Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand

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Abstract
Encephalitis is a complex neurological syndrome caused by inflammation of the brain parenchyma. The management of encephalitis is challenging because: the differential diagnosis of encephalopathy is broad; there is often rapid disease progression; it often requires intensive supportive management; and there are many aetiologic agents for which there is no definitive treatment. Patients with possible meningoencephalitis are often encountered in the emergency care environment where clinicians must consider differential diagnoses, perform appropriate investigations and initiate empiric antimicrobials. For patients who require admission to hospital and in whom encephalitis is likely, a staged approach to investigation and management is preferred with the potential involvement of multiple medical specialties. Key considerations in the investigation and management of patients with encephalitis addressed in this guideline include: Which first-line investigations should be performed?; Which aetiologies should be considered possible based on clinical features, risk factors and radiological features?; What tests should be arranged in order to diagnose the common causes of encephalitis?; When to consider empiric antimicrobials and immune modulatory therapies?; and What is the role of brain biopsy?

Introduction
Encephalitis is a complex condition caused by brain inflammation that is challenging to manage. The diagnosis is rarely confirmed by brain biopsy and instead is inferred by the presence of acute central nervous system (CNS) dysfunction, fever and/or inflammation in the cerebrospinal fluid (CSF) and/or on neuroimaging.1 Differentiation from encephalopathy due to other causes is difficult. There is a wide variety of presentations and a myriad of possible aetiologies but in most cases a cause is not identified.2,3 There is often no definitive treatment1,5 and a high rate of mortality and morbidity.4 The investigation and management of encephalitis worldwide are of

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variable quality. While several international guidelines exist and the International Encephalitis Consortium included Australian authors, a concise guideline for Australian and New Zealand clinicians is required due to differences in the epidemiology of encephalitis.

**Methods**

We reviewed the literature and sought expert opinions in the development of the Consensus guidelines. The guidelines were peer reviewed by the Australasian Society for Infectious Diseases Encephalitis Special Interest Group and Guidelines Committee, the Public Health Association of Australia (PHAA), the Australian and New Zealand Association of Neurologists (ANZAN), and the Australasian College of Emergency Medicine (ACEM).

**Epidemiology**

In Australia, the annual hospitalisation rate for encephalitis has been calculated as 5.2/100 000 and case fatality rate is estimated to be 4.6%. The highest admission rates are observed in males, and those aged less than 9 or over 60 years of age. This is similar to international findings.

**Case definition**

The international case definition of encephalitis (Box 1) requires the presence of altered mental status lasting at least 1 day, and exclusion of encephalopathy from other causes (Box 2). Confirmed diagnosis requires meeting additional criteria such as CSF pleocytosis, neuroimaging and electroencephalography (EEG) changes consistent with encephalitis, and the presence of seizures and new onset of focal neurological signs. Of note, in individual cases, expected features of encephalitis such as headache, fever and CSF pleocytosis may be absent.

**Aetiology**

Multiple infectious agents have been associated with encephalitis, but the syndrome is an uncommon manifestation of most. Viruses are the most commonly identified agent in all settings. Immune-mediated aetiologies are increasingly recognised in up to one third of cases, and are important because they are often treatable.

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**Box 1 Encephalitis case definition from the international encephalitis consortium**

**Major Criterion** (required):
Patients presenting to medical attention with altered mental status – defined as decreased or altered level of consciousness, or lethargy or personality change – lasting ≥24h.

**Minor Criteria** (2 for possible encephalitis; ≥3 for probable or confirmed encephalitis):
1. Documented fever ≥38°C (100.4°F) within the 72h before or after presentation.
2. Generalised or partial seizures not fully attributable to a pre-existing seizure disorder.
3. New onset of focal neurologic findings.
4. CSF WBC count ≥5/mm³.
5. Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset.
6. 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.

**Box 2 Selected differential diagnoses of suspected meningo-encephalitis**

- Meningitis without parenchymal involvement: bacterial, viral, other (e.g. TB, cryptococcus).
- Cerebral abscess and other forms of intra-cranial suppuration.
- Infection associated encephalopathy (e.g. septic encephalopathy, acute necrotising encephalopathy (ANE)).
- Vascular disease: ischaemic/haemorrhagic cerebro-vascular accident (CVA), cerebral vasculitides (e.g. systemic lupus erythematosus).
- Hypertensive encephalopathy including posterior reversible encephalopathy syndrome (PRES).
- Neoplastic: primary CNS or metastatic, haematologic malignancies.
- Toxin induced encephalopathy: alcohol, illicit drugs, other drugs (especially neuroleptics, cyclosporin).
- Neurodegenerative: fronto-temporal dementia, Creutzfeld-Jacob disease (other prion disease), neuroacanthocytosis.
- Demyelinating disease: multiple sclerosis (MS), neuromyelitis optica (NMO or Devic disease).
- Endocrine: Hashimoto’s encephalopathy, steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), Addisonian crisis.
- Psychiatric: psychosis, catatonia.
- Seizure disorder.
- Traumatic brain injury.
- Intussusception.
### Box 3 Selected immune-mediated encephalitides

**ADEM**

Acute disseminated encephalomyelitis is an inflammatory, multi-focal, demyelinating condition of the central nervous system. It presents with encephalopathy and multi-focal neurological deficits. It is most common in children (mean age 5–8 years old), with a slight male predominance. Rarely it may occur in adults. A temporal association following infection or, less commonly, vaccination is often identified. Magnetic resonance imaging (MRI) is central to the diagnosis. Features include multi-focal, high signal lesions most evident on T2 weighted and fluid-attenuated inversion recovery (FLAIR) sequences involving the sub-cortical, central and periventricular white matter and deep grey matter. Approximately one quarter of children with ADEM will have serum antibodies to myelin oligodendrocyte glycoprotein (MOG). Persistence of anti-MOG IgG is associated with recurrent central nervous system demyelination in this group. Corticosteroids are the established first-line therapy, with other immune-modulatory therapies used in refractory cases. Acute haemorrhagic leukoencephalopathy (AHLE) is a rare, hyper-acute form of ADEM that overlaps with cerebral vasculitis.

