – often presenting with focal neurological deficit consistent with a stroke syndrome.
- Optico-chiasmatic arachnoiditis – presenting with sudden visual loss, during treatment or on withdrawal of corticosteroids.
- Seizures – seizures can be multifactorial and related to factors such as cerebritis, encephalopathy, tuberculoma or infarction.
- Cranial neuritis – extensive exudative arachnoiditis encases the multiple traversing cranial nerves, most commonly the abducens, optic, oculomotor and trochlear and cause nerve palsy.
- Tuberculoma – nonspecific presentations are seen more commonly than with TBM. May present with focal neurological deficits at times with features of raise intra cranial pressure.
- Transverse myelitis – will cause motor, reflex, sensory and sphincter involvement.
- Hyponatremia – may present with seizures or drowsiness.

4.4 Diagnosis

The diagnosis should be based on:

- A detailed history (including a contact history of TB and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Investigations

    a) Confirmatory findings

    b) Supportive findings

Confirmatory findings

- CSF
- Cartridge based nucleic acid amplification test CB-NAAT /Xpert (MTB/RIF) ultra assay

  As this is a microbiological confirmatory test send at least 1-2 ml of CSF whenever possible.
- TB culture – Liquid culture is preferred when available as relatively a quick result can be obtained. Samples should be sent to the laboratory under cold condition (2-8˚C) as soon as possible (may be stored at 2-8˚C up to 5 days). It will need at least 1 ml of CSF.

  A larger volume of CSF delivered to a laboratory quickly and analyzed without delay can help to improve the sensitivity.
- Smear for Acid Fast Bacilli – Less sensitive than GeneXpert (send as the last investigation if the collected CSF volume is low)

Supportive findings

- A detailed history (including a contact history of TB and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Investigations
  - Tuberculin skin testing (TST) – Mantoux test/ Interferon gamma release assay. (IGRA)
  - Chest X-ray and other relevant radiological investigations.
  - CSF Lymphocytic pleocytosis high protein and low sugar.
  - CSF Adenosine Deaminase (ADA) measurement-will only give supportive evidence. Send as a last sample if CSF sample is available.

- Investigations for extra-neural involvement.
- HIV testing. In patients with HIV infections, CSF testing should also include cryptococcal antigen testing.
- A trial of treatment with anti-TB medications is not recommended as a method of diagnosing TB in children.

4.4.1 Cerebrospinal fluid (CSF)

Table 4.1: CSF investigations with their usefulness in diagnosing CNS TB

Test Perform in CSF	Confirms tuberculous meningitis	Strengths	Limitations	Sensitivity for tuberculous meningitis diagnosis
Culture for Mycobacterium tuberculosis	Yes	A confirmatory test. Provides drug susceptibility status in positive samples	Takes a long time to obtain a result (a negative test is reported after 6 weeks). Liquid cultures provide relatively early results (may be in 10 days) and more sensitive than conventional solid cultures.	Approximately 40-70%
Ziehl-Neelsen smear microscopy	Yes	Quick Performed in approximately 30min; widely available; little equipment required	Requires laboratory experience to conduct and interpret	Approximately 10–50% (Sensitivity will depend on CSF volume and the technique)
GeneXpert MTB/RIF	Yes	Quick Performed within 2h; offers information on rifampicin resistance in positive samples	Cannot exclude tuberculous meningitis when negative	Approximately 20–60%
GeneXpert MTB/RIF Ultra	Yes	Higher sensitivity than GeneXpert MTB/RIF	Cannot exclude tuberculous meningitis when negative	44–77%

Loop-mediated isothermal amplification	Yes	Quick Performed in <1h; can be read by the naked eye	Cannot identify rifampicin resistance Not widely available in Sri Lanka	76%
Lipoarabinomannan	Yes	CSF or (urine) testing is possible	Not widely available in Sri Lanka	22–33%
Interferon-γ release assay	No		Cannot confirm tuberculous meningitis Can be falsely negative in active disease Can be indeterminate in immunosuppressed. Not confirmatory	
Adenosine deaminase	No		Adenosine deaminase cut-off values uncertain. Not confirmatory	

- The diagnosis of CNS TB can be difficult. Sensitivity of all confirmatory tests are low in children in comparison to adults due to the paucibacillary nature of the disease.
- Furthermore, the CSF findings described above can also be mimicked by partially treated pyogenic meningitis.
- In such a situation, reassessing after 48-72 hours of treatment with a new combination of intravenous antibiotics to evaluate improvement in clinical status as well as in CSF can be useful.
- CSF abnormalities in TBM may take a variable time, even up to a few months, to return to normal.

4.4.2 Tuberculin Skin Test (TST) / Mantoux test

TST is a surrogate markers of *M. tuberculosis* infection and indicates a cellular immune response to recent or remote sensitization with *M. tuberculosis*. TST cannot distinguish TB infection from active TB disease.

Therefore, results of TST should be interpreted in the context of the clinical picture and results of other investigations. A positive tuberculin test is only supportive evidence in favour of a diagnosis of active tuberculosis. It may be nonreactive in 50% of cases of CNS TB. Hence,

it is helpful in supporting the diagnosis of TBM when positive, but a negative test would not exclude TB.

Interpretation of Tuberculin Skin Test

In HIV-negative individuals,

- 0-9 mm : Negative
- 10-14 mm : Positive
- 15 mm or more : Strongly positive

- In immunosuppressed children (HIV positive, severely malnourished etc.) a Mantoux test of 5 mm or more is considered as positive.
- In all the children, irrespective of whether they have received the BCG vaccination or not, a greater than 10mm induration is regarded as positive.

Measurement of IFN-γ released by lymphocytes (IGRA-Interferon Gamma Release Assay)
It is a specific (70%–90%) test but with a low sensitivity (50%–70%) for the diagnosis of latent TB. In younger children especially below 5 years of age the sensitivity of this test is further low. Currently, the use of this test is restricted due to the high cost and poor sensitivity.

4.4.3 Neuroimaging

Neuroimaging is an important diagnostic modality in CNS-TB. It may reveal one or more of the following findings:

- Basal meningeal enhancement
- Hydrocephalus with or without peri-ventricular ooze
- Tuberculoma(s)
- Infarcts in multiple foci, especially in the basal ganglia.

Magnetic Resonance Imaging is the test of choice for visualizing abnormalities of TBM and is superior to CT when evaluating for TB in the brainstem and spine.
Normal neuroimaging does not rule out TBM and in case of strong clinical suspicion of diagnosis, a repeat follow-up scan after a few days may show newly developing lesions.

4.4.4 Evidence of tuberculosis elsewhere

Evidence of tuberculosis in sites other than CNS favours the diagnosis of TB as the causative organism in a child with meningitis.

This includes

- Radiological evidence suggestive of TB
    - Chest radiograph features of active TB, miliary TB.
    - Computed tomography (CT)/magnetic resonance imaging (MRI)/ultrasound evidence for TB outside the central nervous system.
- Microbiological evidence suggestive of TB in other sites.

The following samples should be collected from a patient, who has signs and symptoms of tuberculosis in other sites other than TB meningitis and sent for microscopy (Ziehl-Neelsen), TB culture and Xpert MTB/RIF ultra-assay.

1. Sputum or gastric aspirate if pulmonary TB is suspected
2. Pleural fluid or pleural biopsy if patient is having pleural effusion
3. Lymph node aspirate or biopsy for enlarged lymph nodes
4. Peritoneal fluid – if TB peritonitis is suspected
5. Blood culture – in case of miliary tuberculosis
6. Joint aspirate/synovial biopsy – if septic arthritis suspected
7. Urine
8. Pericardial fluid – if pericardial TB suspected
9. Pus or tissue from any other site suspected of having tuberculosis

4. 5 Management of TB meningitis

- Children with TB meningitis should be hospitalized initially until their clinical state has stabilized.
- Since therapy can be lifesaving, it is important to commence therapy without a delay if TB meningitis is strongly suspected with the available clinical, laboratory and imaging findings.

4.5.1 Anti–TB drugs

All children diagnosed with drug susceptible TB meningitis (irrespective of bacteriological confirmation) should complete 12 months of full course of anti-TB therapy (ATT). Trials of TB treatment (using response to TB treatment as a diagnostic tool) are strongly discouraged. Once initiated, the TB treatment regimen should be continued until completion, unless a very clear alternative diagnosis has been established.

The standard 12-month regimen consists of isoniazid, rifampicin, ethambutol and pyrazinamide daily for the first 2 months followed by isoniazid and rifampicin daily for

an additional 10 months (2HRZE/10HR). The drug doses used in the TBM are same as those for the treatment of pulmonary TB. If multidrug resistance TB is suspected, all children should be referred for specialized care.

Drugs use in tuberculosis

Isoniazid(H)
Rifampicin(R)
Pyrazinamide(Z)

Ethambutol(E) – According to the available evidence, the risk of ocular toxicity due to ethambutol is negligible if recommended dosages are adhered to, especially since the use of ethambutol is limited to the intensive phase of treatment.

Therefore, ethambutol can be used in all ages including children below 5 years of age. It is also useful as a bridging therapy for children who developed anti-TB drug induced hepatotoxicity.

Streptomycin (S) – Streptomycin is no longer recommended as a treatment option for drug susceptible TB in children below 18 years due to its potential risk of ototoxicity (irreversible), nephrotoxicity and its poor tolerability (intramuscular injection).

Amikacin can be used as an alternative for streptomycin in situation such as bridging therapy for children who developed anti-TB drug induced hepatotoxicity.

Table 4.2: Anti TB medication dosing

Anti –TB drug	**Dose and range (mg/kg body weight)**	**Maximum dose (mg)**
Isoniazid (H)	10 (7-15)	300
Rifampicin (R)	15 (10-20)	600
Pyrazinamide (Z)	35 (30-40)	_
Ethambutol (E)	20 (15-25)	_

The higher end of the dosing range for isoniazid applies to younger children. As the children grow older the lower dosing becomes more appropriate.

The child friendly fixed dose combinations (FDC) offer the following advantages

- Correct dose – no need for crushing or chopping of tablets
- Quickly dispersible in water, easy for children
- Palatable flavours

New paediatric fixed dose combinations (FDC) contain,

Paediatric FDC_3 – Rifampicin 75mg +Isoniazid 50mg+ Pyrazinamide 150mg

Paediatric FDC_2 – Rifampicin 75mg +Isoniazid 50mg

4.5.2 Steroids

- Steroids will reduce the organization and fibrosis of exudates and help in reduction of inflammation.
- Recommended to use in TB meningitis and other forms of CNS TB. Also, in spinal TB after liaising with a neurosurgeon.
- Rifampicin increases steroid metabolism.
- The recommendation in children is 1-2mg/kg/day of prednisolone for 4 weeks and tapered down over 1-2 weeks before stopping.
- Some patients may need longer treatment with steroids, of up to 6–8 weeks. This decision should be made based on disease severity and complications of TBM.

