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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 possibile aetiologies but in most cases a cause is not identified.[2–4] There is often no definitive treatment[1,5] and a high rate of mortality and morbidity.[6] The investigation and management of encephalitis worldwide are of

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variable quality.[7–9] While several international guidelines exist[10–13] and the International Encephalitis Consortium consensus included Australian authors,[14] 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%.[4] The highest admission rates are observed in males, and those aged less than 9 or over 60 years of age.[4] This is similar to international findings.[15–17]

Case definition

The international case definition of encephalitis (Box 1)[10] 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.[14]

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.[5] Immune-mediated aetiologies are increasingly recognised in up to one third of cases, and are important because they are often treatable (Box 3).

Box 1 Encephalitis case definition from the international encephalitis consortium[14]

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/mm^3.
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 nectrotising 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).

Metabolic encephalopathy: hepatic, renal, hypoglycaemia, hyponatraemia, hypocalcaemia, thiamine deficiency, Wilson disease.

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.

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Box 3 Selected immune-mediated encephalitides

ADEM[18,19]

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 leuco-encephalopathy (AHLE) is a rare, hyper-acute form of ADEM that overlaps with cerebral vasculitis.

Anti-NMDAR[20–22]

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[23–26]

Anti-voltage-gated potassium channel-complex (including antibodies against leucine-rich glioma-inactivated 1 protein (Lgi1) and contactin-associated protein 2(Caspr2)) 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 Caspr2 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[27,28]

'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-amphiphysin. 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-amino-butyric acid B receptor (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).[29] An algorithm addressing approaches to testing and management has been recently published.[30]

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).[17,18,20]

Aetiology varies with age, immune status, geography, climate and pathogen 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.[4,31]

A confirmed laboratory diagnosis is frequently not obtained. Almost 70% of cases in a retrospective Australian study did not have an identified aetiology, although

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Box 4 Clinical, risk factor and radiologic pointers to direct targeted (second line) 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, delerium: rabies, ABLV.
- Parkinsonian features: flaviviruses (esp. JEV), anti-DR2 (basal ganglia encephalitis).
- Brainstem dysfunction: 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.
- Rash: enteroviruses, VZV, HHV6, measles , dengue, rickettsiae, *Neisseria meningitidis* (Meningococcus).
- Associated pneumonia: *Mycoplasma pneumoniae*, influenza, Nipah#, Hendra, *Coxiella burnetii* (Q fever).
- Parotitis, testicular pain: mumps.
- Cervical lymphadenopathy: EBV, CMV.
- SIADH: anti-VGKC, SLEV†.
- Chronic symptoms: HIV, JCV, BKV, trypanosomiasis#, SSPE, *T. pallidum* (syphilis), Whipple disease.
- Cranial nerve palsy: neuroborreliosis†.

Risk factors

- Neonate (<4 weeks): HSV-2, CMV, toxoplasmosis, *T. pallidum* (syphilis), *L. monocytogenes*, enteroviruses parechovirus.
- 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, CTFV, EEEV, neuroborreliosis, *Rickettsia rickettsii* (RMSF), ehrlichiosis (HME), anaplasmosis (HGA), babesiosis, coccidiomycosis.
  - 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 hensellae.
  - Horse: Hendra, KUNV.
  - Rodents: LCMV, leptospirosis.
  - Snails/other moluscs: Angiostrongylus cantonensis.
  - Swine: Nipah.
  - Mosquito or Tick bite history.
  - Arboviruses: MVEV, KUNV, JEV, dengue in Australia + by region.
  - Rickettsiae: Rickettsia typhi, R. australis, R.honei, Orientalis tsutsugamushi in Australia + by region.
  - Other: neuroborreliosis†, ehrlichiosis (HME)†, anaplasmosis (HGA)†.
- Recreational
  - Sexually transmitted: HIV.
  - Fresh water§: leptospirosis, *Naegleria fowleri*.
  - Soil/mud§: Balamuthia mandrillis.
- Occupational
  - Animal husbandry, farming: *C. burnetii* (Q fever), leptospirosis.
  - Abbatoir workers: *C. burnetii* (Q fever).
- Unvaccinated: measles, mumps, rubella, VZV.

