Guideline

Infectious encephalitis: investigation & initial management

Document ID	CHQ-GDL-60818		
Version No.	2.0		
Risk Rating	Medium		
Primary Document	N/A		
Custodian	Director, Infection Management and Prevention service	**Approval date**	02/05/2025
Accountable Officer	Executive Director Medical Services	**Effective date**	09/05/2025
Applicable to	All clinical staff at CHQ	**Review date**	02/05/2029

Standard 3
Preventing and Controlling Infections

HUMAN RIGHTS

This governance document has been human rights compatibility assessed. No limitations were identified indicating reasonable confidence that, when adhered to, there are no implications arising under the *Human Rights Act 2019.*

PURPOSE

This guideline aims to optimise the assessment, investigation, and initial management of infectious encephalitis in children.

SCOPE

This guideline provides information for all Queensland Health employees (permanent, temporary, and casual) and all organisations and individuals acting as its agents (including Visiting Medical Officers and other partners, Contractors, Consultants, and Volunteers).

GUIDELINE

INTRODUCTION

Encephalitis is a syndrome of neurological dysfunction caused by inflammation of the brain parenchyma. Encephalopathy is a clinical syndrome of altered mental status, manifesting as reduced level of consciousness, altered cognition and/or personality and behavioural changes.

The diagnosis of encephalitis is usually based on the presence of acute central nervous system (CNS) dysfunction, fever and/or signs of inflammation in the cerebrospinal fluid (CSF) and/or neuroimaging (Table 1). Encephalitis in children can be caused by numerous infectious and non-infectious causes. The Australian Childhood Encephalitis (ACE) study is the most comprehensive study evaluating childhood encephalitis in Australia (2). It showed that the most common causes of infectious encephalitis in children are enterovirus (10%) and parechovirus (10%, only in children <1 year), followed by influenza (6%), herpes simplex virus (HSV) (6%) and *Mycoplasma pneumoniae* (6%) (2). Amongst the immune-mediated causes, ADEM and anti-NMDA receptor encephalitis were the most common causes (2).

This guideline provides guidance for clinicians in their initial investigation and management of potential infectious encephalitis. It also provides further guidance on empiric prescription of intravenous (IV) aciclovir for suspected neonatal HSV or HSV encephalitis in children.

Table 1: Diagnostic criteria for encephalitis and encephalopathy

Major criteria (required)
Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥ 24 hours with no alternative cause identified
Minor criteria (2 required for possible encephalitis, ≥ 3 required for probable or confirmed encephalitis)
Documented fever ≥ 38°C within the 72 hours before or after presentation
Generalised or focal seizures not fully attributable to a pre-existing seizure disorder
New onset of focal neurologic findings
CSF WBC count ≥ 5 cells/mm^3
Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause
AND exclusion of encephalopathy caused by trauma, metabolic disturbance, tumour, alcohol abuse, sepsis and other non-infectious causes

Flowchart 1: Investigation and empiric management for infectious encephalitis

The child fulfils the diagnostic criteria for possible or probable encephalitis, with exclusion of encephalopathy caused by other non-infectious causes (see **Table-1 "Diagnostic criteria for encephalitis & encephalopathy"**)

Initial investigation recommendations:

CSF (need for additional CSF for multiple tests, liaise with lab re required volume): Opening pressure; cell count, gram stain; culture and sensitivities; glucose; protein; lactate; PCR for *S. pneumoniae*, *N. meningitidis,* HSV, varicella, enterovirus, HHV6/7, *M. pneumoniae*, EBV; cryptococcal antigen & India ink stain, Parechovirus PCR in infants < 6 months of age, consider cytology

- If CSF eosinophilia present test for *Angiostrongylus cantonensis PCR* and *Angiostrongylus* IgG on CSF (sent to Westmead)
- One tube for storage/further investigations (e.g if immune causes are considered in the early phase based on history, anti-NMDA Antibodies, Oligoclonal bands, Auto-immune panel can be added – seek guidance from Neurology)

Blood: FBC, EUC, LFTs, CRP, glucose, blood gas, lactate, ammonia, blood culture, serology for: EBV, *M. pneumoniae*, ASOT and serum to store. Consider parechovirus PCR in infants <6 months of age and HSV PCR in neonates (<1 month).

- If CSF eosinophilia present perform *Angiostrongylus* serology
- One tube for storage/further investigations (e.g if immune causes are considered in the early phase based on history, anti-NMDA Antibodies, Auto-immune panel can be added – seek guidance from Neurology)

Stool: Consider viral PCR for enterovirus, parechovirus (<6 months) and adenovirus regardless of GIT symptoms, particularly where CSF is negative and there is a high clinical suspicion for enterovirus or parechovirus (<6 months). MC+S and rotavirus [if diarrhoeal illness].

Vesicles (if any): Swab for culture, HSV-1, HSV-2, varicella PCR and enterovirus PCR. Consider *Rickettsial* PCR if exposure to ticks in past 7 days.