4.5.3 Pyridoxine supplementation

- Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on highly active antiretroviral therapy (HAART).
- Pyridoxine (5–10 mg/day) is recommended in HIV-positive children, malnourished children with TB, breastfed infants and pregnant adolescents.
- It should be given with 12 hours gap with INAH.

4.5.4 Nutritional support

Severe malnutrition is associated with increased mortality in children and adults with TB. A child's nutritional status should be assessed regularly during treatment of TB.

All children diagnosed with TB even when they do not need treatment for severe acute malnutrition require nutritional support. This includes early efforts to continue breastfeeding (until at least 24 months of age where possible) and to ensure adequate nutrient intake using locally available and affordable foods.

Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods, provided as part of a balanced varied diet. Infants under 6 months of age with concern about malnutrition or growth failure require referral to a therapeutic feeding programme.

If this is not available or feasible, breastfeeding mothers should be given support to optimize breastfeeding.

Nutritional supplementation cannot be given directly to an infant under 6 months of age but can be provided for the lactating mother.

4.6 Management of adverse effects of medications – Refer National Manual for Tubeculosis Control: 2021 Update for further information.

Adverse events caused by anti-TB drugs are much less common in children than in adults.

- The most important adverse event is hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide.
- Serum liver enzyme levels do not need to be monitored routinely, as asymptomatic mild elevation (less than five times the upper normal value) is not an indication to stop treatment.
- However, the occurrence of liver tenderness, hepatomegaly or jaundice should prompt investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs and should start on bridging therapy with the expert opinion.
- Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized.
- An expert with experience in managing drug-induced hepatotoxicity should be involved in the further management of such cases.
- Early signs of ethambutol toxicity can be tested in the older child through red green colour discrimination.
- Monitoring for optic neuritis can be sought early when appropriate.

Table 4.3: Side effects of anti TB drugs

Drug	Common side effects	Rare side effects
Isoniazid	Hepatitis, nausea, vomiting, peripheral neuropathy, histamine reaction after red fish, skin rashes	Convulsions, pellagra, psychosis, optic neuritis, hematological abnormalities, SLE like syndrome
Rifampicin	nausea, anorexia, hepatitis, reduce efficacy of drugs, reddish discolouratin of body	Acute renal failure, shock, hemolytic anemia, pseudomembranous colitis, adrenal crisis, exfoliative dermatitis
Ethambutol	Optic neuritis, colour blindness(extremely unlikely with recommended doses and duration)	Skin rash, joint pains, peripheral neuropathy
Pyrazinamide	Nausea, vomiting, skin rashes, joint pains, hepatitis	Sideroblatic anemia, thrombocytopenia

Extracted from National Manual for Tuberculosis Control 2021 update.

4.7 Multi drug resistant tuberculosis

It is very rare in paediatric age group.

While sending samples, should ensure they are tested for DRTB using relevant investigations such as Gene Xpert MTB/RIF and second line drug sensitivity testing with Xpert MTB/RIF ultra, Xpert MTB/XDR and TB culture. However, detecting DRTB is a challenge in management of tuberculosis.

Refer Programmatic Management of Drug Resistant Tuberculosis (PMDT) guidelines 2021 for further management. (Available at NPTCCD website)

4.8 Immune reconstitution inflammatory syndrome (IRIS)

TB-IRIS is a paradoxical worsening or recurring of pre-existing TB lesions or the development of new lesions in patients on effective anti TB treatment.

Usually occurs at a mean of 15 days after starting anti-TB treatment up to12 weeks later. This may happen even after the completion of anti-TB treatment.

It is due to an increased lymphoproliferative response due to release of large amount of mycobacterium antigens and is more common in children with HIV after the commencement of antiretroviral therapy (ART).

It is usually characterized by large lymphadenopathy, abscess formation, miliary TB with large nodules and cavity formation, worsening of CNS TB as well as radiological and constitutional deterioration.

Multi drug resistant TB needs to be excluded before diagnosis, as this may mimic IRIS.

4.8.1 Prevention of IRIS

- Exclude TB before starting ART treatment.
- First treat TB and start ART treatment once the patient clinically improved and is tolerating anti TB treatment.

4.8.2 Treatment of IRIS

- Continue anti TB treatment.
- Exclude treatment failure or drug resistance.
- Exclude the presence of a second infectious agent or possible an alternative diagnosis.
- Add prednisolone starting at 1-2 mg/kg /day followed by a taper. Usual duration is 4 weeks.
- Aspiration of abscess.

4.9 Management of complications

Table 4.3: Complications of CNS TB and their management

Complication	Management
Hydrocephalus	Ventriculo-peritoneal shunt insertion is indicated for patients of all stages of severity with hydrocephalus or raised ICP. Early shunt insertion may be beneficial. Medical management of raised intra cranial pressure such as with hypertonic NaCl and mannitol should be limited to emergency situations until shunt insertion can be performed.
Stroke	There is no evidence on the most effective treatment strategy. Acute stroke or other evidence of on-going vasculopathy may warrant continuation of steroids, usually intravenously. Need to refer to paediatric neurologist
Optico-chiasmatic Arachnoiditis	Steroid therapy is the 1st line treatment, using intravenous dexamethasone.
Seizures	Acute management is with anti-seizure medications (ASMs) as per local protocol. The use of ASM alongside ATT must be done while being mindful of the potential for drug interactions and increased risk of liver dysfunction with multiple hepatotoxic agents. Prophylactic ASMs are not required. Continued treatment with ASM are necessary only in patients with recurrent seizures. The decisions about duration and withdrawal should be individualized.

4.10 Treatment of CNS tuberculoma

Tuberculoma of the central nervous system (CNS) is less common than TBM and has a lower morbidity and mortality but remains an important cause of intracranial space-occupying lesions.

The aims of treatment are:

a) Resolution of neurological and constitutional symptoms
b) Resolution of the lesion on neuroimaging

There is a lack of evidence as to the optimum duration of treatment in CNS tuberculoma. Expert opinion suggests that ATT should be given for 12 months initially, with repeat

neuroimaging at 3 months and 9–12 months to monitor response to treatment. Treatment should then be tailored to the clinical and radiological response of the patient.

4.10.1 Paradoxical reaction with an increase in the size and number of lesions

It can occur usually, in the first 3 months of treatment, and requires treatment with steroids as well as continuation of ATT.

4.10.2 Treatment failure

It should be suspected when lesions either increase in size or fail to reduce in size after 3 to 6 months of ATT despite appropriate dosing and good adherence. The treating clinician needs to weigh the benefits and risks of biopsy against those of commencing second-line treatment empirically for suspected MDR-TB or persisting with first-line treatment for suspected paradoxical reaction. If a biopsy is performed due to strong consideration of an alternative diagnosis, the specimens should be sent for:

a) Gene Xpert ultra-assay
b) Histopathology with staining for AFB
c) TB culture and drug susceptibility testing
d) Other microbiological tests as indicated by the case history.

4.11 Prevention

- Notification – H816A form which is available in triplicate need to be filled. Send 2 copies to the National Programme for Tuberculosis and Chest Diseases (NPTCCD) and keep one in the hospital. Need to fill H544 form also and send to MOH office.
- This ensures follow up preventive activities at the field level including screening of close contacts for TB.
- Tracing defaulters – If the patient defaults treatment, ensure follow up till completion of treatment.
- Once diagnosed of TB, all patients need to be registered in district chest clinics with a district TB number. This ensures continuous supply of anti TB drugs which are available only with the national programme and chest clinics operating under it. Drugs are issued under the registered district TB number.

4.12 References

1. National Manual for Tubeculosis Control- 2021 Update.
2. Paediatric TB guideline Sri Lanka 2018.
3. Aulakh R, Chopra S. Pediatric tubercular meningitis: a review. Journal of Pediatric Neurosciences. 2018 Oct;13(4):373.
4. WHO Guidance for National tuberculosis programmes on the management of tuberculosis in children, Second edition.
5. WHO Guidelines for co - trimoxazole prophylaxis for HIV related infections among children adolescence and adults. 2006.
6. WHO - operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. 2022.
7. WHO - consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. 2022.
8. WHO - Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children. 2006.
9. INDEX-TB GUIDELINES - Guidelines on extra-pulmonary tuberculosis for India. 2016.

5. MANAGEMENT OF CNS FUNGAL INFECTIONS IN CHILDREN

5.1 Introduction

Invasive mycoses of the central nervous system (IMCNS) encompass a diverse group of diseases that have emerged as opportunistic infections in patients who are immune compromised due to congenital or acquired immune deficiency (including poorly controlled HIV). Of note, absence of above risk factors does not exclude the possibility of fungal aetiology in CNS infections.

These guidelines are focused on clinical syndromes caused by relatively common organisms namely *Cryptococcus neoformans, Aspergillus* sp. And *Candida* sp.

5.2 Risk factors of IMCNS

immunodeficiency disorders
immunomodulation therapy
solid organ and stem cell transplantation
hematological malignancies
chronic steroid use
low birth weight and preterm infants
shunted hydrocephalus and external ventricular drains
long term recipients of broad-spectrum antibiotics
total parenteral nutrition
central venous catheterization
chronic renal failure
diabetes mellitus
skull base surgery
head injury

5.3 Clinical spectrum

IMCNS often presents with focal neurological deficits and or generalized seizures whereas fever and headache maybe absent. They can initially present with mild and nonspecific symptoms, rapidly progressing to potentially fatal disease, which is difficult to diagnose and treat successfully. Therefore, early suspicion, diagnosis and initiation of antifungal therapy is important.

They can cause a variety of clinical syndromes including meningitis (*Cryptococcus neoformans, Candida* sp.), mass lesions in the form of cerebral abscesses (*Cryptococcus neoformans*, *Aspergillus* sp., and *Candida* sp.) and invasion of the cerebral vasculature causing strokes (*Aspergillus* sp.).

5.4 Investigations

5.4.1 Neuroimaging

MRI brain is a useful imaging tool in identifying fungal abscesses and may point to individual fungal type although there are no pathognomonic radiological features.