**Anti-N-methyl-D-aspartate receptor (NMDAR)**

Anti-N-methyl-D-aspartate receptor encephalitis has been shown to be one of the principal causes of encephalitis in recent large prospective studies. It typically presents with psychiatric symptoms, seizures, memory loss and mutism. The syndrome evolves to include movement disorders, dysautonomia and sometimes hypoventilation. Although initially described as a para-neoplastic disorder with ovarian teratoma in young adults (usually female), this tumour association is uncommon in young children where the female gender predominance is also less pronounced. MRI is most often normal. It is diagnosed by identifying CSF or serum antibodies against the NR1 subunit of the NMDA receptor. Anti-NMDAR can be identified in a proportion of relapsing HSV encephalitis, in particular if associated with chorea. Immuno-modulatory therapy improves outcomes.

**Anti-VGKC**

Anti-voltage-gated potassium channel-complex (including antibodies against leucine-rich glioma-inactivated 1 protein (Lgi1) and contactin-associated protein 2(Casp2)) encephalitis includes a broad clinical spectrum. In adults it typically presents in older male (>40 yrs) patients with ‘limbic encephalitis’; sub-acute evolution of memory loss, confusion, medial-temporal lobe seizures and psychiatric features; hyponatraemia is common. Lgi1 antibodies are often identified and it is rarely associated with malignancy. In children it presents as temporal lobe focal seizures, *status epilepticus* and encephalopathy (behavioural disturbance, hallucinations) and cognitive decline. Specific Lgi1 or Casp2 antibodies may not be identified. Diagnosis is by identifying serum antibodies that bind to the VGKC-complex, although low titre antibodies are of questionable significance. Immuno-modulatory therapy should probably be similar to NMDAR encephalitis although there is less evidence.

**Para-neoplastic ‘limbic encephalitis’**

‘Limbic encephalitis’ (see above for clinical features) occurring in adults is often associated with malignancy. The encephalitis may occur prior to the diagnosis, or during the course of cancer treatment. The tumours most often associated with limbic encephalitis are small cell lung carcinomas (SCLC), testicular germ cell tumours, breast cancer, ovarian teratoma, Hodgkin lymphoma and thymoma. The most commonly identified antibodies in this group are against intracellular neuronal antigens: anti-Hu, anti-Ma2(Ta), anti-CV2/CRMP5, and anti-ampiphysin. A spectrum of neurological syndromes may overlap with ‘limbic encephalitis’ including features of brainstem encephalitis, basal ganglia syndromes, cerebellar ataxia and peripheral neuropathies. Specific antibodies associate with specific tumours, clinical features and neurological outcome; for example, anti-Hu with SCLC, isolated limbic encephalitis and poorer prognosis, and anti-Ma2 with testicular tumour, brainstem features and better prognosis. Treatment is directed towards the underlying tumour; immuno-modulatory treatments are often used adjunctively.

**Other**

Increasing numbers of serum auto-antibodies are being associated with paraneoplastic and non-paraneoplastic limbic encephalitis. These include: anti-Ri, anti-Yo, anti-glutamic acid decarboxylase (GAD), anti-gamma-aminobutyric acid B receptor (gAB-A-B-R), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), anti-glycine receptor (GlyR), anti-dipeptidyl-peptidase-like protein-6 (DPXP), anti-metabotropic glutamate receptor 5 (mGlu-R5). An algorithm addressing approaches to testing and management has been recently published.

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These include acute disseminated encephalomyelitis (ADEM), primarily seen in children and antibody-mediated encephalitides (e.g. anti-N-methyl-D-aspartate receptor (NMDAR) and anti-voltage-gated potassium-channel (VGKC) complex). Aetiology varies with age, immune status, geography, climate and population endemicity, and has changed over time due to changes in immunisation, changing behaviours (Box 4), improved testing and discovery of novel aetiologies. Herpes simplex virus (HSV), varicella zoster virus (VZV), toxoplasma, ADEM and enteroviruses are the most commonly identified encephalitides from studies based on hospital admission records. These studies also demonstrate that deaths from toxoplasmosis, HSV and measles-related encephalitis and subacute sclerosing panencephalitis (SSPE) have declined in recent decades. A confirmed laboratory diagnosis is frequently not obtained. Almost 70% of cases in a retrospective Australian study did not have an identified aetiology, although
Clinical, risk factor and radiologic pointers to direct targeted investigation

Clinical features

- Psychosis, movement disorder, hypoventilation: anti-NMDAR.
- Cognitive dysfunction, seizures: anti-VGKC, anti-NMDAR, HSV, HHV6, anti-GAD, anti-Hu, anti-Ma (other antibody mediated see Box 3).
- Subacute behavioural/personality change: HSV, anti-NMDAR, anti-VGKC, HIV, *Treponema pallidum* (syphilis), Whipple disease, trypanosomiasis, SSPE, anti-GAD, anti-Hu, anti-Ma (other antibody mediated see Box 3).
- Hydrophobia, hypersalivation, delirium: rabies, ABLV.
- Parkinsonian features: flaviviruses (esp. JEV), anti-DR2 (basal ganglia encephalitis).
- Acute encephalopathy: enteroviruses (esp. EV71), flaviviruses (esp. MVEV, JEV, KUNV), Nipah, *Listeria monocytogenes*, *Burkholderia pseudomallei*, MTB, anti-Hu, anti-Ma (other paraneoplastic see Box 3).
- Associated limb weakness (flaccid paralysis) or tremor: enteroviruses (esp. EV71, poliovirus), flaviviruses.
- Parotitis, testicular pain: mumps.
- Cervical lymphadenopathy: EBV, CMV.
- SIADH: anti-VGKC, SLEV†.
- Chronic symptoms: HIV, JCV, BKV, trypanosomiasis, SSPE, T. pallidum (syphilis), Whipple disease.