Nasopharyngeal aspirate/throat swab: PCR for respiratory virus panel, *M. Pneumoniae*, enterovirus and SARS Cov2.

Imaging: MRI brain to include T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast

EEG: If chronic symptoms, psychiatric presentation, mildly altered behaviour or concern re subclinical seizures

Empiric management recommendations: Administration of antibiotics and aciclovir should be commenced within 60 minutes of presentation and should not be delayed if LP is contraindicated.

Less than one month old: Ampicillin IV (or Amoxicillin IV) AND Cefotaxime IV AND Aciclovir IV

- Refer to neonatal dosing for Ampicillin (or Amoxicillin), Cefotaxime and Aciclovir on ANMF monographs if <1 month of age

More than one month old: Cefotaxime IV (or Ceftriaxone IV) AND Aciclovir IV (consider azithromycin in consultation with ID) as per CHQ Antibiocard

If encephalitis is likely but initial investigations are inconclusive, **second line investigations** should be guided by risk factors, clinical & radiological features (progress to second line investigations as listed below **AND** consult neurology and infectious diseases).

Second line investigations (all children):

CSF: JEV PCR and Flavivirus IgM to CSF (at least 1 ml). PCR for CMV, EBV, HHV6/7, LCMV, adenovirus, Fungal culture, Acid fast bacilli staining, mycobacterial culture. Consider measles PCR (if unvaccinated)

- CSF HSV PCR may be falsely negative within 72 hours of symptom onset. For persistent symptoms of unknown cause, consider repeating CSF HSV PCR after 72 hours, especially before stopping aciclovir.

Blood: Add JEV PCR to serum & do flavivirus IgM (convalescent serology should be completed) (need 2-5mls). Serology for varicella, measles (unvaccinated), *Bartonella henselae*, syphilis, PCR for CMV, EBV, HHV6, adenovirus, HIV immunoassay +/- viral load

If less than one month old	CSF: PCR for CMV, Listeria monocytogenes (available on request at Pathology Queensland via Biofire FilmArray ME panel), *Treponema pallidum* (Syphilis) and VDRL (if serology positive). Consider PCR for *Toxoplasma* (available on request at Mater laboratory) Blood: Syphilis serology, Consider HIV serology +/- HIV pro-viral DNA
If immunocompromised	CSF: *Toxoplasma gondii,* Consider PCR for JC virus (if PML present) and BK virus Blood: Serology for *Toxoplasma gondii*
If returned traveller/ tropical Australia (specific to region of travel) or specific risk factors (animal contact)	CSF: *Flavivirus* PCR (discuss with laboratory for specific target), Amoebic PCR (only available at S&N at this stage), Australian bat lyssavirus (ABLV) PCR Saliva: ABLV bat lyssavirus PCR Blood: 3 thick/thin malaria films, rapid malaria antigen test, Serology for *Rickettsial* diseases, *Leptospira*, *Brucella*, *Strongyloides*, Schistosomiasis, *Burkholderia pseudomallei,* Serology for HIV if patient(s) from high endemic country, Leptospirosis PCR if <10 days of symptoms and high clinical suspicion. Flavivirus serology (Zika, Murray Valley Encephalitis, Kunjin, Stratford, JEV). PCR if high suspicion (please discuss with laboratory).

EMPIRIC ACICLOVIR FOR SUSPECTED HSV ENCEPHALITIS

A recent review of aciclovir prescribing for suspected HSV disease in neonates and children in Australia and New Zealand found frequent and often unnecessary use of IV aciclovir for suspected HSV encephalitis in older children, as shown by incomplete HSV investigations and only 0.6% having a confirmed diagnosis (3). Empiric aciclovir prescribing in neonates was generally consistent with guideline recommendations (3). By contrast, microbiological investigations for HSV in neonates were incomplete (3). Investigations and empiric management recommendations for suspected infective encephalitis are provided in Flowchart-1, however further guidance on when to stop IV aciclovir and when not to start is provided below.

WHEN TO STOP IV ACICLOVIR?

- If there is no ongoing clinical suspicion of HSV encephalitis (a definitive alternative diagnosis becomes apparent, or it seems very unlikely that the patient has HSV encephalitis).
- Aciclovir may be stopped if a negative HSV PCR result is obtained (on CSF +/- serum in a neonate +/- swab in children with suspected concurrent mucocutaneous disease) **AND** there is a low clinical suspicion of HSV encephalitis.

WHEN NOT TO START?

- Child with simple febrile convulsions
- Other obvious cause for symptoms e.g. blocked VP shunt, child with epilepsy (who has an increase in seizures with a febrile illness), acute head injury, drug overdose.
- CSF and clinical picture are highly suggestive of bacterial meningitis.