MRI brain characteristics (differentiation from bacterial abscesses)

Bacterial aetiology	Fungal aetiology
Double halo appearance in the cavity wall (in almost all)	Not a feature
Restriction in DWI sequence (in 60%)	Not a feature
Smooth-walled and fluid filled	Irregular wall

Other useful MRI features helpful to identify common fungal types are as follows,

Cryptococcosis

- Pachymeningeal enhancement (TW1 post contrast), as well as choroid plexus and ependymal contrast uptake
- Gelatinous pseudocysts in Virchow – Robin spaces of the basal ganglia and mesence-phalon (bilateral, symmetrical, iso-intense in TW1, TW2)
- Cryptococcomas in basal ganglia and in the ependymal lining of the ventricular system (hypo-intense in TW1, TW2, very little enhancement)

Aspergillosis

- ❖ Nonspecific, diffuse meningeal enhancement (TW1 post contrast)
- ❖ Granulomas progressing to abscesses (50% in corpus callosum, characteristic T2 hypointense signal rim produced by microhemorrhages and hemosiderin laden macrophages with or without peri-lesional restricted diffusion)
- ❖ Mycotic aneurisms (saccular and usually located in the proximal carotid arteries, more distal fusiform lesions could also be seen)

Candidiasis

- ❖ Meningeal inflammatory changes (FLAIR, TW1 post contrast sequences)
- ❖ Diffuse micro abscesses
- ❖ Macro abscesses (uncommon, usually in parieto-occipital and posterior fossa)
- ❖ Basal ganglia infarcts
- ❖ Mycotic aneurisms
- ❖ Secondary subarachnoid haemorrhages

5.4.2 Laboratory diagnosis

The laboratory diagnosis of IMCNS generally goes through 3 phases, which are

1. **Microscopic detection (India ink stain for cryptococcus neoformans and 10% KOH smear for other fungi) of fungi in clinical samples (aspirated abscess fluid and or resected tissue / CSF).**
2. Isolation and identification of the agent in fungal cultures.
3. Measurement of markers of immune response against the fungi or fungal elements.

Examples

- Cryptococcal antigen titres – can be done with CSF / serum.
- **BDG (beta D Glucan) assay** – serum test, high sensitivity and specificity, which also can measure the treatment efficacy. It is a pan fungal test which is not specific for any fungus – can be done with serum.

The pitfalls in diagnosing IMCNS would be that negative mycotic cultures do not exclude the possibility of fungal aetiology and there could be serological cross reactivity between many of these agents causing false positivity.

Organism specific tests

Cryptococcosis

Cryptococcus is the commonest cause of fungal meningitis and of note, initial CSF parameters could be normal in 30% of cases.

- The positivity of direct microscopic examination of CSF in India ink preparation is about 50%. Cryptococci may be seen as yeasts in gram stain as well.
- CSF, blood and biopsy from any other suspected sites (e.g., skin nodules) can be used for culture, which is more sensitive than direct microscopy. Culturing the organism is important to confirm the sterilization of CSF/blood following antifungal treatment and to perform antifungal sensitivity testing. This is important in treating patients with relapse and those who are intolerant to fluconazole maintenance therapy.
- Cryptococcal antigen can be detected both in serum and CSF using lateral flow assay, latex agglutination test whereas ELISA with high sensitivity and specificity. This can be used to assess treatment response. Since this test has a sensitivity of >95%, it can be positive at early stages of the infection whereas India ink stain and culture could be still negative. In these instances, treatment has to be initiated with the positive cryptococcal antigen test results.
- Multiple PCR bio-fire array has emerged as a tool with 100% diagnostic sensitivity. (Not freely available)
- Histological specimens (biopsy or surgical debridement of abscesses) could show granulomas with varying degree of fibrotic and necrotic tissue with numerous oval or rounded budding, relatively thin walled yeast like cells of varying sizes surrounded by wide clear spaces or "halos" that represent unstained mucopolysaccharide capsules which lacks affinity with H&E stain. With Mayer's Mucicarmine stain, the cell wall and capsule appear in red, which is diagnostic.

Aspergillosis

- CSF microscopy sensitivity rate is increased when it is done using the deposit of the centrifuged sample (at least 1 ml of CSF should be sent to the laboratory)
- CSF fungal culture is more sensitive and specific than direct microscopy (sensitivity is more when it is done using the deposit of the centrifuged sample).
- Normally Aspergillus does not isolate in blood cultures.
- GM (Galactomannan) antigen in serum is specific for invasive aspergillosis, but the titres could be normal or very low.
- Histopathological samples – uniform septate hyphae with characteristic dichotomous branching.

Candidiasis

- Should be suspected in any patient with clinical or CSF evidence of CNS involvement and candidemia. This is especially important in premature neonates and those with ventricular peritoneal shunts.
- CSF parameters of Candida meningitis usually shows evidence of haemorrhage, mild to moderate leukocytosis, normal or low glucose and elevated proteins.
- Negative CSF gram stains does not exclude CNS candidiasis.
- The sensitivity of positive blood culture falls between 62-80%, however the specificity is nearly 100%.
- **Candida mannan antigen** and **Candida anti mannan antibody assays**, both done in serum have high sensitivity and specificity and this is a specific marker for invasive Candida infections.
- Performing both tests at the same time will help to increase the diagnostic yield.
  In an immunocompromised patient (who are unable to produce antibodies), it is recommended to perform Candida mannan antigen test repeatedly to see elevating titres to diagnose invasive candida infections.

5.5 Management

Prompt diagnosis and effective treatment often require a medical-surgical team approach supported by radiology and microbiology inputs.

Consultation with microbiologist and/or neurologist is recommended in all patients

<u>Treatment principals</u>

- Reversal/minimization of immunomodulation therapies.
- Prompt pharmacological management with antifungal agents.
- Removal of infected CNS devices including ventricular shunts (if possible).
- Resection of the abscess / abscesses.
- Anti-fungal therapy – Amphotericin B is the empirical treatment of choice when the fungal organism is unknown. This should be changed if necessary, once the organism is identified.

5.5.1 Pharmacological management

Cryptococcus

- Initiation phase – Start treatment with IV **Amphotericin B (deoxycholate)** until CSF becomes sterile.
- Consolidation phase – Convert to **fluconazole** once CSF becomes sterile. Continue for at least 8 weeks.
- Maintenance phase – Fluconazole is continued. Maintenance duration is 6-12 months depending on the clinical, radiological and mycological response. In HIV infected children maintenance phase should be continued until CD4 count >200cells/µl.
  - **Liposomal amphotericin B** is the alternative for patients with renal impairment (please refer "Administration of Amphotericin B (AMB)" – Mycology – Sri Lanka College of Microbiologists (slmicrobiology.lk))
  - In severe infections or when the response to Amphotericin B is poor, **combine IV Amphotericin B with 5-flucytosine.** This drug should be used in conjunction with amphotericin B due to emerging resistance to this drug.
  - If any allergy or resistance to **fluconazole**, start **voriconazole or itraconazole** depending on sensitivity. Convert to oral therapy after significant clinical improvement.

Aspergillus

- Initiation phase – Start treatment with IV **voriconazole**
- Consolidation / maintenance phase – Convert to oral therapy after significant clinical improvement. Continue oral voriconazole for 6-12 months depending on the clinical, radiological and mycological response.
- If IV voriconazole cannot be used, treat with IV **amphotericin B**.

Candida

- Initiation phase – Start treatment with IV **amphotericin B (deoxycholate).** This should be continued until CSF becomes sterile. The timing of repeat LP should be guided by clinical response. It is usually 2 weeks after treatment.
- Consolidation phase – If good response, convert to **fluconazole** 12 mg/kg/day. (At least for 2 weeks after last CSF sterilization, or 4 weeks after clinical remission and complete radiological resolution is achieved).

- **Liposomal amphotericin B is** the alternative for patients with renal impairment (please refer "Administration of Amphotericin B (AMB)" – Mycology – Sri Lanka College of Microbiologists (slmicrobiology.lk))
- In severe infection or when the response to amphotericin is poor, **combining IV amphotericin B with 5-flucytosine is recommended**. (This drug should be used in conjunction with amphotericin B due to emerging resistance to this drug).

Table 5.1: Anti-fungal drug dose, route and dosing interval

Anti-fungal therapy	Dose/ route/ dosing interval
Amphotericin B (Deoxycholate) Please read manufacturer's advice See annexure 1 for prevention of side effects	Test dose is essential. (100mcg/kg IV over 20-30 mins, should be included as part of the first dose) Start with 250 micrograms/kg IV and increase to 1 mg/kg/day over 2-4 days May increase to 1.5mg/kg daily or EOD in severe infections and reduce later with response (1mg/kg)
Amphotericin B (liposomal) Please read manufacturer's advice	Test dose is essential 100 mcg/kg, max. 1mg to be given over 10 minutes) 3mg /kg/day (max. 5 mg/kg) once daily as intravenous infusion
Caspofungin	Neonate, IVI 25mg/m^2 once daily Child 1-3 months, IVI 25 mg/m^2 once daily 3 months – 1 year, IVI 50 mg/m^2 once daily 1-18 years 70 mg/m^2 once daily on first day and then 50 mg/m^2 (max. 70 mg)
Fluconazole	Given as IVI/PO 6-12 mg/kg/day Consolidation therapy: 10-12 mg/kg /day orally) Maintenance therapy: 6 mg/kg/day orally In Neonates 0-14 days of age (every 72 hours), 14-28 days of age (every 48 hours), and beyond 28 days of age daily dosing
5-Flucytosine	50 mg/kg 12 hourly as PO/IVI for neonates 50 mg/kg 6 hourly as PO/IVI for child 1 month to 18 years of age
Anti Fungal	**Dose/ route/ dosing interval**
Itraconazole	Child 1 month to 18 years IVI 2.5mg/kg (max. 200 mg) every 12 hours for 2 days, then 2.5 mg/kg once daily for max. 12 days. Maintenance in HIV-infected patients, PO 5mg/kg once daily increased to 5 mg/kg twice daily if low plasma Itraconazole concentration. Prophylaxis in patients with haematological malignancy or undergoing bone marrow transplantation. PO (liquid preparation only) 2.5mg/kg twice daily before transplantation or chemotherapy and continue until neutrophil count recovers.

Voriconazole	Child 2-12 years, loading dose 9 mg/kg by IVI every 12 hours for 2 doses Maintenance dose of 8 mg/kg by IVI every 12 hours as intravenous infusion Child 12-18 years or above 50 kg, 6 mg/kg every 12 hours for 2 doses then 4 mg/kg every 12 hours Reduce the dose in steps of 1mg/kg if not tolerated Convert to oral after significant clinical improvement

5.5.2 Neurosurgical management of IMCNS

Urgent neurosurgical opinion should be sought towards the following management goals.

- Removal of ventricular drains detected to harbor the fungus
- Removal of space occupying lesions which pose a threat to life or eloquent function
- Drainage of macro-abscesses
- Obtaining a histological sample for microscopy and culture
- Endoscopic surgical lavage and resection of infected tissue
- Debridement of necrotic cerebral tissue especially with Aspergillosis
- Raised intracranial hypertension and hydrocephalus associated with Cryptococcal meningitis.