Risk factors

- Infant/Child: HSV, VZV, enteroviruses, HHV6/7, M. pneumoniae, EBV, parechovirus, *Bartonella* sp., ADEM.
- >60 years: *L. monocytogenes*, VZV, HSV.
- Female: anti-NMDAR.
- Immunocompromised patient: HHV6, CMV, EBV, measles, VZV, LCMV, toxoplasma, cryptococcus, JCV, BKV, *Bartonella* sp.
- Tropical Australia: JEV, dengue, MVEV, KUNV, *B. pseudomallei*.
- Travel history‡
  - Asia: JEV, dengue, malaria, MTB, Nipah, *Angiostrongylus cantonensis*.
  - Pacific: JEV, dengue, malaria, MTB, *Angiostrongylus cantonensis*.
  - North America: WNv, LACV, SLEV, EEEV,eneforoborrelia, *Rickettsia rickettii* (RMSF), ehrlichiosis (HME), anaplasmosis (HGA), babesiosis, coccidiodymycosis.
  - South America: WNV, VEEV, dengue, MTB, trypanosomiasis (Chagas).
  - Europe: TBEV, TOSV, neuroborreliosis, anaplasmosis (HGA).
  - Africa: malaria, trypanosomiasis, MTB.
- Animal exposure
  - Monkeys: herpes B, rabies†.
  - Bats: rabies†, ABLV.
  - Dogs and other canids outside Australia: rabies.
  - Cats: Bartonella henselae.
  - Horse: Hendra, KUNV.
  - Rodents: LCMV, leptospirosis.
  - Snails/other moluscs: *Angiostrongylus cantonensis*.
  - Swine: Nipah.
  - Mosquito or Tick bite history.
- Recreational
  - Sexually transmitted: HIV.
  - Fresh water§: leptospirosis, *Naegleria fowleri*.
  - Soil/mud§: *Balamuthia mandrillis*.
- Occupational
  - Animal husbandry, farming: *C. burnetii* (Q fever), leptospirosis.
  - Ablatoir workers: *C. burnetii* (Q fever).
  - Unvaccinated: measles, mumps, rubella, VZV.
testing for immune-mediated and vector-borne causes was limited. Rigorous implementation of systematic testing will likely reduce this proportion but in many cases the cause will remain unknown. In Australia, endemic viruses, including Hendra virus, Australian bat lyssavirus (ABLV), Murray Valley encephalitis virus (MVEV) and West Nile virus (WNV) (Kunjin clade (KUNV) – WNV/KUNV), should be considered as possible aetiologies as well as regional infections such as Japanese encephalitis virus (JEV), enterovirus 71 (EV71), dengue and Nipah virus. Key differences to note when applying this guideline in New Zealand are that there are currently no endemic flaviviruses, nor are Hendra virus, ABLV and Q fever endemic. Novel agents, particularly viruses, or a changing geographical distribution of diseases should be considered where unexplained encephalitis clusters occur.

Causality

Experts agree that identification of an infectious agent that is an established cause of encephalitis from a CNS specimen is strong evidence of causality. Identification of an encephalitic infectious agent outside of the CNS is less conclusive. Identification of a specific antibody response within the CSF in temporal association with an episode of encephalitis is more convincing evidence of causality than identification of a systemic antibody response, especially on a single specimen. Causality may be classified as confirmed/definite, probable or possible to reflect the level of evidence achieved. Investigation of patients may require specimens from multiple sites, with repeated sampling for pathogen identification and to identify a specific serologic response. This is necessary to avoid missing treatable causes, especially where there are two or more potential infectious agents and/or autoantibodies.

Clinical assessment

We present two algorithms to assist clinicians with diagnosis and management. The first (Fig. 1) will assist clinicians to: identify possible meningocencephalitis patients, consider differential diagnoses, initiate empiric acyclovir and antibiotic therapy, and discriminate between patients in whom encephalitis can be excluded from those where a more rigorous assessment is required. Table 1 details first-line investigations. The second algorithm (Fig. 2) follows on from the first and is applied when encephalitis is likely. It provides a multidisciplinary, staged approach to investigation and management.

History

Collecting a comprehensive history is essential to enable a diagnosis. The onset and evolution of altered consciousness, lethargy, cognition, behaviour or personality change, seizures, weakness, abnormal movements and

Box 4 Continued

Radiologic features

- Brainstem: enteroviruses (esp. EV71), MVEV, JEV, WNV, nipah†, B. pseudomallei, L. monocytogenes, anti-NMO (anti-AQP4), anti-Hu, anti-Ma (other paraneoplastic see Box 3).
- “Limbic”: HSV, HHV6, anti-NMDAR, anti-VGKC, anti-GAD, anti-Hu, anti-Ma (other antibody mediated see Box 3).
- Cerebellum: EBV, VZV, enteroviruses, M. pneumonic.
- Subcortical grey matter (basal ganglia, thalami): EBV, flaviviruses (esp. JEV, MVEV), influenza, MTB, post-streptococcal, M. pneumonic, anti-DR2.
- Frontal lobe: N. fowleri, B. mandrillis.
- “Vasculitic”: VZV, systemic lupus erythematosis (SLE) and other cerebral vasculitides.
- White matter lesions: ADEM, JCV-PML.

†If travelled to an endemic region. Other important aspects of the travel history include the season (especially spring/summer for vector borne pathogens) and specific activities engaged in. §In New Zealand natural geothermal pools pose a particular risk for amoebic meningoencephalitis, particularly where there is the direct contact of the water with soil or run-off of water into the pool from soil.