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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. pneumoniae*.
- Subcortical grey matter (basal ganglia, thalami): EBV, flaviviruses (esp. JEV, MVEV), Influenza, MTB, post-streptococcal, *M. pneumoniae*, 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 activites engaged in. §In New Zealand natural geothermal pools pose a particular risk for amoebic meningo-encephalitis, particularly those 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, Colarado tick fever virus; DR2, dopamine-2 receptor; EBV, Epstein–Barr virus; EEEV, eastern equine encephalitis virus; GAD, glutamic acid decarboxylase; HGA, human granulocytotropic anaplasmosis; HHV6, human herpes virus-6; HIV, human immunodeficiency virus; HME, human monocytotropic ehrlichiosis; HSV, herpes simplex virus; JCV, John Cunningham virus; JEV, Japanese encephalitis virus; KUNV, Kunjin virus; LACV, Lacrosse virus; LMCV, 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; SLEV, St Louis encephalitis virus; SSPE, sub-acute sclerosing panencephalitis; TBEV, tick bourne encephalitis virus; TOSV, Toscana virus; VEEV, Venezeulan equine encephalitis virus; VGKC, voltage-gated potassium channel; VZV, varicella zoster virus; WNV, West Nile virus.

testing for immune-mediated and vector-borne causes was limited.[4] Rigorous implementation of systematic testing will likely reduce this proportion but in many cases the cause will remain unknown.[17]

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.[32] 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.[33] 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.[2,3,14,17] 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,[17] 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 meningoencephalitis 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

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Table 1 Recommended first-line investigation of encephalitis in Australia and New Zealand

Specimen/Investigation	Tests
CSF†	Opening pressure, microscopy, Gram stain and bacterial culture
	Cell count and type‡
	Biochemistry: protein, glucose
	PCR: HSV§, enterovirus, VZV
	Antibodies: oligoclonal bands, VZV IgG¶
	Antigen: cryptococcal Ag
	Other: VDRL (adult); consider cytology; to store
Serum‖	Serology: HIV††, flavivirus (Australia)‡‡, *M. pneumoniae*, EBV (child/adolescent), *T. pallidum* (syphilis – adult)
Respiratory	PCR testing for enterovirus, influenza A and B, adenovirus
Faeces	PCR or antigen testing for enterovirus, adenovirus, rotavirus (child); enterovirus culture/typing
Skin swabs (where lesions present)	PCR testing for HSV 1/2, VZV, enterovirus
Neuroimaging	MRI (sequences to include: T1,T2, FLAIR, DWI, gradient-echo, gadolinium contrast) or if unavailable CT with contrast
EEG	

†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. ‖Collect up to 20 mL blood in a clotting tube in adults and children; and up to 5 mL in a small child (<2 years old). ††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, electro-encephalogram; 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.

altered sensation should be elicited and any localisation (focality) 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).[36] 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, meningism, 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, particuarly 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 avaiable, other biomarkers of CNS inflammation including CSF oligoclonal bands[37] and CSF neopterin[38] should

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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.[33,43]

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.[10,33]

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, nuchal 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¶.