5.5.3 Management of specific complications of Cryptococcal meningitis

a) Persistent infection and relapse

- Persistent infection is defined as persistently positive cultures despite adequate antifungal therapy for 4 weeks. LP should be repeated on completion of 2 weeks of treatment in all cases.
- Relapse is a recurrence of signs and symptoms in a child who had microbiologically proven infection and was in remission. (Negative CSF culture and absence of new CNS lesions).

b) Treatment of relapse/recurrence

- Ensure correct antifungal dose, duration and compliance.
- Implement measures to improve immune status (decrease immunosuppressants, introduce retro-viral therapy in HIV infected patients).
- Seek expert microbiology / mycology advice to reinstitute induction therapy, for higher doses or longer treatment duration and for use of alternative agents.

c) Elevated CSF pressure

- One of the key determinants of outcome in cryptococcal meningitis would be management of raised ICP (>25 cm CSF).
- Opening pressure should be measured during the initial lumbar puncture. Acute symptomatic elevated CSF pressure should be treated with CSF drainage by daily lumbar punctures until CSF pressure is < 25cm. Consider temporary percutaneous lumbar drain or ventriculostomy.
- Ventricular shunting should only be considered in patients who are on antifungal agents and where the initial conservative measures have failed.

d) IRIS (Immune Reconstitution Inflammatory syndrome)

- The majority of cryptococcal infection related IRIS represents reactivation of previously treated cases. The clinical presentation consists of fever, lymphadenopathy and CNS symptoms.
- The clinician should be alert about the other causative agents of this syndrome such as Mycobacterium, Herpes group of viruses, HIV etc. as well. There is no need to change the antifungal therapy.
- For major complications such as CNS inflammation with raised ICP, consider corticosteroids (0.5 – 1 mg/kg/day prednisolone or equivalent) for 2 - 6 weeks.

Table 5.2: Preventing, monitoring and managing amphotericin B toxicity

Pre-emptive hydration and electrolyte supplementation	
Adults and adolescents	One litre of normal saline solution with 20 mEq of potassium chloride (KCI) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An additional 8-mEq KCI tablet twice daily may be added during the second week.
Adolescents and children	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). Up to one litre of normal saline solution with one ampoule (20 mmol) of KCl at 10-15 ml/kg over 2-4 hours before each controlled infusion of amphotericin B.

Monitoring	
Serum potassium	Baseline and daily (especially in the second week of IV amphotericin B administration)
Serum creatinine	Baseline and daily (especially in the second week of IV amphotericin B administration)
Haemoglobin Ca Mg Liver enzymes	Baseline and weekly Baseline and weekly Baseline and weekly 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	If creatinine increases by ≥2 fold from the baseline value, increase pre-hydration (to 1L in adolescents) every eight hours and consider temporarily omitting a dose of IV amphotericin B. Once creatinine improves, restart IV amphotericin B at 0.7 mg/ kg/day and consider alternative-day IV amphotericin B. If creatinine continues to rise, consider discontinuing IV amphotericin B and continuing with fluconazole with microbiology opinion, especially if seven doses of IV amphotericin B have been received. Consider fluconazole dose adjustment with significant renal impairment. Monitor creatinine daily.
Severe anaemia	Transfusion should be undertaken, if possible, for severe amphotericin B–related anaemia (anaemia may also be a reason to discontinue IV amphotericin B prematurely in the second week of a planned two-week induction course of IV amphotericin B with fluconazole)

*Extracted from Guidelines for the Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children: Supplement to the 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.Geneva: World Health Organization; 2011December/ 2018 March.

Additional notes:

- Potassium replacement should not be given to people with pre-existing renal impairment or hyperkalaemia.
- Careful attention should be given to monitoring of intake and output of fluid and daily weight, especially among children.
- The incidence of renal dysfunction and electrolyte disturbance is much less with IV liposomal amphotericin B preparations, but renal function and electrolytes still need to be monitored.

5.6 References

1. Caceres A, Avila ML, Herrera ML. Fungal infections in pediatric neurosurgery. Child's Nervous System. 2018 Oct;34:1973-88.
2. Swaiman's Pediatric Neurology Principles and Practice- 5th Edition.
3. Sato Y, Osabe S, Kuno H, Kaji M, Oizumi K. Rapid diagnosis of cryptococcal meningitis by microscopic examination of centrifuged cerebrospinal fluid sediment. Journal of the Neurological Sciences. 1999 Mar 15;164(1):72-5.
4. BNF for children, September 2016-17.
5. Blyth CC, Hale K, Palasanthiran P, O'Brien T, Bennett MH. Antifungal therapy in infants and children with proven, probable or suspected invasive fungal infections. Cochrane Database of Systematic Reviews. 2010(2).
6. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America.
7. Christopher C. Blyth P, Tracey A. O'Brien. Antifungal Therapy in Children with Invasive Fungal Infections: A Systematic Review. Pediatrics 2007;119;772-784 DOI: 10.1542/peds.2006-2931
8. Patterson TF, Thompson III GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016 Aug 15;63(4):e1-60.
9. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016 Feb 15;62(4):e1-50.
10. Walsh TJ, Katragkou A, Chen T, Salvatore CM, Roilides E. Invasive candidiasis in infants and children: recent advances in epidemiology, diagnosis, and treatment. Journal of Fungi. 2019 Jan 24;5(1):11.

6. MANAGEMENT OF CNS INFECTIONS DUE TO UNCOMMON PATHOGENS

This chapter deals with uncommon pathogens that are known to cause CNS infections in Sri Lanka. It is recommended that the relevant microbiological specialist and paediatric neurologist are consulted during management of these rare conditions.

6.1 Cerebral Malaria (CM)

6.1.1 Clinical features

CM is caused by *Plasmodium falciparum* (*Pf*) species.

Initial clinical symptoms can be non-specific (even without fever) or overlap with CNS infections caused by bacteria or viruses. However, as CM is rapidly fatal, it should be suspected in any febrile illness with neurological signs and travel (within 1 year) to malaria endemic countries (e.g. India, Pakistan, Southeast Asia, Haiti, and African Countries) history of malaria within the past 3 years or in a recipient of blood or blood products within past 3 months.

Impaired consciousness, multiple convulsions along with multi organ involvement (acute pulmonary oedema, ARDS, circulatory collapse or shock, acute kidney injury, clinical jaundice with evidence of vital organ dysfunction and abnormal bleeding) may occur.

Fundoscopy may reveal characteristic retinal changes including. 1) peri macular whitening 2) vessel colour change 3) white centered retinal haemorrhages.

6.1.2 Serological findings

Malaria Rapid Diagnostic test (RDT)and or blood detects HRP2 (by *Pf*) and pLDH (by all species) antigens released by malarial parasites to blood.

Hypoglycaemia is a well-known complication (blood glucose should be monitored 4 hourly, particularly in unconscious patients). Prognosis may be worse if unconsciousness does not improve with dextrose in those who get recurrent bouts of hypoglycaemia.

Metabolic acidosis is an important feature of severity. Elevated serum lactate levels in CM indicate poor outcome.

Anaemia is a common complication. Thrombocytopenia had been a finding in some malaria cases in recent years in Sri Lanka.

6.1.3 CSF abnormalities

White cells will be absent. CSF Glucose will be lower than in encephalitis with levels usually below 3.4 mmol/l. Proteins will be high. CSF ADA/Serum ADA ratio will be low. (<0.38 is a good discriminator from viral encephalitis)

6.1.4 Management

1. Monitor vital signs, coma scale and urine output during the acute state.
2. Treating malaria based on clinical suspicion without laboratory confirmation should be avoided.
3. However, as a life saving measure antimalarial treatment can be given based on clinical suspicion after informing AMC and preserving blood.
4. Blood (2ml in EDTA or 1.5ml of dried blood on 4 spots on filter paper) should be collected before administering anti-malarials. Further daily blood smear should be done until parasitaemia is cleared.
5. Initiation of anti -malarial treatment

   Intravenous artesunate, (2.4mg/kg BW) is given on admission (time = 0), then at 12 hour and 24 hour, then once a day until the patient can take oral medication. If intravenous administration is not possible, it can also be given as an intramuscular injection.

   Artesunate is dispensed as a powder of artesunic acid. This powder is dissolved in 1ml of 5% sodium bicarbonate to form sodium artesunate. The solution is then diluted with 5 ml of 5% dextrose and given immediately by intravenous bolus injection or by intramuscular injection (to the anterior thigh). The solution should be prepared freshly for each administration and should not be stored.

   IV artesunate can be made available within two hours in any part of the country.

   Please contact the AMC immediately for IV artesunate (011 7626626)

   In the treatment of severe malaria, intravenous artesunate should be given for a minimum of 24 hours, even if the patient can tolerate oral medication.

   An acutely ill child requires careful clinical monitoring as she/he may deteriorate rapidly.

   The solution should be prepared freshly for each administration and should not be stored. Any balance should be discarded.

6. Follow up on oral treatment

   In a patient with severe malaria, the treatment schedule should be completed giving a full course of ACT (Artemether and lumefantrine) as soon as the patient is able to take oral medication.

   This should be followed by a single dose of primaquine (0.75 mg/ body weight). (CI: children of less than 1 year of age, in severe G6PD deficiency).

Treatment should be completed by giving a full course of artemisinin based combination therapy (ACT) (Coartem®) which is the first line treatment for *Pf* when the patient is able to take oral medication. It is given as a 6-dose regimen over a three-day period according to the body weight as indicated in the table.

Number of ACT tablets administered based on weight of the patient

Interval between doses	**5-14kg Yellow pack**	**15-24kg Blue pack**	**25-34kg Orange pack**	**>35kg Green pack**
0 Hrs	1	2	3	4
8 Hrs	1	2	3	4
24 Hrs	1	2	3	4
36 Hrs	1	2	3	4
48 Hrs	1	2	3	4
60 Hrs	1	2	3	4
Total	6	12	18	24

ACT should be taken with milk or fat containing food.

7. All laboratory confirmed cases or anyone with strong suspicion of malaria should immediately be notified by telephone to regional malaria officer or anti malaria headquarters.

6.2 Toxoplasmosis

6.2.1 Clinical features

Usually asymptomatic or presents with fever with mild systemic features and lymphadenopathy.

CNS infection is seen mostly in an immunocompromised child leading to a febrile illness, with encephalopathy, visual changes, and seizures. Toxoplasma encephalitis (TE) is a common complication of AIDS. Patient may, but not always have a contact history to a

house cat or a litter box or ingestion of raw or undercooked meat or raw fruits and vegetables.

Fundoscopy shows a characteristic choreo-retinitis with an active whitish infiltrate attached to the darkly pigmented border of an older scar.

6.2.2 Serological findings

An IgM antibody response is seen in cases of newly acquired toxoplasmosis. A negative IgM test essentially excludes recent infection, but a positive IgM test is difficult to interpret as *Toxoplasma*-specific IgM antibodies may last as long as 18 months after acute acquired infection. Another major problem with *Toxoplasma*-specific IgM testing is the lack of specificity. Newborns and infants suspected of congenital toxoplasmosis should be tested by both an IgM- and IgA-capture EIA.

A positive IgG titre indicates infection with the organism at some time. Rising titres of anti-toxoplasma IgG antibodies may be seen.

Usefulness of serology is limited in immunocompromised patients in determining active toxoplasmosis in central nervous system. Disseminated infection may exist in AIDS patients without demonstrable IgM antibody titres.

6.2.3 CSF abnormalities

White cell count and glucose will be variable. Proteins are elevated. Detection of *T gondii* DNA on polymerase chain reaction testing of cerebrospinal fluid facilitates the diagnosis.

6.2.4 Management

As these infections are uncommon need to discuss with paediatric neurologist/ microbiologist before starting treatment.