ABLV, Australian bat lyssavirus; ADEM, acute disseminated encephalomyelitis; CMV, cytomegalovirus; CTFV, Colorado tick fever virus; DR2, dopamine-2 receptor; EBV, Epstein-Barr virus; EEEV, eastern equine encephalitis virus; GAD, glutamic acid decarboxylase; HGA, human granulocytic anaemia; HHV6, human herpes virus-6; HIV, human immunodeficiency virus; HME, human monocytic encephalitis; HSV, herpes simplex virus; JCV, John Cunningham virus; JEV, Japanese encephalitis virus; KUNV, Kunjin virus; LACV, La Crosse virus; LMIC, lymphocytic choriomeningitis virus; MTB, Mycobacterium tuberculosis; MVEV, Murray valley encephalitis virus; NMDAR, N-methyl-D-aspartate receptor; NMO, neuromyelitis optica (AQP4, aquaporin-4); RMSF, Rocky Mountain spotted fever; SLE, St Louis encephalitis virus; SSPE, sub-acute sclerosing panencephalitis; TBEV, tick borne encephalitis virus; TOSV, Toscana virus; VEEV, Venezuelan equine encephalitis virus; VGKC, voltage-gated potassium channel; VZV, varicella zoster virus; WNV, West Nile virus.
Altered sensation should be elicited and any localization (locality) recorded. Details of current or recent fever, headache, rash or any other prodromal illness, and an exposure history should be sought including contact with sick persons, immunisation history, travel, mosquito, tick or other insect bites, animal exposures (wild, farm or domestic), and occupation and outdoor activities (e.g. hiking, camping, water sport). Public health authorities should be consulted about seasonal/epidemic activity of infectious agents (e.g. flaviviruses and other arboviruses, enteroviruses).

Risk factors (Box 4) including age, immunisation and immune status (e.g. immune suppressive treatment, immunodeficiency virus (HIV) risk factors) should be considered.

### Examination

Physical examination should include an objective assessment of the level of consciousness, and look for subtle seizure activity, meninges, abnormal movements (e.g. chorea, parkinsonism), weakness, sensory loss and cranial nerve involvement (including deafness and anosmia), noting any focal findings and for features suggesting other diagnoses (Box 2). Temperature and other vital signs should be assessed for features of raised intracranial pressure or autonomic dysfunction. Mental status examination should be recorded, particularly if there are psychotic features (hallucinations and delusions). A rash or other skin lesions (e.g. bite marks, eschar, mouth/palate ulcers, lymphadenopathy and shingles lesions), respiratory or gastrointestinal signs may give clues to the aetiology. Clusters of clinical features (e.g. psychosis and movement disorder and anti-NMDAR encephalitis, or hydrophobia, delirium and hypersalivation with rabies/ABLV) (Boxes 3, 4) may be strongly indicative of a specific cause.

### Investigations

First-line investigation of all patients with suspected/probable encephalitis

Investigations to exclude differential diagnoses (Box 2) and guide initial management are listed in Table 1 and Figure 1. Blood cultures should be taken prior to the administration of empiric antibiotics. A lumbar puncture (LP) should be performed if there is no contraindication or following appropriate imaging and/or clinical observation. CSF analysis is needed to confirm encephalitis (Fig. 1) and identify a cause. Sufficient volumes should be sampled (Table 1) to enable microscopy and cell counts, Gram stain, bacterial culture (mycobacterial culture or fungal cultures if indicated), biochemistry (protein, glucose) and exclusion of HSV, Cryptococcus, VZV and syphilis in those patients meeting the more rigorous definition of encephalitis (Fig. 2). Where available, other biomarkers of CNS inflammation including CSF oligoclonal bands and CSF neopterin should

<table>
<thead>
<tr>
<th>Specimen/Investigation</th>
<th>Tests</th>
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<tbody>
<tr>
<td>CSF†</td>
<td>Opening pressure, microscopy, Gram stain and bacterial culture</td>
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<tr>
<td></td>
<td>Cell count and type§</td>
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<td>Biochemistry: protein, glucose</td>
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<td>PCR: HSV§, enterovirus, VZV</td>
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<td></td>
<td>Antibodies: oligoclonal bands, VZV IgG¶</td>
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<td></td>
<td>Antigen: cryptococcal Ag</td>
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<td></td>
<td>Other: VDRL (adult); consider cytology; to store</td>
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<tr>
<td>Serum</td>
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<tr>
<td>Respiratory</td>
<td>PCR testing for enterovirus, influenza A and B, adenovirus</td>
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<tr>
<td>Faeces</td>
<td>PCR or antigen testing for enterovirus, adenovirus, rotavirus (child); enterovirus culture/typing</td>
</tr>
<tr>
<td>Skin swabs (where lesions present)</td>
<td>PCR testing for HSV 1/2, VZV, enterovirus</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>MRI (sequences to include: T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast) or if unavailable CT with contrast</td>
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</tbody>
</table>

†Collect up to 10 mL, if able, in four tubes in adults and children, and up to 5 mL in a small child (<2 years old). §Formal cytological examination is required to reliably differentiate eosinophils from other leukocytes and identify malignant cells. ¶HSV PCR is highly sensitive (>96%) between days 3 and 7 of the illness, its sensitivity decreases slightly in the second week of the illness. False negatives prior to day 3 have been described. After day 10, CSF HSV IgG can be used to make a late diagnosis. ¶¶Where available, CSF VZV IgG may be more sensitive than PCR. Testing requires the demonstration of intrathecal synthesis of VZV IgG, that is a reduced serum/CSF ratio of VZV IgG compared with the serum/CSF ratio of albumin. ††HIV is very uncommon in children in Australia, and encephalopathy is an uncommon presentation; some experts would still undertake HIV testing as the diagnosis impacts upon possible aetiologies of encephalitis, and is treatable. §§Flaviviral IgM should be tested after 5 days of symptoms. A negative result makes the diagnosis unlikely. CSF IgM is specific for these viruses and should be performed in patients in whom the diagnosis is likely in terms of risk factors, clinical and radiologic features (see Boxes 4 and 5). Ag, antigen; CSF, cerebro-spinal fluid; CT, computed tomography scan; DWI, diffusion-weighted imaging; EEG, electroencephalogram; FLAIR, fluid-attenuated inversion recovery; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VZV, varicella zoster virus; WBC, white blood cell.
be considered. A serum specimen (Table 1) should be stored for testing with convalescent sera. All patients (Fig. 2) should have serology for HIV, mycoplasma and flaviviruses, and syphilis serology in adults and Epstein–Barr virus (EBV) serology in children. A respiratory tract specimen and stool for viral testing, and viral and bacterial swabs from any skin lesions should be collected.