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

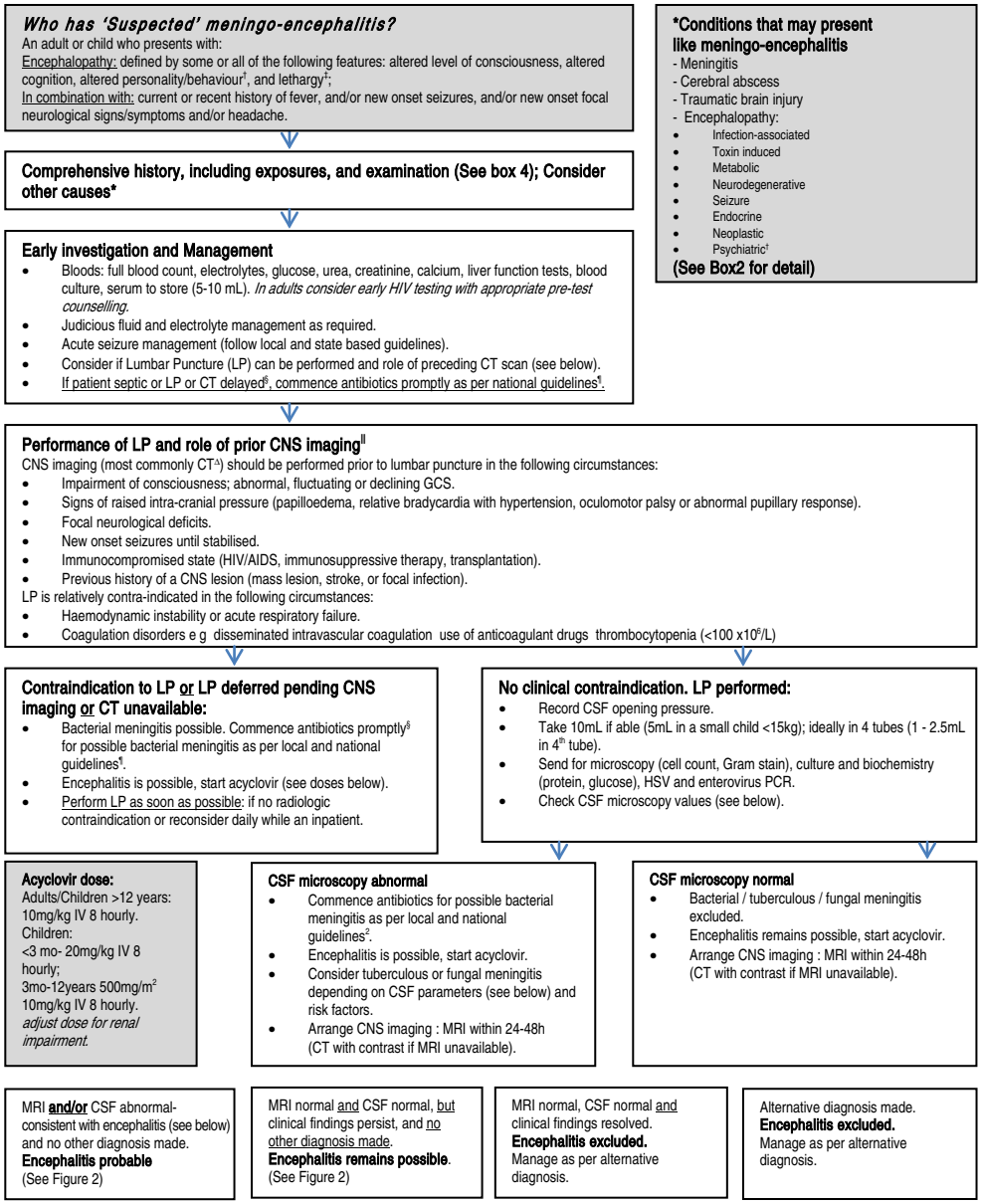
‡Convalescent for practical purposes is 2–4 weeks following symptom onset.

§Includes: Japanese encephalitis virus (JEV), Murray valley encephalitis virus (MVEV), West Nile virus/Kunjin 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-para-neoplastic limbic encephalitis include: anti-amphiphysin, anti-CV2/CRMP5, anti-Ri, anti-Yo, anti-glutamic acid decarboxylase (GAD), anti-gamma-amino-butyric 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.