Following combinations can be used to treat toxoplasma encephalitis.

1) Pyrimethamine-sulfadiazine (first line)
2) Pyrimethamine-clindamycin (for those who cannot tolerate sulfadiazine or do not respond to first-line therapy)
3) Trimethoprim-sulfamethoxazole

Folinic acid should be administered concomitantly to prevent bone marrow suppression. (Weekly blood counts are needed.)

Paediatric dose:

Pyrimethamine 2mg/kg first day*(maximum 50mg), then 1mg/kg each day (maximum 25 mg),

Plus, sulfadiazine 50 mg/kg two to four times per day (maximum 1–1.5 g/dose),

Plus Folinic acid (to be given during treatment and at least week after treatment) (neonate: 5 mg 3 times a week; increased if necessary up to 20 mg 3 times a week, if the patient is neutropenic. Child 1–11 years: 10 mg 3 times a week).

Duration:

Treatment for TE should be given for at least 6 weeks; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks.

Role of corticosteroids:

Is uncertain. They may be prescribed sparingly in addition to antiparasitic agents but only when they are indicated such as in severe abscess related oedema or in presence of significant mass effect.

Anticonvulsants: should **not** be administered **prophylactically.**

Follow-up:

Neuro imaging should be repeated after 2-3 weeks of treatment to assess whether the lesion has reduced in size.

6.3 Cysticercosis

6.3.1 Clinical features

Neurocysticercosis is acquired by ingestion of eggs passed in faeces of a person who has intestinal pork tapeworm (*Taenia solium*) infection. Most are asymptomatic during the early stages of the disease following which they commonly develop seizures (50%–70%), headaches (43%), and findings related to hydrocephalus (30%) when the scolexes begin to die or from cysts in the ventricular system.

This may be further complicated with cranial nerve palsies and cerebrovascular events including progressive midbrain syndrome due to multiple infarcts in midbrain and thalamus.

6.3.2 Serological findings

Cysticercus specific immunoglobulin G (IgG) antibody can be tested in serum. Currently available antibody detection tests for cysticercosis do not distinguish between active and inactive infections. Antigen testing is available only at special centers (E.g., CDC, USA).

6.3.3 CSF abnormalities

Cysticercus specific immunoglobulin G (IgG) antibody can be tested in CSF.

6.3.4 Management

The choice of treatment for neurocysticercosis depends on the clinical manifestations and the location, number, size, and stage of cysticerci.

In patients with untreated hydrocephalus or diffuse cerebral oedema, mainstay of management is treatment of intracranial pressure before commencing antiparasitic treatment.

In the absence of elevated intracranial pressure, antiparasitic drugs should be started in symptomatic patients with live (non-calcified) cystercerci. Adjunctive corticosteroid therapy should be started prior to anti parasitic treatment in all.

Treatment of active disease may include surgery and/or long courses with praziquantel and/or albendazole, as well as supportive therapy with corticosteroids and/or anti-epileptic drugs, since the destruction of cysts may lead to an inflammatory response. The dosage and the duration of treatment can vary greatly and depend mainly on the number, size, location and developmental stage of the cysts, their surrounding inflammatory oedema, acuteness and severity of clinical symptoms or signs.

1–2 viable parenchymal cysticerci; albendazole monotherapy for 8–30 days. 15 mg/ kg/day in 2 divided doses for 15 days with fat containing food. (Max 800mg/day) >2 viable parenchymal cysticerci; albendazole combined with praziquantel (50-100 mg/kg/day in 3 divided doses) for 15 days is required rather than albendazole monotherapy

Retreatment may be needed with antiparasitic therapy for parenchymal cystic lesions persisting for 6 months after the end of the initial course of antiparasitic drugs.

6.4 Toxocariasis

6.4.1 Clinical features

Caused by accidental ingestion of eggs of *Toxocara canis*, a roundworm in dogs, puppies, and *Toxocara cati* of cats.

Nervous system manifestations include.

1) Eosinophilc meningo-encephalitis or granuloma formation in brain
2) Eosinophilic myelitis

3) Optic neuritis
4) Vasculitis leading to infarcts.
5) Epilepsy
6) Involvement of the peripheral nervous system
   I. Facial nerve palsy
   II. Skeletal muscle involvement.
   III. Radiculitis

6.4.2 Serological findings

Eosinophilia, which is almost always found in Visceral Lava Migrans, may be frequently absent in CNS toxocariasis. Serum IgE may be elevated.

Usual diagnostic test is the ELISA with TES-antigen. A positive ELISA can be confirmed by Western blot.

Using the levels of specific IgM is not useful in toxocariasis to assess the age of the infection because IgM antibodies can be found throughout the course of toxocariasis.

6.4.3 Management

Albendazole (400mg twice a day) is the most commonly used treatment regime. Mebendazole (100-200mg twice a day) can also be used.
Corticosteroids may be particularly effective in optic neuritis due to Toxocara.
There is no recommended treatment duration. Duration can be vary from 5-21 days.

6.5 Rickettsial disease

6.5.1 Clinical features

Presents as an acute febrile encephalopathy and symptoms overlap with viral aetiologies.

Fever may be present for a long duration with a mean of around 7 days, before altered sensorium develops. Severe headache invariably occurs and is a key criterion for suspicion.

Unilateral or bilateral 6^{th} nerve palsy is a common finding.

Other symptoms may include seizures, myoclonus, parkinsonism, sensorineural hearing loss and tinnitus.

Pathognomonic eschars are reported from 20% to 86% of patients.
Multi system involvement may be present with acute kidney injury and hepatitis.

6.5.2 Serological findings

Diagnosis is supported by increase in antibody titers in Weil-Felix agglutination test or immunofluorescent/immune chromatography.

Rickettsial PCR when available may support the diagnosis.

Liver enzymes may be elevated with disproportionate rise of SGOT over SGPT. Thrombocytopenia, coagulopathy, and electrolyte abnormalities may be seen.
When there is rash or eschar PCR from skin biopsy will help the diagnosis.

6.5.3 CSF abnormalities

Mild lymphocytic pleocytosis may be seen. CSF glucose may be low to normal. Proteins may be elevated mild to moderately. CSF ADA is elevated, thus is not useful to differentiate from TB meningitis.

6.5.4 Management

Doxycycline is the treatment of choice.

- Children under 45 kg body weight (100 lbs): 2.2 mg/kg/day given twice a day (Maximum dose 200mg/day).
- Children with body weight 45 kg or above:100 mg twice daily

Patients should be treated with doxycycline for at least 3 days after the fever subsides and there is evidence of clinical improvement. Minimum course of treatment is 7 days.

Alternatives

- Tetracycline (for children more than 8 years of age) 25-50 mg/kg/day divided every 6hrly PO is an alternative for doxycycline.
- Chloramphenicol also remains a possible treatment option (Dose 50-100 mg/kg/day divided every 6hrly IV: maximum 4g per day). It should be reserved for patients with doxycycline allergy. However, epidemiologic studies suggest that RMSF patients treated with chloramphenicol are at higher risk for death than people who received a tetracycline-class antibiotic.
- For Mediterranean spotted fever (MSF) and Scrub typhus, Azithromycin is an effective treatment option.
  (Dose MSF – 10mg/kg/day once daily for 3days and for Scrub typhus 10mg/kg PO on day 1, then 5mg/kg PO: maximum 500mg/day for minimum of 5days and until the patient has been afebrile for at least 3days to avoid relapse.

6.6 Lyme disease/neuroborreliosis

6.6.1 Clinical features

Lyme borreliosis is a multisystem inflammatory disease that is caused by a spirochete *Borrelia burgdorferi* sensu lato and transmitted through the bite of the Ixodes ricinus tick.

The disease can go through the following stages.

Stage 1: **Early localized phase** with erythema migrans.

Stage 2: **Acute disseminated phase**

Neurological manifestations include lymphocytic meningitis (30%) and facial paresis (55%). Other cranial nerves excluding olfactory nerve can get involved. Myelitis, acute hemiparesis, opsoclonus-myoclonus syndrome, and ataxia have been reported.

Stage 3: **Late lyme neuroborreliosis**

Very rare in children. Clinical pictures include seizures, neurological deficits with paralysis and excretory disorders. Cognitive impairment and mood disorders can also occur.

6.6.2 Serological findings

Borrelia-specific IgM antibodies can be detected starting week 3 and IgG antibodies starting week 6.

6.6.3 CSF abnormalities

The CSF typically exhibits **lymphocytic pleocytosis** with plasma cells, activated lymphocytes and a significant **increase in the total protein** or albumin ratio. Suspected clinical diagnosis can be confirmed by detecting borrelia-specific intrathecal antibody synthesis.

6.6.4 Management

Treatment of neuroborreliosis should be with one of the following: doxycycline, ceftriaxone, cefotaxime, penicillin G for 14-21 days

Disease restricted to cranial or peripheral nerves.

Children under 9 years

- Amoxicillin oral, 30 mg/kg 3 times per day, Weight > 33 kg 1 g 3 times per day

Children 9-12 years

- Doxycycline oral, 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses. For severe infections, up to 5 mg/kg daily. If weight > 45 kg 100 mg twice daily or 200 mg once daily.
- Amoxicillin oral, 30 mg/kg 3 times per day oral, weight > 33 kg 1 g 3 times per day

>12 years

- Doxycycline oral 100 mg twice daily or 200 mg once day
- Amoxicillin oral 1 g 3 times per day

Affecting the central nervous system

Age < 9 years

- Ceftriaxone (intravenous), 80 mg/kg once daily, maximum dose 4g

Age 9 -12 years

- Doxycycline oral, 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses. For severe infections, up to 5 mg/kg daily. If weight > 45 kg 100 mg twice daily or 200 mg once daily
- Ceftriaxone (intravenous) 80 mg/kg once daily, maximum dose 4g

Age > 12 years

- Doxycycline oral, 100 mg twice daily or 200 mg once daily
- Ceftriaxone intravenous 2 g twice daily or 4 g once daily

Alternative

- Penicillin G 200,000-500,000 daily, 6 hourly for 4 to 21 days.

6.7 *Mycoplasma* pneumoniae infections

6.7.1 Clinical features

Neurological manifestations include encephalitis, optic neuritis, acute psychosis, stroke, cranial nerve palsies and aseptic meningitis.

It may also be implicated in immune mediated neurological diseases such as acute demyelinating encephalomyelitis, Guillain-Barre syndrome and transverse myelitis.

Central nervous system infections and inflammatory or autoimmune disorders may cause secondary central nervous system vasculitis.

6.7.2 Serological findings

- Specific IgM by complement fixation or ELISA
- Four-fold rise in IgG
- PCR for mycoplasma – Specific and rapidly available. Therefore, ideal for acute management if available.
- Culture

6.7.3 Management

Treatment must be adjusted according to pathogenic mechanism such as antibiotics for the organism, corticosteroids, intravenous immunoglobulin, or plasmapheresis when immunopathology is active.