CNS imaging (Fig. 1) should be performed on all patients, by magnetic resonance imaging (MRI) wherever possible using T1, T2 and fluid-attenuated inversion recovery, diffusion-weighted imaging, gradient echo or similar sequences and gadolinium contrast. A chest X-ray is needed to detect associated lung disease (e.g. tuberculosis (TB) and Cryptococcus). EEG is highly sensitive in encephalitis, but often non-specific. It is particularly important in patients with chronic symptoms and those with psychiatric presentations to identify encephalopathy or to diagnose subtle seizure activity and non-convulsive status epilepticus.\(^{11,12}\) Localised EEG activity may suggest specific aetiologies (e.g. temporal localisation with HSV).

**Targeted testing of patients with encephalitis**

Where encephalitis is likely, second and third-line testing of patients should be guided by risk factors, clinical and radiologic features (Boxes 4, 5; Fig. 2) in consultation with specialists in neurology, infectious diseases, microbiology/virology and neuroradiology. Remote consultations (by telephone) may be necessary, and transfer to a referral centre considered.

**Patient subgroups**

**Children**

Encephalitis is challenging to identify in very young infants as features are non-specific (lethargy, excessive irritability, poor feeding). Diagnosis requires a high index of suspicion and consultation with experienced clinicians. The most common causes of childhood encephalitis globally are HSV-1, VZV, enteroviruses and JEV in endemic regions. Other causes include: ADEM, EBV and adenovirus in children, and HSV-2 and parechovirus in neonates. Human herpesvirus (HHV)-6 and HHV-7 may be associated with febrile seizures and encephalopathy in immune-competent children and may uncommonly cause encephalitis in the immunocompromised.\(^{42}\) *Mycoplasma pneumoniae* has been associated with childhood encephalitis (less commonly in adults) when a positive *M. pneumoniae* IgM is detected in blood, although causality remains controversial without concurrent pathogen identification.\(^{31,43}\)

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**Box 5 Tests of choice for the more common and regionally important aetiologies\(^{33,39-41}\)**

For an extensive review of indicated tests for other aetiologies see Granerod et al., 2010 and Tunkel et al., 2008.\(^{11,12}\) Direct discussion with a medical microbiologist/virologist and local laboratory scientist is good practice before ordering uncommon tests.

**HSV**: CSF PCR 3–10 days into illness. May be negative < 3 days, repeat lumbar puncture and re-test CSF PCR (between days 3 and 10) if other features suggest HSV (see Fig. 2). CSF IgG (in combination with serum IgG) > 10 days.

**Enteroviruses**: CSF PCR, stool and upper respiratory tract specimen for PCR/viral culture.

**VZV**: CSF PCR, CSF IgG (in combination with serum IgG), Acute serum IgM, serum IgG acute/convalescent.

**EBV/CMV/HHV6**: CSF PCR, Acute serum IgM, serum IgG acute/convalescent.

**Flaviviruses**: CSF IgM after 5 days into illness, Acute serum IgM, serum IgG acute/convalescent.

**WNV/KUNV**: As for other flaviviruses and CSF PCR.

**Dengue**: As for other flaviviruses and acute blood NS1 Antigen, PCR.

**Measles**: CSF IgM, acute serum IgM and acute/convalescent serology, urine or upper respiratory specimen for PCR or antigen testing.

**Rabies or ABLV**: CSF PCR. Serum and CSF IgG. DFA on saliva, inuclial skin, corneal impression, brain.

**Hendra or Nipah**: PCR on CSF, serum, respiratory, urine specimens ± serum IgM/G.

**Ab-mediated**: Serum and/or CSF anti-NMDAR Ab; serum anti-VGKC complex Ab; serum anti-Hu, anti-Ma2 Ab\(^{¶}\).

Quantitative PCR may contribute to diagnosis. Exclusion of HHV6 chromosomal integration may be required to confirm its aetiologic role.

Convalescent for practical purposes is 2–4 weeks following symptom onset.

Includes: Japanese encephalitis virus (JEV), Murray valley encephalitis virus (MVEV), West Nile virus (WNV/KUNV), dengue, St Louis encephalitis virus (SLEV), tick-borne encephalitis virus (TBEV). Other encephalitic arthropod-borne viruses (arboviruses) are investigated in the same way including togaviruses (eastern equine encephalitis virus (EEEV), western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV), bunyaviruses (Lacrosse virus (LACV), Toscana virus (TOSV)), and reoviruses (Colorado tick fever virus (CTFV)).

Includes: Japanese encephalitis virus (JEV), Murray valley encephalitis virus (MVEV), West Nile virus (WNV/KUNV), dengue, St Louis encephalitis virus (SLEV), tick-borne encephalitis virus (TBEV). Other encephalitic arthropod-borne viruses (arboviruses) are investigated in the same way including togaviruses (eastern equine encephalitis virus (EEEV), western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV), bunyaviruses (Lacrosse virus (LACV), Toscana virus (TOSV)), and reoviruses (Colorado tick fever virus (CTFV)).

Other serum antibodies that have been implicated in paraneoplastic and non-paraneoplastic limbic encephalopathies include: anti-ampiphysin, anti-CV2/CRMP5, anti-Ri, anti-Yo, anti-glutamic acid decarboxylase (GAD), anti-gamma-aminobutyric acid A and receptor B (GABA-A-R, GABA-B-R), anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R), anti-glycine receptor (GlyR), anti-dipeptidyl-peptidase-like protein-6 (DPPX), anti-metabotropic glutamate receptor 5 (mGlu-R5).