SUPPORTING DOCUMENTS

STANDARDS:

- National Safety and Quality Health Service (NSQHS) Standards

SUPPORTING DOCUMENTS:

- CHQ Paediatric Antibiocard: Empirical Antimicrobial Guideline
- Empiric Antimicrobial Guidelines for Paediatric Intensive Care Unit (PICU)
- CHQ-PROC-01036 Antimicrobial: Prescribing and Management
- CHQ Antimicrobial restrictions
- CHQ-PROC-60579 Infiltration and Extravasation - Prevention, Recognition, Management and Treatment
- CHQ-GDL-60008 Meningitis - Emergency management in children

CONSULTATION

Key stakeholders who reviewed this version:

• Director, IMPS, Immunology/Allergy and Rheumatology, CHQ • Paediatric Infection Specialists and Fellow, IMPS, CHQ • Paediatric Infection Specialist Consultant, Gold Coast University Hospital	• Pharmacist Advanced – Antimicrobial Stewardship, CHQ • Clinical Microbiologist, Pathology Queensland and Mater Pathology • Paediatric neurology, CHQ • Medicines Advisory Committee – endorsed 17/04/2025

DEFINITIONS

Term	Definition
ABLV	Australian bat lyssa virus
ADEM	Acute disseminated encephalomyelitis
CMV	Cytomegalovirus
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
EBV	Epstein Barr virus
EUC	Electrolytes, urea and creatinine
FBC	Full blood count
GIT	Gastro-intestinal tract
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
HSE	Herpes simplex virus encephalitis
HHV-6	Human herpes virus 6
IgG	Immunoglobulin G
IV	Intravenous
JEV	Japanese encephalitis virus
LFTs	Liver function tests
MCS	Microscopy, culture and susceptibility
MRI	Magnetic resonance imaging

PCR	Polymerase chain reaction
QCH	Queensland Children's hospital
S&N	Sullivan and Nicolaides Laboratory
WBC	White blood cell count
VDRL	Venereal disease research laboratory test
VP	Ventriculo-peritoneal (shunt)
VZV	Varicella Zoster virus

REFERENCES

No.	Reference
1	Britton PN, Eastwood K, Paterson B, Durrheim DN, Dale RC. (2015). Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Internal Medicine Journal, 45: 565-576. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1111/imj.12749
2	Britton PN, Dale RC, Blyth CC et al Causes and Clinical Features of Childhood Encephalitis: A Multicenter, Prospective Cohort Study. Clin Infect Dis. 2020 Jun 10;70(12):2517-2526
3	Berkhout A, Clark JE, Jones CA, Grimwood K, McMullan B, Britton PN, Palasanthiran P, Lim S, Yeoh DK, Wong S, Cheng DR, Gwee A, Cross J, Nguyen T, Jeffs E, Walls T, Mahony M, Yan J, Nourse C. Parenteral aciclovir for suspected herpes simplex virus infection in children: 0-18 years. J Antimicrob Chemother. 2024
4	Teutsch S, Berkhout A, Raynes-Greenow C, Zurynski Y, Britton PN, Jones CA; APSU Neonatal HSV study advisory group. Characteristics of neonatal herpes simplex central nervous system disease in Australia (1997-2020). J Clin Virol. 2023 Aug;165:105526
5	Berkhout A, Kapoor V, Heney C, Jones CA, Clark JE, Britton PN, Vaska VL, Lai MM, Nourse C. Epidemiology and long-term neurological sequelae of childhood herpes simplex CNS infection. J Paediatr Child Health. 2022 Aug;58(8):1372-1378
6	Kneen R, Michael BD, Menson E, Mehta B, Easton A, et al. Management of suspected viral encephalitis in children- Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines. Journal of Infections, 2012: 64: 449-447.
7	Thompson C, Kneen R, Riordan A, Kelly D, Pollard A. (2012). Encephalitis in children. Arch Dis Child, 97:150-161
8	Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, et al. (2008). The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America, 7: 303-327.
9	Venkatesan A, Tunkel AR, Bloch KC, et al. (2013). Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus Statement of the International Encephalitis Consortium. Clinical Infectious Diseases, 57(8):1114-28.
10	Australasian Neonatal Medicines Formulary. [Available online: https://www.anmfonline.org/clinical-resources/] Accessed 07/09/2022.

GUIDELINE REVISION AND APPROVAL HISTORY

Version No.	Modified by	Amendments authorised by	Approved by	Comments
1.0 07/03/2022	Infectious Diseases SMO	Director IMPS	Executive Director Medical Services	
2.0 02/05/2025	Infectious Diseases SMO Director, IMPS Pharmacist Advanced - AMS	CHQ Medicines Advisory Committee	Executive Director Medical Services	

Key words	Children, Encephalitis, Investigation, Initial infection Management, Aciclovir, 60818
Accreditation references	NSQHS Standards (1-8): • 3 Preventing and Controlling Healthcare-Associated Infection • 4 Medication Safety