- During the first 7 days of fever onset the mainstay of treatment is antibiotics
- After 7 days of onset the addition of corticosteroids (intravenous methyl prednisone 10- 30 mg/kg for 2 to 3 days, tapering within a week) with or without

intravenous immunoglobulin (1-2g/kg over 2-3 days) or plasmapheresis is recommended.

- The antibiotics with the best minimum inhibitory concentration (MIC) values are macrolides, tetracyclines and fluoroquinolones. Their usage is limited in young children due to side effect profile. Age limit tetracyclines: 8 years; fluoroquinolones: adolescence with skeletal maturity although musculoskeletal adverse effects of fluoroquinolones are reported to be reversible.
- Macrolide antibiotics are usually used due to favorable side effect profile in children.
- In cases of macrolide resistance alternatives need to be used.

Antimicrobial dosages

- Clarithromycin oral or as an intra venous infusion 15 mg/kg/day (maximum daily dose 1g) in two divided for 10- 14 days.
- Doxycycline oral can be used for older children and where resistance to macrolides is suspected.
    - Children under 45 kg body weight: 2.2 mg/kg/day given in two divided doses(Maximum dose 200mg/day)
    - Children with body weight 45 kg or above:100 mg twice daily
    - Duration 10 days

6.8 Melioidosis

6.8.1 Clinical features

Caused by *Burkholderia pseudomallei,* a soil-based gram-negative pyogenic bacterium readily found in paddy fields.

Causes either a localized infection in skin and soft tissue such as abscesses or a more serious septicaemic illness associated with neuromeliodosis leading to fever, headache and seizures altered level of consciousness, cerebellar signs, cranial nerve palsies, limb weakness and hemiparesis.

6.8.2 Serological /Laboratory findings

Detection of antibodies for Melioidosis can be detected in serum.

Can be isolated in blood culture

6.8.3 CSF abnormalities

The Gram stain appearance may give initial clues with Gram negative bacilli with densely staining ends and a pale middle (safety pin appearance)

Definitive diagnosis is by PCR based methods and culture

6.8.4 Management

- Initial intensive therapy: ceftazidime 50mg/kg (up to 2g) IV every 6h for at least 14d or meropenem 25 mg/kg (up to 1 g) IV every 8 h for at least 4-8 weeks. Adding trimethoprim/sulfamethoxazole should be considered for severe brain infections for the duration of the intensive phase.
- Eradication therapy: trimethoprim + sulfamethoxazole 6 + 30 mg/kg (up to 240 + 1200 mg) orally every 12 h for at least 3 months plus folic acid 0.1 mg/kg (up to 5 mg) orally.

Extracted from McLeod C, Morris PS, Bauert PA, Kilburn CJ, Ward LM, Baird RW, Currie BJ. Clinical presentation and medical management of melioidosis in children: a 24-year prospective study in the Northern Territory of Australia and review of the literature. Clinical Infectious Diseases. 2015 Jan 1;60(1):21-6.

Refer to clinical microbiologist and paediatric neurologist early in the management.

6.9 References

1. Guidelines on malaria chemotherapy and management of patients with malaria, Anti-Malaria Campaign, Sri Lanka, 2021 update.
2. Treatment guidelines of NIH, Toxoplasmosis, Sowmya Madireddy; Emanuel D. Rivas Chacon; Rupinder Mangat., 2022.
3. Treatment guidelines of parasitic infections, CDC guidelines, 2018.
4. Joint Formulary Committee. (2017). British national formulary for children 2016-2017. London: BMJ Publishing and the Royal Pharmaceutical Society.
5. Kliegman R. Nelson Textbook of Pediatrics. Edition 21. Philadelphia, PA: Elsevier, 2020.
6. Rauer S, Kastenbauer S, Hofmann H, Fingerle V, Huppertz HI, Hunfeld KP, Krause A, Ruf B, Dersch R. Guidelines for diagnosis and treatment in neurology–Lyme neuroborreliosis. GMS German Medical Science. 2020;18.
7. Bitnun A, Ford-Jones EL, Petric M, MacGregor D, Heurter H, Nelson S, Johnson G, Richardson S. Acute childhood encephalitis and Mycoplasma pneumoniae. Clinical Infectious Diseases. 2001 Jun 15;32(12):1674-84.
8. Spuesens EB, Meyer Sauteur PM, Vink C, van Rossum AM. Mycoplasma pneumoniae infections--does treatment help? J Infect. 2014 Nov;69 Suppl 1:S42-6. doi: 10.1016/j.jinf.2014.07.017. Epub 2014 Sep 26. PMID: 25267596
9. Corea E, Thevanesam V, Perera S, Jayasinghe I, Ekanayake A, Masakorala J, Inglis T. Melioidosis in Sri Lanka: an emerging infection. Sri Lankan Journal of Infectious Diseases. 2012 Jan 31;2(1).

10. Hsu CC, Singh D, Kwan G, Deuble M, Aquilina C, Korah I, Norton R. Neuromelioidosis: craniospinal MRI findings in Burkholderia pseudomallei infection. Journal of Neuroimaging. 2016 Jan;26(1):75-82.
11. Lipsitz R, Garges S, Aurigemma R, Baccam P, Blaney DD, Cheng AC, Currie BJ, Dance D, Gee JE, Larsen J, Limmathurotsakul D. Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei infection, 2010. Emerging Infectious Diseases. 2012 Dec;18(12):e2.
12. Carpenter TC. Corticosteroids in the treatment of severe mycoplasma encephalitis in children. Critical care medicine. 2002 Apr 1;30(4):925-7.
13. McLeod C, Morris PS, Bauert PA, Kilburn CJ, Ward LM, Baird RW, Currie BJ. Clinical presentation and medical management of melioidosis in children: a 24-year prospective study in the Northern Territory of Australia and review of the literature. Clinical Infectious Diseases. 2015 Jan 1;60(1):21-6.

7. MANAGEMENT OF NONINFECTIOUS MENINGITIS IN CHILDREN

7.1 Introduction

Noninfectious meningitis is a type of aseptic meningitis caused by noninfectious conditions. Many cases of noninfectious meningitis are sub-acute or chronic. Overall, these conditions are uncommon. They are not contagious.

Disorders most commonly cause noninfectious meningitis include disorders that cause inflammation such as rheumatoid arthritis and systemic lupus erythematosus (lupus), certain malignancies, antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs),

7.2 Clinical features

Usually, noninfectious meningitis causes symptoms that are similar to those of bacterial meningitis but are milder and may develop more slowly.

7.3 Investigations

CSF findings may include,

- Lymphocytic or neutrophilic pleocytosis
- Elevated protein
- Usually, normal glucose
- Does not contain any infectious agent

Magnetic resonance imaging (MRI) of the brain or computed tomography (CT) is performed based on the clinical need.

7.4 Management / treatment

Treatment of noninfectious meningitis involves treating causative disorders and stopping causative drugs. Otherwise, treatment is supportive.

If patients appear seriously ill, appropriate antimicrobials are started immediately (without waiting for tests results) and continued until acute infections are ruled out (ie, CSF is shown to be sterile

7.5 References

1. Noninfectious Meningitis - Brain, Spinal Cord, and Nerve Disorders - MSD Manual Consumer Version [Internet]. MSD Manual Consumer Version. 2022 [cited 3 July 2022]. Available from: https://www.msdmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/meningitis/noninfectious-meningitis
2. Noninfectious Meningitis - Neurologic Disorders - MSD Manual Professional Edition [Internet]. MSD Manual Professional Edition. 2019 [cited 21 April 2019]. Available from: https://www.merckmanuals.com/professional/neurologic-disorders/meningitis/noninfectious-meningitis
3. Cold F, Health E, Disease H, Disease L, Management P, Conditions S et al. What is Meningitis? [Internet]. WebMD. 2019 [cited 21 April 2019]. Available from: https://www.webmd.com/children/understanding-meningitis-basics

8. MANAGEMENT OF AUTOIMMUNE ENCEPHALITIS IN CHILDREN

8.1 Introduction

Autoimmune encephalitis (AE) is considered one of the most common causes of noninfectious acute encephalitis. This is typically an acute or sub-acute onset disease which may become chronic later. Autoimmune encephalitis presents an immune response against neuronal antigens with production of autoantibodies. This autoimmune process may be triggered by an infection, vaccine, or an occult neoplasm – paraneoplastic (less likely in paediatric age group) or may be cryptogenic.

Anti-neuronal antibodies

Anti-neuronal antibodies are divided into three groups.

(1) Antibodies to intracellular antigens (classic paraneoplastic antibodies) - anti-Hu, anti-Yo, anti-Ma antibodies, etc.

(2) Antibodies to cell-surface antigens - anti- N-Methyl-D-Aspartic Acid (NMDAR) antibodies; Leucine-rich Glioma Inactivated 1 (LGI1) and Contactin-associated protein like 2 (Caspr2) antibodies were collectively known as Voltage Gated Potassium Channel (VGKC) complex antibodies, GABA receptor and AMPA receptor antibodies

(3) Antibodies to intracellular synaptic antigens – Glutamic Acid Decarboxylase (GAD65)

8.2 Clinical spectrum

Autoimmune encephalitis can manifest with several distinct syndromes, complicating its recognition. However, sub-acute onset and a constellation of neuropsychiatric and/or autonomic manifestations (table – 01) should lead the clinician towards a likely diagnosis of AIE.

Table 8.1: Symptoms commonly associated with AIE

- Psychiatric manifestations – psychosis, aggression, panic attacks, compulsive behaviors, euphoria or fear, hallucinations, disinhibition)
- Seizures / status epilepticus (refractory)
- Decreased level of consciousness (unresponsiveness, catatonia or coma)
- Dystonia, chorea

- Hyperekplexia
- Faciobrachial dystonic seizures
- Neuromyotonia, muscle spasms, fasciculations
- New onset type 1 diabetes
- Stiff-person syndrome
- Autonomic disturbances – hypertension, tachycardia and hypoventilation
- Gastrointestinal manifestations – diarrhea, gastroparesis and constipation
- Sleep disruption – severe insomnia, hypersomnia, parasomnia syndromes
- Cranial neuropathies
- Cerebellitis

8.3 Investigation and diagnosis

Diagnosis of AE in a developing child is challenging because of overlap in clinical presentations with other diseases and complexity of normal behavior changes. Therefore, children with clinical presentations suggesting AE will have neuroimaging, EEG, lumbar puncture, and serologic testing for appropriate biomarkers.

8.3.1 Autoantibody screening

Commercial tests for autoantibodies to NMDAR, LGI1, Caspr2, AMPAR (GluR1, GluR2 subunits), GABA-B-R, etc. are currently available. However, commercial kits are not often updated to incorporate new or rare antigens. Hence, negative results do not exclude an autoimmune disorder. Unfortunately, antibody testing laboratories are not easily accessible in many institutions. It is suggested to liaise with the Department of Immunology, Medical Research Institute, Colombo, Sri Lanka for further information regarding auto-antibody screening.