CSF, cerebrospinal fluid; DFA, direct fluorescent antibody test; HSV, herpes simplex virus; NMDAR, N-methyl-D-aspartate receptor; PCR, polymerase chain reaction; VGKC, voltage-gated potassium channel.
**Who has “Suspected” meningo-encephalitis?**

An adult or child who presents with:

- **Encephalopathy**, defined by one or all of the following features: altered level of consciousness, altered cognition, altered personality/behaviour, and lethargy

- **Infection associated**, current or recent history of fever, and/or new onset seizures, and/or new onset focal neurological signs/symptoms and/or headache.

Comprehensive history, including exposure, and examination (see box 4): Consider other causes.

Early investigation and Management

- Basic full blood count, electrolytes, glucose, urea, creatinine, calcium, liver function tests, blood culture, serum to store (5-10 mL), in adult consider early HIV testing with appropriate pre-test counselling
- Judicious fluid and electrolyte management as required
- Acute seizure management (follow local and state-based guidelines)
- Consider if Lumbar Puncture (LP) can be performed and role of preceding CT scan (see below)

**Performance of LP and role of prior CNS imaging**

CNS imaging (most commonly CT) should be performed prior to lumbar puncture in the following circumstances:

- Impairment of consciousness, abnormal, fluctuating or declining GCS.
- Signs of raised intra-cranial pressure (papilloedema, relative bradycardia with hypertension, coexistent poly or abnormal papillary responses).
- Focal neurological deficits.
- New onset seizures until stabilised.
- Immunocompromised state (HAV/IVD, immunosuppressive therapy, transplantation).
- Previous history of a CNS lesion (mass lesion, stroke, or focal infection).

LP is relatively contra-indicated in the following circumstances:

- Haemodynamic instability or acute respiratory failure.
- Coagulation disorders e.g. disseminated intravascular coagulation, use of anticoagulant drugs, thrombocytopenia (<100 x106/L).
- Signs of raised intra-cranial pressure (papilloedema, relative bradycardia with hypertension, oculomotor palsy or abnormal pupillary response).

- Impairment of consciousness; abnormal, fluctuating or declining GCS.

**Contraindication to LP or LP deferred pending CNS Imaging or CT unavailable:**

- Bacterial meningitis possible. Commence antibiotics promptly
- Encephalitis is possible, start acyclovir (see doses below).
- Perform LP as soon as possible. If no radiologic/contrastation or neurosurgery likely, make a diagnosis.

**No clinical contraindication, LP performed:**

- Take 10mL if able (5mL in a small child <15kg); ideally in 4 tubes (1 - 2.5mL in 3rd tube, 2.5mL in 4th tube).
- Send for microscopy (cell count, Gram stain), culture and biochemistry (protein, glucose), HSV and enterovirus PCR.
- Check CSF microscopy values (see below).

**Acyclovir dose:**

- Adults/Children >12 years: 300mg/m2 Six hourly
- <3 mo- 20mg/kg IV 8 hourly
- Children: 10mg/kg IV 8 hourly
- Adults/Children >12 years: Acyclovir dose:

***Typical cerebro-spinal fluid patterns***

<table>
<thead>
<tr>
<th>Opening pressure</th>
<th>Normal</th>
<th>Viral meningo-encephalitis</th>
<th>Bacterial meningitis</th>
<th>Tuberculous meningitis</th>
<th>Fungal meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count (uL)</td>
<td>&lt;5</td>
<td>5-1000</td>
<td>100-50 000</td>
<td>5-500</td>
<td>5-1000</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>&lt;0.5</td>
<td>Normal</td>
<td>Low (&lt;0.4)</td>
<td>Very Low (&lt;0.5)</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Protein (mg/L)</td>
<td>&lt;0.5</td>
<td>0.5-1.0</td>
<td>&gt;1.0</td>
<td>1.0-5.0</td>
<td>0.2-5.0</td>
</tr>
</tbody>
</table>

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Consult Therapeutic Guidelines: Antibiotic: Version 15. Therapeutic Guidelines Limited, Melbourne (2014). ||If CT or MRI are unavailable locally, consultation with specialists in neurology and infectious diseases should be pursued and collaborative discussion as to the need for transfer to a referral centre should be included in these discussions. A Early MRI should be advocated because of its increased sensitivity, particularly in children where stroke is less common. ††There are exceptions to these ‘typical patterns’; infectious diseases consultation should be sought where particular risk factors or clinical features suggest a specific aetiology and CSF findings are inconsistent with this. CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography scan; GCS, Glasgow coma score; HIV/AIDS, human immunodeficiency syndrome/acquired immune deficiency syndrome; LP, lumbar puncture; MRI, magnetic resonance imaging; RBC, red blood cell; WBC, white blood cell.

Immunocompromised hosts

The aetiology of encephalitis in the immunocompromised varies depending on the timing, nature and intensity of immunosuppression. CSF pleocytosis may be lacking in these patients. CNS reactivation of latent infection (e.g. VZV, cytomegalovirus (CMV), HHV-6, EBV) can occur, but is less common than systemic reactivation. HHV-6 post-transplant limbic encephalitis is now well described.44,45 VZV reactivation and primary infection in immunocompromised hosts causes a small vessel vasculitis. Encephalitis may be caused by opportunistic pathogens (e.g. Toxoplasma, Cryptococcus). HIV testing is essential as encephalitis may be the presenting illness of HIV/AIDS. A variety of neurological syndromes is associated with HIV; patients at highest risk are those with severe immune suppression (CD4 count < 200). Toxoplasma gondii, Cryptococcus neoformans and CMV are the most important pathogens. John Cunningham virus-associated progressive multifocal leucoencephalopathy (PML) can present in a variety of ways including fulminant encephalopathy.46,47 Initiation of anti-retroviral therapy can result in CNS immune reconstitution inflammatory syndrome (IRIS) encephalitis, including a non-pathogen-associated CNS IRIS, so-called CD8-positive encephalitis.48 The role of corticosteroids in this group should be discussed with an HIV specialist.