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***Typical cerebro-spinal fluid patterns††[11,34,35]

	Normal	Viral meningo-encephalitis	Bacterial meningitis	Tuberculous meningitis	Fungal meningitis
Opening pressure	<25cm H20	Normal-high	High	High	Very High
Cell count (uL or 10^6/L)	<5	5–1000	100–50 000	5–500	5–1000
Cell type	Lymphocyte/monocytes, no neutrophils or RBC	Lymphocytes predominate (neutrophils if early)	Neutrophils predominate	Lymphocytes predominate	Lymphocytes predominate
Glucose (CSF:plasma) (mmol/L)	>0.5	Normal	Low (<0.4)	Very Low (<0.3)	Normal-low
Protein (g/L)	<0.5	0.5–1.0	>1.0	1.0–5.0	0.2–5.0

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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 – (WBC blood × 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. 1000×10^6/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. ¶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. Δ 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]

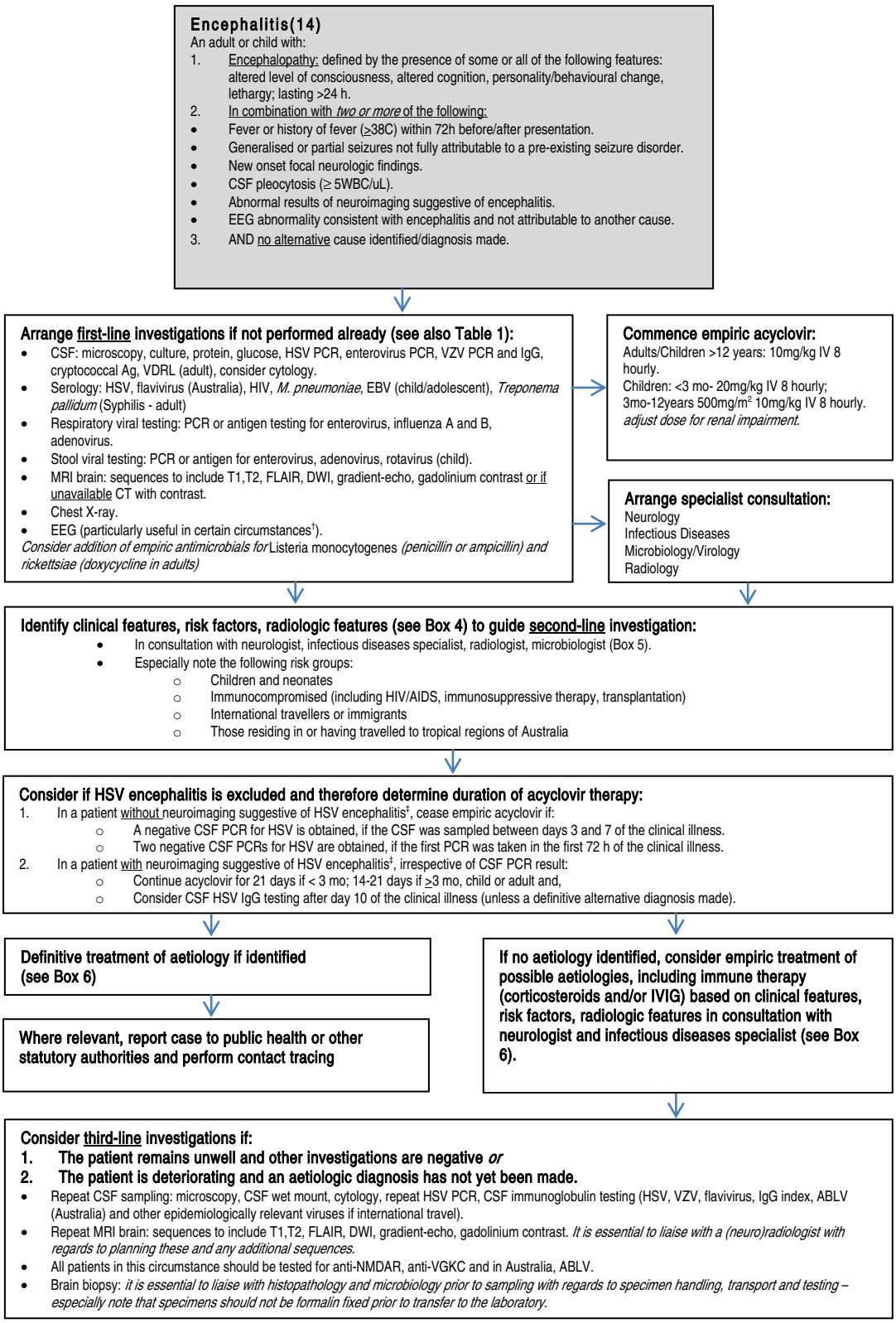
Unknown or 'cryptic' encephalitis

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.[52] 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