Testing for surface receptor antibodies should always be performed in both serum and CSF of the patients. NMDAR and other cell surface antibody tests are most sensitive and specific with CSF. Serum may offer a low false positive rate and a higher false negative rate.

8.3.2 Imaging

MRI findings are neither sensitive nor specific for AE. In children, FLAIR or T2 hyper intensities in medial temporal lobes, brainstem or, in some cases, subcortical regions, and cerebellum may be present. Gadolinium enhancement is variable.

8.3.3 Electroencephalography (EEG)

An EEG should be performed to exclude non-convulsive seizures. Nonspecific findings of AE are focal or generalized slowing, epileptiform activity and periodic lateralized epileptiform discharges. Generalized rhythmic delta (slow wave) activity with superimposed fast activity (extreme delta brush) is present in some patients with anti-NMDAR. A 24h video-EEG recording may be useful, in differentiating seizures from dyskinesia.

8.3.4 Cerebrospinal fluid (CSF) analysis

CSF analysis should include the cell count, protein, and glucose. Studies to exclude viral infection and other pathogens should also be performed. In AE, CSF may be normal or abnormal, and in these cases, mild elevation of protein (<100 mg/dl) is the most common finding. A minority has a mild lymphocytic pleocytosis (<100 white blood cells/μL) or marked elevation of proteins. In children, elevated CSF neopterin can be used as an additional marker of CNS inflammation.

8.3.5 Electrolytes

Hyponatremia has been noted in up to 90% of these patients with LGI1 autoantibody spectrum disease, at least half being secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Evaluation for malignancy should also be done including chest, abdomen and pelvis imaging depending on the relevance.

8.4 Diagnostic criteria

Following criteria should be applied with caution in children; particularly when they are younger than 5 years.

Table 8.2: Diagnostic criteria for possible autoimmune encephalitis (all three of the following criteria met):

1 – Subacute onset (rapid progression of less than three months) of working memory deficits (short-term memory loss), altered mental status (decreased level of consciousness, lethargy or personality changes), or psychiatric symptoms
2 – At least one of the following: • New focal CNS findings • Seizures not explained by a previously known seizure disorder • CSF pleocytosis (white blood cell count of more than five cells per mm3) • MRI features suggestive of encephalitis
3 – Reasonable exclusion of alternative causes (Table 8.4)

Table 8.3: Criteria for autoantibody-negative but probable autoimmune encephalitis (all four criteria met):
1 – Subacute onset (rapid progression of less than three months) of working memory deficits (short-term memory loss), altered mental status (decreased level of consciousness, lethargy or personality changes), or psychiatric symptoms
2 – Exclusion of well-defined syndromes of autoimmune encephalitis (typical limbic encephalitis, Bickerstaff, brainstem encephalitis, acute disseminated encephalomyelitis)
3 – Absence of well-characterized autoantibodies in serum and CSF, and at least two of the following criteria: MRI abnormalities suggestive of autoimmune encephalitis CSF pleocytosis, oligoclonal bands or elevated CSF IgG index, or both brain biopsy showing inflammatory infiltrates and excluding other disorders
4 – Reasonable exclusion of alternative causes (Table 4)

Table 8.4: Conditions to be excluded before considering possible AIE
CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity, cerebrovascular disease, neoplastic disorders, creutzfeldt-jakob disease, epileptic disorders, rheumatologic disorders (e.g., lupus, sarcoidosis, other), Kleine-Levin, Reye syndrome (children), mitochondrial diseases, inborn errors of metabolism (children)

Extracted from Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis. Frontiers in neurology. 2018:706.

8.5 Treatment

Once the diagnosis of AE is suspected or autoantibody testing is positive, immunotherapy should be started as early as possible, after sufficiently ruling out infectious and oncologic entities. In the management of a child with AE consulting paediatric neurology team is important.

8.5.1 Acute treatment

Immunotherapy

At present, no clinical trials have assessed the optimal treatment in AE. Treatment options for AE range from broadly immune-suppressing agents to those targeting processes in antibody-mediated disease pathogenesis. Combined therapy (coupling steroids with immunoglobulin and/or plasma exchange) may be considered if the initial clinical picture is severe. If an associated tumor is present, specific oncologic treatment is essential. (Figure 1, Table 5)

If there is no clinical or radiological response to optimized first-line therapy after 2–4 weeks the addition of a second-line agent can improve the outcome.

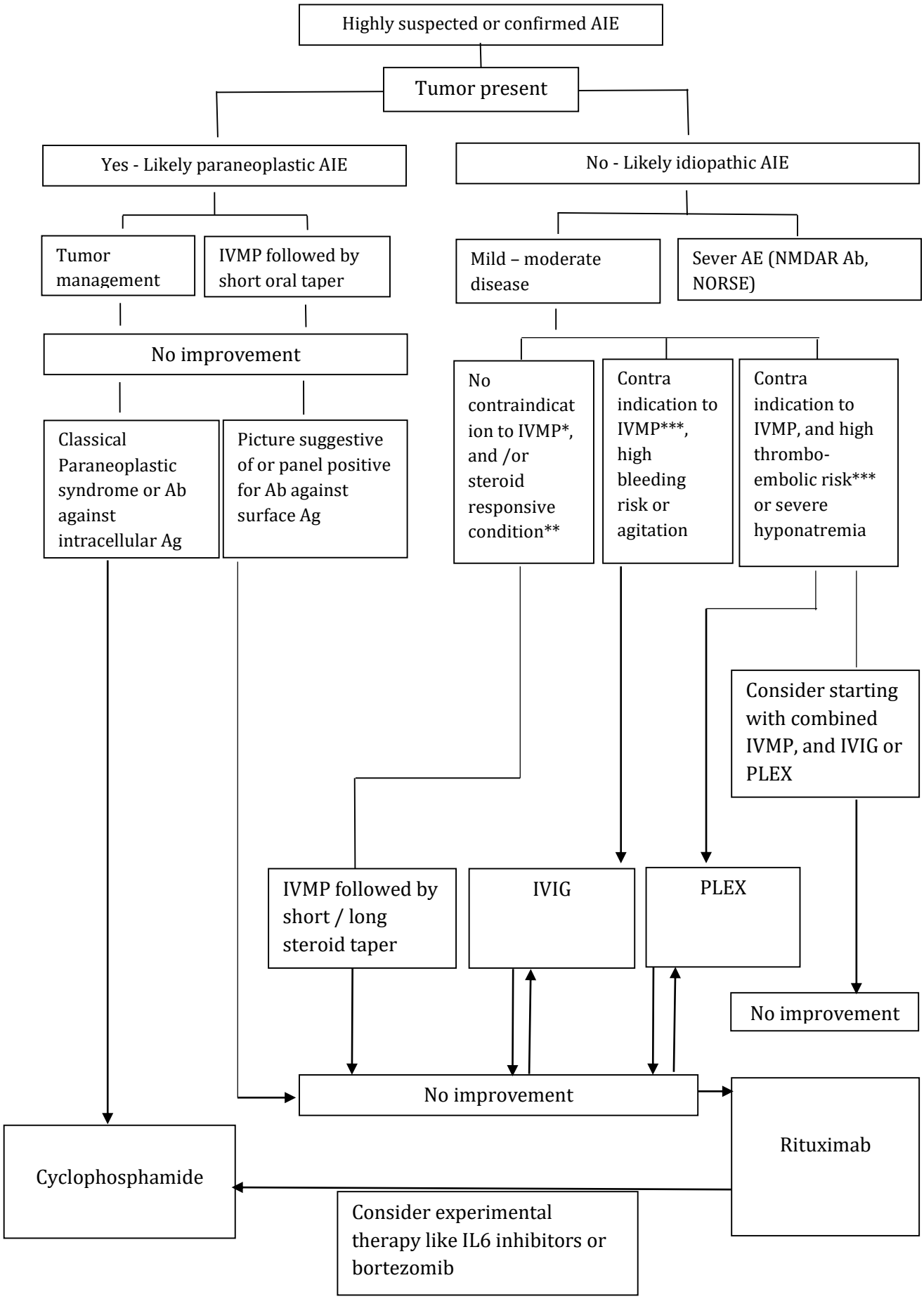

Figure 1. Therapeutic algorithm for autoimmune encephalitis.

*Relative contraindications to steroids include uncontrolled hypertension, uncontrolled diabetes, acute peptic ulcer and severe behavioural symptoms that worsen with corticosteroid therapy. **Steroid-responsive conditions include faciobrachial dystonic seizures suggestive of LGI1-antibody encephalitis, autoimmune encephalitis in the setting of immune checkpoint inhibitors, central demyelination, autoimmune GFAP astrocytopathy, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, and steroid-responsive encephalopathy associated with autoimmune thyroiditis. ***High thromboembolic risk includes patients with known or suspected cancer, smoking history, hypertension, diabetes, hyperlipidaemia and hypercoagulable states. Ab, antibody; AIE, autoimmune encephalitis; Ag, antigen; IVMP, intravenous methylprednisolone; IVIg, intravenous Ig; IL-6: interleukin 6; NORSE, new-onset refractory status epilepticus; PLEX, plasma exchange.

Extracted from Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman M et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurology - Neuroimmunology Neuroinflammation. 2020;7(2):e663.

Table 8.5: First line agents in AIE					
Medication /intervention	**Dose**	**Maximum dose**	**Route**	**Frequency**	**Duration**
Methylprednisolone	30 mg/kg/day	1 g daily	Intravenous	Once daily	3–7 days
Intravenous immunoglobin (IVIg)	2 g/kg		Intravenous	Continuous infusion	Divided over 2–5 days
Plasma exchange (PLEX)	5–10 exchanges			Every other day/daily	Over 10 days
Second line agents					
Medication /intervention	**Dose**	**Maximum dose**	**Route**	**Frequency**	**Duration**
Cyclophosphamide	750(600-1000) mg/m^2		Intravenous	Monthly	3–6 months
Rituximab	375 mg/m^2		Intravenous	Weekly	4 weeks.

- Steroids are tapered using prednisolone 1–2 mg/kg/day orally, on average for another 12 weeks, adjusting the dose according to patient tolerability or possible side effects.

- Rituximab therapy increases the risk of reactivation of chronic viral infections such as hepatitis B, and serologic screening tests should be considered prior to initiation of the treatment.
- Tocilizumab and bortezomib are other possible therapeutic agents.
- Intrathecal administration of methotrexate was reported to be a promising option in pediatric cases with anti-NMDAR encephalitis.

Management of seizures

Antiseizure medications (ASM) are often used in adjunct with immunotherapy, although their overall efficacy is relatively low.

Nevertheless, some evidence suggests that ASMs with sodium-channel blocking properties (eg, Carbamazepine and Lacosamide) may be more effective.

Although those with intracellular neuronal antibodies (eg, GAD65) require lifelong ASM therapy, those with neuronal surface antibodies (eg, NMDAR) may require only short-term therapy.

Currently, the exact duration of ASM therapy for the latter group is not known.