International travellers or immigrants

Overseas travellers may be exposed to a wide array of infections that can cause encephalitis. Common aetiologies as well as the exotic should be considered. Testing should be guided by a detailed history including timing of symptom onset in relation to travel, destination and in-location movements and activities, pre-departure immunisation, antimicrobial prophylaxis and adherence, animal and vector exposure, and ingestion of raw or unusual foods. Cerebral malaria is a potential cause in the febrile returned traveller with encephalopathy. Tuberculous meningoencephalitis should be considered, especially in young children and vector-borne pathogens (e.g. flaviviruses, Rickettsia spp.) after travel to overseas rural locations, especially in summer/spring. A history of insect bites is not always given.

Tropical Australia

In those living in or returning from tropical Australia, dengue, JEV and the endemic flaviviruses (MVEV and KUNV) should be considered. Parts of the Northern Territory (above 21°S) are endemic for melioidosis, which can present as brainstem encephalitis with cranial nerve palsies and limb weakness.49 Leptospirosis may occur following flooding events and exposure to water.50

Unknown or ‘cryptic’ encephalitis

Brain biopsy is not necessary in most encephalitis patients; however, it should be considered in patients without a diagnosis who remain unwell or are deteriorating, especially if there are focal lesions on imaging or where CNS vasculitis is suspected.51 Potentially treatable aetiologies may be diagnosed using biopsy in these circumstances,51–54 and other occult diagnoses can be made, for example, CNS Whipple disease, TB, PML and neurosarcoidosis.55 Liaison with histopathology and microbiology prior to sampling is essential to ensure correct specimen handling, transport and testing. A proportion of patients will not have an aetiological diagnosis made despite extensive investigation. Patients

Figure 1 Algorithm for the assessment and management of a patient with suspected meningo-encephalitis. Where traumatic sampling occurs with elevated red blood cells on microscopy, the WBC can be corrected using the formula: True CSF WBC – actual CSF WBC × RBC × RBC CSF/RBC blood) or approximately 1 WBC per 500 RBC. The ratio of WBC types in the CSF can be compared with that in blood. 1000 × 106/L RBC in CSF raises CSF protein by approximately 0.1 g/L. †Particular note should be made of apparently psychiatric presentations. ‡In young children, the clinical features of encephalopathy may be difficult to discern and may include poor feeding, excessive irritability and unusual crying. §The Australasian College of Emergency Medicine (ACEM) recommends that antibiotics may be delayed if the lumbar puncture will be performed within 20 min of presentation. Antibiotics should be administered prior to LP where: there is no doctor present, there will be a delay to a required CT, lumbar puncture is not able to be performed (due to other contraindication or the healthcare professional does not have the requisite skills) or possible systemic sepsis.

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Identify clinical features, risk factors, radiologic features (see Box 4) to guide second-line investigation:

- In consultation with neurologist, infectious diseases specialist, radiologist, microbiologist (Box 5).
- Especially note the following risk groups:
  - Children and neonates
  - Immunocompromised (including HIV/AIDS, immunosuppressive therapy, transplantation)
  - International travellers or immigrants
  - Those residing in or having travelled to tropical regions of Australia

Encephalitis (14)

An adult or child with:

1. Encephalopathy, defined by the presence of some or all of the following features: altered level of consciousness, altered cognition, personality/behavioral change, lethargy; lasting >24 h.
2. In combination with any or more of the following:
   - Fever or history of fever (≥38°C) within 72h before/after presentation.
   - Generalized or partial seizures not fully attributable to a pre-existing seizure disorder.
   - New onset focal neurologic findings.
   - CSF pleocytosis (>5 WBC/uL).
   - Abnormal results of neuroimaging suggestive of encephalitis.
   - EEG abnormality consistent with encephalitis and not attributable to another cause.
3. AND no alternative cause identified/diagnosis made.

Arrange specialist consultation:
- Neurology
- Infectious Diseases
- Microbiology/Virology
- Radiology

Arrange first-line investigations if not performed already (see also Table 1):

- CSF: microscopy, culture, protein, glucose, HSV PCR, enterovirus PCR, VZV PCR and IgG, cryptococcal Ag, VDRL (adult), consider cytology.
- Serology: HSV, flavivirus (Australia), HIV, M. pneumoniae, EBV (child/adolescent), T. pallidum (Syphilis - adult).
- Respiratory viral testing: PCR or antigen testing for enterovirus, influenza A and B, adenovirus.
- Stool viral testing: PCR or antigen for enterovirus, adenovirus, rotavirus (child).
- MRI brain: sequences to include T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast or if unavailable CT with contrast.
- Chest X-ray.
- EEG (particularly useful in certain circumstances). Consider addition of empiric antimicrobials for Listeria monocytogenes (penicillin or ampicillin) and rickettsiae (doxycycline in adults).

Consider addition of empiric antimicrobials for Listeria monocytogenes (penicillin or ampicillin) and rickettsiae (doxycycline in adults).

If no aetiology identified, consider empiric treatment of possible aetiologies, including immune therapy (corticosteroids and/or IVIG) based on clinical features, risk factors, radiologic features in consultation with neurologist and infectious diseases specialist (see Box 6). Definitive treatment of aetiology if identified (see Box 6). Where relevant, report case to public health or other statutory authorities and perform contact tracing.