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Figure 2 Algorithm for the investigation and management of encephalitis.
†Patients with chronic symptoms, those with primarily psychiatric presentations or to diagnose subtle seizure activity and non-convulsive status epilepticus. ‡Imaging findings characteristic of HSV are medial temporal lobe and inferior frontal cortex involvement; lesions may be unilateral or bilateral. Ab, antibody; ABLV, Australian bat lyssavirus; Ag, antigen; AIDS, acquired immunodeficiency syndrome; CSF, cerebrospinal fluid; CT, computed tomography scan; DWI, diffusion weighted index; EEG, electroencephalogram; HIV, human immunodeficiency virus; HSV, herpes simplex virus; mo, months; NMDAR, N-methyl D aspartate receptor; PCR, polymerase chain reaction ; VZV, varicella zoster virus; WBC, white blood cell; yo, years old; VGKC, voltage gated potassium channel; MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery.

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.[10]

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/m^2 8 hourly). Consider repeat lumbar puncture for CSF HSV PCR at planned completion of treatment especially in immunocompromised and children.
VZV: Consider 7–14 days intravenous acyclovir (adults and children > 12 years: 10 to 12.5 mg/kg 8 hourly; children: 500 mg/m^2 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 and/or foscarnet in consultation with infectious diseases specialist.
Rabies or ABLV: Consider Milwaukee protocol[55,56] in consultation with infectious diseases specialist.
ADEM: Methylprednisolone 30 mg/kg daily in children up to 1000 mg (adult daily dose) for 3–5 days 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.

with 'cryptic' encephalitis should be tested for anti-NMDAR and anti-VGKC complex encephalitis and in Australia for ABLV.

Management (Figs 1,2; Box 6)

Supportive and empiric

Seizure control, management of raised intracranial pressure (occasionally by surgical decompression), circulatory and respiratory support, fluid and electrolyte balance, nutritional support, skin integrity and pressure area care, and prevention of hospital-acquired infections should all be addressed.

Patients with 'suspected meningo-encephalitis' should be commenced on acyclovir. Antibiotics for possible meningitis or sepsis should be administered promptly as per local and national guidelines (ACEM advise within 20 min of presentation) and should not be delayed if LP is contraindicated or neuroimaging delayed.

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 availabile. 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 evidence[18,66]; intravenous immunoglobulin and plasma exchange may be used where there is steroid resistance.[18] Evidence of benefit from immune suppression in NMDAR encephalitis in increasing[21] and similar approaches are recommended for other immune-mediated encephalitides.[67] An extensive search for an underlying malignancy should be performed whenever NMDAR encephalitis is diagnosed[68] and in adults with 'limbic encephalitis'[69] (Box 3). There is no evidence that antimicrobials are beneficial in *M. pneumoniae*-associated encephalitis.

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Outcome, prognosis and follow-up

Overall mortality of encephalitis is approximately 10%.[2,3,17] 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, focal neurologic signs, abnormal MRI findings, extremes of age and immune compromise, a diagnosis of HSV in adults, and JEV or *Mycoplasma pneumoniae* in children,[5] 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.

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BRIEF COMMUNICATIONS

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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Abstract

This study assessed infection prevention and antimicrobial stewardship (AMS) practices in Australian residential aged-care facilities (RACF). Two hundred and sixty-five surveys (15.6%) were completed with all states represented and the majority (177 (67.3%)) privately run. Only 30.6% RACF had infection control trained staff on site. Few facilities had AMS policies, only 14% had antimicrobial prescribing restrictions. Most facilities offered vaccination to residents (influenza vaccination rates >75% in 73% of facilities), but pneumococcal vaccination was poor.

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