Management of movement disorders

Mild movement may improve with immunotherapy alone. Severe, dangerous or disabling movement disorders will require symptomatic treatment.

Severe dystonia may be treated with anticholinergics or muscle relaxants (eg, trihexyphenidyl, baclofen, respectively)

Myoclonus, stiff person syndrome, rigidity and myoclonus can be treated with benzodiazepines.

Severe chorea, athetosis and ballism can be treated with a cautious use of dopamine-blockers or depleters (eg, risperidone, tetrabenazine, respectively).

Catatonia may respond to intravenous lorazepam and/or electroconvulsive therapy, should be managed with the neuro-psychiatry team.

Management of dysautonomia

In most cases, supportive therapy with continuous monitoring in an ICU setting along with immunotherapy is all that is needed in patients with dysautonomia. Symptomatic treatment with non-selective beta-blockers, alpha-2 agonists and/or acetylcho-linesterase inhibitors may be required to ameliorate sympathetic overactivity on rare occasions.

Management of psychiatric symptoms

Sedative and sleep medications (other than benzodiazepines) seem to be the most effective, while antipsychotic drugs may be difficult to use due to side cardiac, and extrapyramidal side effects and the possibility of reducing seizure threshold.

8.5.2: Chronic treatment

Chronic immunosuppression (e.g., mycophenolate mofetil, azathioprine) should be considered only in AE with a known risk for relapsing. To date, no formal studies have assessed the duration of adequate immunosuppression. Thus, risks versus benefits must be analyzed and discussed with patients and their families. The following strategies can be applied in the management of a relapse or as alternative therapy.

1. Re-administration of first-line immunotherapeutic agents
2. Extended use of second line immunotherapy
3. Long-term maintenance of prednisolone or steroid-sparing agents such as azathioprine and mycophenolate mofetil (MMF)
4. Other monoclonal antibodies targeting B cells (eg. bortezomib, tocilizumab)
5. Proteasome inhibitor Bortezomib
6. IL-6 receptor inhibitors such as tocilizumab,
7. Direct infusion of immune mediators - low-dose IL-2 therapy

8.6 References

1. Lancaster E, Dalmau J. Neuronal autoantigens – pathogenesis, associated disorders and antibody testing. Nature Reviews Neurology. 2012 Jul;8(7):380-90.
2. Barbagallo M, Vitaliti G, Pavone P, Romano C, Lubrano R, Falsaperla R. Pediatric autoimmune encephalitis. Journal of Pediatric Neurosciences. 2017 Apr;12(2):130.
3. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. Journal of Clinical Neurology. 2016 Jan 1;12(1):1-3.
4. Ding JB, Dongas J, Hu K, Ding M. Autoimmune Limbic Encephalitis: A Review of Clinicoradiological Features and the Challenges of Diagnosis. Cureus. 2021 Aug 28;13(8).
5. Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis. Frontiers in Neurology. 2018:706.
6. Cellucci T, Van Mater H, Graus F, Muscal E, Gallentine W, Klein-Gitelman M et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurology - Neuroimmunology Neuroinflammation. 2020;7(2):e663.
7. Lancaster E, Leypoldt F, Titulaer MJ, Honnorat J, Waters PJ, Reindl M, Höftberger R. Immunoglobulin G antibodies to the N-Methyl-D-aspartate receptor are distinct from

immunoglobulin A and immunoglobulin M responses. Annals of Neurology. 2015 Jan;77(1):183.
8. Masdeu JC, GonzáLez-Pinto A, Matute C, Ruiz De Azúa S, Palomino A, De Leon J, Berman KF, Dalmau J. Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia. American Journal of Psychiatry. 2012 Oct;169(10):1120-1.
9. Dahm L, Ott C, Steiner J, Stepniak B, Teegen B, Saschenbrecker S, Hammer C, Borowski K, Begemann M, Lemke S, Rentzsch K. Seroprevalence of autoantibodies against brain antigens in health and disease. Annals of Neurology. 2014 Jul;76(1):82-94.
10. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. The Lancet Neurology. 2011 Jan 1;10(1):63-74.
11. Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. 2012 Sep 11;79(11):1094-100.
12. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, Schott JM, Armstrong RJ, S. Zagami A, Bleasel A, Somerville ER. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Annals of Neurology. 2011 May;69(5):892-900.
13. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, Clover L, Parkinson A, Bien CG, Omer S, Lang B. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain. 2004 Mar 1;127(3):701-12.
14. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA. A clinical approach to diagnosis of autoimmune encephalitis. The Lancet Neurology. 2016 Apr 1;15(4):391-404.
15. Abboud H, Probasco J, Irani S, Ances B, Benavides D, Bradshaw M et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. Journal of Neurology, Neurosurgery and amp; Psychiatry. 2021;92(7):757-768.
16. Martin ST, Cardwell SM, Nailor MD, Gabardi S. Hepatitis B reactivation and rituximab: a new boxed warning and considerations for solid organ transplantation. American Journal of Transplantation. 2014 Apr;14(4):788-96.
17. Nosadini M, Thomas T, Eyre M, Anlar B, Armangue T, Benseler SM, Cellucci T, Deiva K, Gallentine W, Gombolay G, Gorman MP. International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. Neurology-Neuroimmunology Neuroinflammation. 2021 Jul 1;8(5).

18. Tatencloux S, Chretien P, Rogemond V, Honnorat J, Tardieu M, Deiva K. Intrathecal treatment of anti-N-Methyl-D-aspartate receptor encephalitis in children. Developmental Medicine and Child Neurology. 2015 Jan;57(1):95-9.
19. Feyissa AM, Chiriboga AS, Britton JW. Antiepileptic drug therapy in patients with autoimmune epilepsy. Neurology-Neuroimmunology Neuroinflammation. 2017 May 1;4(4).
20. Baizabal-Carvallo J, Jankovic J. Autoimmune and paraneoplastic movement disorders: An update. Journal of the Neurological Sciences. 2018; 385:175-184.
21. Abboud H, Probasco J, Irani S, Ances B, Benavides D, Bradshaw M et al. Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management. Journal of Neurology, Neurosurgery and Psychiatry. 2021;92(8): 897-907.
22. Bost C, Pascual O, Honnorat J. Autoimmune encephalitis in psychiatric institutions: current perspectives. Neuropsychiatric Disease and Treatment. 2016;12:2775.

9. MANAGEMENT OF EOSINOPHILIC MENINGITIS IN CHILDREN

9.1 Introduction

Eosinophilic meningitis (EM) is diagnosed when more than 10% of cells in CSF are eosinophils or when there are more than 10 eosinophils/mm^3 of CSF. Most common causes are parasitic infections, hyper eosinophilic syndrome and neoplasms.

Table 9.1 Causes of eosinophilic meningitis

Adapted from Lo Re and Gluckman (2003)

Bacteria and viruses presenting with EM

- Streptococci
- Coxsackie virus
- Lymphocytic choriomeningitis virus
- Rickettsia
- Rocky mountain spotted fever
- Neurosyphilis
- Tubercular meningitis

Infectious	**Noninfectious**
<u>Parasites</u>	Malignancy
Angiostrongylus cantonensis	Hodgkin lymphoma
Gnathostoma spinigerum	Non-Hodgkin lymphoma
Baylisascaris procyonis	Multiple sclerosis
Ascaris	Eosinophilic leukaemia
Neurocysticercosis (Taenia solium)	<u>Drugs</u>
Cerebral paragonimiasis	Ibuprofen
Onchocerca volvulus	Ciprofloxacin
Echinococcus	Intra ventricular
Neurotrichinosis	Gentamicin
Toxoplasma	Vancomycin
Cerebral toxocariasis	Ventriculoperitoneal shunts
Cerebral/spinal schistosomiasis	Hypereosinophilic syndrome
Some bacteria/virus and fungi (Coccidioidomycosis)	Other prosthetic shunts

9.2 Clinical manifestations

Eosinophilic meningitis of parasitic origin is due to CNS invasion by maggots and larvae. EM has a male predominance (69%) and is more prevalent in adolescence.

Headache is a universal symptom and can last even up to 30 days and is often severe and intermittent with temporal or occipital distribution.

Other manifestations are vomiting, neck stiffness, fever, 6^{th} cranial nerve palsy, 7^{th} cranial nerve palsy, focal numbness or hyperesthesia of lower limbs. Paraparesis or incontinence can result from radiculitis or myelitis.

Concomitant features like creeping skin eruptions, pleurisy, abdominal pain can occur in helminthic infections. These parasites can be acquired by eating raw and under cooked fish and meat products mainly. The incubation period may be as long as 90 days.

9.3 Diagnosis

This condition may be underdiagnosed due to nonspecific clinical features. Diagnosis is most often based on CSF findings and peripheral eosinophilia.

Travel and exposure history is important in presumptive diagnosis. CSF fluid direct visualization is difficult due to low yield. Serologic investigations like ELISA has a place but is limited due to lack of availability and non-specificity. MRI brain can show Virchow-Robin spaces prominence, enhancing lesions in sub cortical region and high T2 abnormal lesions around the peri ventricular area. In addition, some parasitic infections can manifest significant MRI changes.

Eg – Various shapes nodules in gadolinium enhanced images in angiostrongylus infection

9.4 Treatment

Treatment is mainly supportive as EM is usually self-limited. Albendazole can be used to eradicate parasitic organisms.

Steroids have a place in some helminthic infections according to studies in adults though data regarding the use among paediatric population is limited.

9.5 Prognosis

EM is usually having a good prognosis. Mortality is less than 5% in eosinophilic meningitis.

9.6 References

1. Kliegman R. Nelson Textbook of Pediatrics. Edition 21. Philadelphia, PA: Elsevier, 2020.
2. Sawanyawisuth K, Chotmongkol V. Eosinophilic meningitis. Handbook of Clinical Neurology. 2013 Jan 1;114:207-15.
3. Varghese B, Menon MK, Pratap T, Moheen A, Mathew J, Vijayan TP, Tomy MP, Jalal MJ. Eosinophilic meningitis: report of three cases from a hilly area in Kerala. Annals of Indian Academy of Neurology. 2019 Jan;22(1):108.
4. Centers for disease control and prevention chapter on meningitis, 2022 March.
5. Kanpittaya J, Jitpimolmard S, Tiamkao S, Mairiang E. MR findings of eosinophilic meningoencephalitis attributed to angiostrongylus cantonensis. American Journal of Neuroradiology. 2000 Jun 1;21(6):1090-4.
6. Jin EH, Ma Q, Ma DQ, He W, Ji AP, Yin CH. Magnetic resonance imaging of eosinophilic meningoencephalitis caused by Angiostrongylus cantonensis following eating freshwater snails. Chinese Medical Journal. 2008 Jan 5;121(01):67-72.
7. Naotunna C, Vithanage D, Munasinghe T, Fernando A, Samararathna R, Jayawardena P. A case of eosinophilic meningitis. Sri Lanka Journal of Child Health. 2020 Mar 5;49(1).

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