Consider if HSV encephalitis is excluded and therefore determine duration of acyclovir therapy:

1. In a patient without neuroimaging suggestive of HSV encephalitis, cease empiric acyclovir if:
   - A negative CSF PCR for HSV is obtained, if the CSF was sampled between days 3 and 7 of the clinical illness.
   - Two negative CSF PCRs for HSV are obtained, if the first PCR was taken in the first 72 h of the clinical illness.
2. In a patient with neuroimaging suggestive of HSV encephalitis, irrespective of CSF PCR result:
   - Continue acyclovir for 21 days if < 3 mo; 14-21 days if >3 mo, child or adult and,
   - Consider CSF HSV IgG testing after day 10 of the clinical illness (unless a definitive alternative diagnosis made).

Comence empiric acyclovir:

- Adults/Children >12 years: 10mg/kg IV 8 h.
- Children: <3 mo- 20mg/kg IV 8 hourly;
  3mo-12years 500mg/m² 10mg/kg IV 8 hourly. Adjust dose for renal impairment.

Consider third-line investigations if:

1. The patient remains unwell and other investigations are negative or
2. The patient is deteriorating and an aetiological diagnosis has not yet been made.

- Repeat CSF sampling: microscopy, CSF wet mount, cytology, repeat HSV PCR, CSF immunoglobulin testing (HSV, VZV, flavivirus, IgG index, ABLV (Australia) and other epidemiologically relevant viruses if international travel).
- Repeat MRI brain: sequences to include T1, T2, FLAIR, DWI, gradient-echo, gadolinium contrast. It is essential to liaise with a (neuro)radiologist with regards to planning these and any additional sequences.
- All patients in this circumstance should be tested for anti-NMDAR, anti-VGKC and in Australia, ABLV.
- Brain biopsy: it is essential to liaise with histopathology and microbiology prior to sampling with regards to specimen handling, transport and testing – especially note that specimens should not be formalin fixed prior to transfer to the laboratory.
**Box 6 Directed management of viral and immune-mediated encephalitis**

For an extensive review of antimicrobial treatments for other aetiologies see Tunkel et al., 2008.19

**HSV:** Minimum 14 days intravenous acyclovir for immunocompetent patients and 21 days for immunocompromised patients (adults and children > 12 years: 10 mg/kg 8 hourly; children < 3 mo 20 mg/kg 8 hourly; 3 mo-12 yo 500 mg/m² 8 hourly). Consider repeat lumbar puncture for CSF HSV PCR at planned completion of treatment especially in immunocompromised children.

**VZV:** Consider 7-14 days intravenous acyclovir (adults and children > 12 years: 10 to 12.5 mg/kg 8 hourly; children: 500 mg/m² 8-hourly (approximately 20 mg/kg for child 5 years or less, 15 mg/kg for child 5-12 years)) with or without corticosteroids in consultation with an infectious diseases specialist.

**Enterovirus:** Intravenous immunoglobulin if hypogammaglobulinaemic. Intravenous immunoglobulin is used widely in Asia for enterovirus 71.

**CMV/HHV6:** Reduce immunosuppression and consider ganciclovir or foscarnet in consultation with infectious diseases specialist.

**Rabies or ABLV:** Consider Milwaukee protocol55,56 in consultation with a neurologist. Second-line treatments in consultation with a neurologist.

**Ab-mediated:** Immunosuppressive therapy in consultation with a neurologist. Investigation for underlying tumour and removal (where indicated). Ongoing tumour surveillance.

**ADEM:** Acute disseminated encephalomyelitis; CMV, cytomegalovirus; CSF, cerebrospinal fluid; DFA, direct fluorescent antibody test; HHV, human herpes virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

**Directed management of encephalitis with an identified aetiology (Box 6)**

When a cause is identified, directed therapy (Box 6) should be determined in consultation with relevant specialists and national/international antimicrobial guidelines.10

With the exception of the herpesviruses, most viral causes have no specific treatment. For HSV and VZV encephalitis, guidelines regarding acyclovir duration and corticosteroids vary.57-64 as does advice regarding antivirals for CMV or HHV-6 encephalitis.10 Antivirals are not recommended for EBV encephalitis.10 Pleconaril for enteroviral encephalitis has limited documented efficacy and is not widely available. Intravenous immunoglobulin is used, without strong evidence of efficacy, to treat EV71-associated encephalo-myelitis,65 and also for chronic enteroviral infections in antibody deficient hosts. It is increasingly being used as adjunctive therapy for other encephalitides. Corticosteroids have an established role in the management of ADEM, although this is not based on high-quality evidence18,66; intravenous immunoglobulin and plasma exchange may be used where there is steroid resistance.18 Evidence of benefit from immune suppression in NMDAR encephalitis in increasing21 and similar approaches are recommended for other immune-mediated encephalitides.57 An extensive search for an underlying malignancy should be performed whenever NMDAR encephalitis is diagnosed68 and in adults with “limbic encephalitis”69 (Box 3). There is no evidence that antimicrobials are beneficial in M. pneumoniae-associated encephalitis.
Outcome, prognosis and follow-up

Overall mortality of encephalitis is approximately 10%, 3,17 Up to 50% of patients experience short-term deficits with 20% experiencing severe sequelae; long-term outcome is poorly characterised, and neurocognitive sequelae likely underestimated.70,71 Depression of consciousness at presentation is the main adverse prognostic feature; poor outcome has also been associated with refractory status epilepticus, intensive care unit admission, local neurologic signs, abnormal MRI findings, extremes of age and immune compromise, a diagnosis of HSV in adults, and JEV or Mycoplasma pneumoniae in children, or delay in the initiation of directed therapy. Recovery from encephalitis reaches a plateau at approximately 6–12 months. Rehabilitation assessment (medical and non-medical) should be considered, especially in those with neurological or neuropsychological deficits at discharge. We recommend early formal discharge planning to facilitate referrals and follow-up including development and learning in children, and seizure management.

Conclusion

Further research is needed to inform better local management guidelines; however, many patients will benefit from the optimal application of existing knowledge.

References

Consensus guidelines for encephalitis


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Survey of infection control and antimicrobial stewardship practices in Australian residential aged-care facilities

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Key words
residential care, infection control, antibiotic stewardship.

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