

Infective Encephalitis in Adults - Microbiology - Full Clinical Guideline

Reference number: CG-ANTI/2017/019

Introduction

- Encephalitis is inflammation of the brain parenchyma with associated neurological dysfunction.
- Inflammation can be secondary to infectious or non-infectious causes.
- Manifestations of encephalitis include fever with altered mental status:
 - Altered consciousness; and/or
 - Confusion, disorientation; and/or
 - Altered behaviour; and/or
 - Personality change; and/or
 - New focal neurological deficits (e.g. sensory deficit, speech disorder, or motor deficit); and/or
 - New seizures.
- Viruses are the most commonly diagnosed microbial cause of encephalitis.
- The commonest cause of viral encephalitis is **herpes simplex virus (HSV)**; specifically, HSV-1. Enterovirus and varicella zoster virus (VZV) are other relatively common viral causes ([Appendix 1](#)).
- Bacteria, fungi, and parasites are other less common microbial causes ([Appendix 2](#)).

Differential Diagnosis

- Central nervous system (CNS) infectious diseases include encephalitis and meningitis.
- In general, cerebral function remains normal in meningitis; whereas neurological dysfunction can be a differentiating feature of encephalitis.
- If the history or examination reveal symptoms or signs, respectively, of meningeal irritation – photophobia, headache, neck stiffness, nuchal rigidity, Brudzinski neck sign positive, Kernig sign positive, etc. – please note hospital guidelines re [meningitis](#).
- Please also note, symptoms and signs can overlap, and meningoenkephalitis can be diagnosed, investigated, and treated.
- The fever and altered mental status of encephalitis can also be secondary to non-infectious aetiologies.
- Non-infectious causes of encephalitis include:
 - Autoimmune disease.
 - Anti-neuronal antibody disease can be divided into extracellular and intracellular antigen phenomena; examples include **anti-N-methyl-D-aspartate receptor encephalitis** and antineuronal nuclear antibody encephalitis, respectively.
 - Intracranial tumours, both primary and metastatic.
 - Iatrogenic side effects.
- Neurologist review of inpatients diagnosed with encephalitis is recommended within 24 hours of diagnosis.

Investigation

± Radiology; **before lumbar puncture**

- Neuroimaging is indicated before lumbar puncture (LP) in those patients with:
 - Focal neurological symptoms or signs; and/or
 - Seizures; and/or
 - GCS ≤ 12.
- In these patients, computed tomography (**CT**) **head** is required to investigate ± exclude brain swelling and shift that could predispose to neurological complication – i.e. **cerebral herniation/‘coning’** – after LP.
- NB Within the Queen’s Hospital Burton (QHB) and the Royal Derby Hospital (RDH), the CT service operates 24 hours per day, 7 days per week.

Biochemistry, blood sciences, and microbiology; **without history of immunocompromise**

- Contraindications to LP include:
 - Continuous or uncontrolled seizures.
 - Risk of cerebral herniation/‘coning’ identified on CT head scan, e.g. brain swelling or shift.
 - Infection at the site of LP.
 - Rapidly evolving rash.
 - Respiratory or cardiac compromise.
 - Sepsis-septic shock.
 - Low platelet count/thrombocytopenia.
 - Clotting disorder.
 - Anticoagulant therapy.
- CSF for:
 - Opening pressure.
 - Biochemistry: protein and glucose.
 - Microbiology:
 - Microscopy (white blood cells [WBC], red blood cells [RBC], and Gram stain); and
 - Culture; and
 - Polymerase chain reactions (PCR; HSV, enterovirus, and VZV).
 - **If the first CSF is negative, and if there is ongoing clinical concerns re encephalitis, repeat LP/second CSF for investigation after 24-48 hours.**
- Plasma for: glucose.
- Serum for:
 - Blood-borne virus (human immunodeficiency virus [HIV], hepatitis B, and hepatitis C) screen.
 - If liver function tests (LFTs) indicate hepatitis, add hepatitis A, hepatitis E, cytomegalovirus (CMV), and Epstein Barr virus (EBV) testing.
 - Storage (i.e. for possible future investigation; e.g. comparing acute and convalescent serology).
- NB Case by case – in collaboration with the neurologist, virologist, and/or microbiologist – vesicle swabs, convalescent serum, throat swabs, and rectal swabs can be considered for further microbiology and virology investigation.

Biochemistry, blood sciences, and microbiology; **with history of immunocompromise**

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 - Continuous or uncontrolled seizures.
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 - Sepsis-septic shock.
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 - Anticoagulant therapy.
- CSF for:
 - Opening pressure.
 - Biochemistry: protein and glucose.
 - Microbiology:
 - Microscopy (WBC, RBC, Gram stain, acid alcohol fast bacilli stain, and India ink stain [or cryptococcal antigen assay]); and
 - Culture (including for *Mycobacterium* species ± *Coccidioides* species ± *Histoplasma* species); and
 - PCR (HSV, enterovirus, VZV, CMV, and EBV; ± extended testing – in discussion with a clinical virologist – for adenovirus, BK virus, hepatitis E virus, human herpes virus 6 [HHV6], HHV7, influenza A virus, influenza B virus, JC virus, measles virus, mumps virus, and parvovirus B19).
 - **If the first CSF is negative, and if there is ongoing clinical concerns re encephalitis, repeat LP/second CSF for investigation after 24-48 hours.**
- Plasma for: glucose.
- Serum for:
 - Blood-borne virus (HIV, hepatitis B, and hepatitis C) screen.
 - If LFTs indicate hepatitis, add hepatitis A, hepatitis E, CMV, and EBV testing.
 - Storage (i.e. for possible future investigation; e.g. comparing acute and convalescent serology).
 - *Treponema* species/syphilis screen (if positive, CSF for syphilis investigation).
 - *Toxoplasma gondii*/toxoplasmosis screen (if positive, CSF for *Toxoplasma gondii* PCR).
- Blood cultures.

NB Case by case – in collaboration with the neurologist, virologist, and/or microbiologist – vesicle swabs, convalescent serum, throat swabs, and rectal swabs can be considered for further microbiology and virology investigation.

Radiology; after lumbar puncture

- CT and magnetic resonance imaging (MRI) are neuroimaging modalities commonly utilised in the investigation of encephalitis.
- With its greater sensitivity and specificity, MRI is the preferred imaging modality, and is recommended if: (i) the differential diagnosis includes HSV or VZV encephalitis; or (ii) the CSF is indicative of viral encephalitis; or (iii) the initial neuroimaging is indicative of viral encephalitis.
- NB1 Within the QHB and RDH, the MRI service operates 0900-1700 Mondays to Fridays.

- NB2 In the QHB, there is no MRI service out-of-hours.
- NB3 In the RDH, discussion with the medical consultant and – if the senior physician deems MRI essential – liaison with the on call radiology consultant is required from 1700-0900 Mondays to Fridays, and all-day Saturdays and Sundays.

Neurology

- Case by case, in collaboration with the neurology team, electroencephalogram (EEG) can be considered.

Neurosurgery and Neurohistopathology

- With the encephalitis differential diagnosis including:
 - Infectious and **non-infectious** aetiologies; and
 - With the non-infectious aetiologies including **intracranial tumors**
 Case by case, in collaborative discussions between neurology and neurosurgery, biopsy can be considered; with neurohistopathologist review of stereotactic or open biopsies.

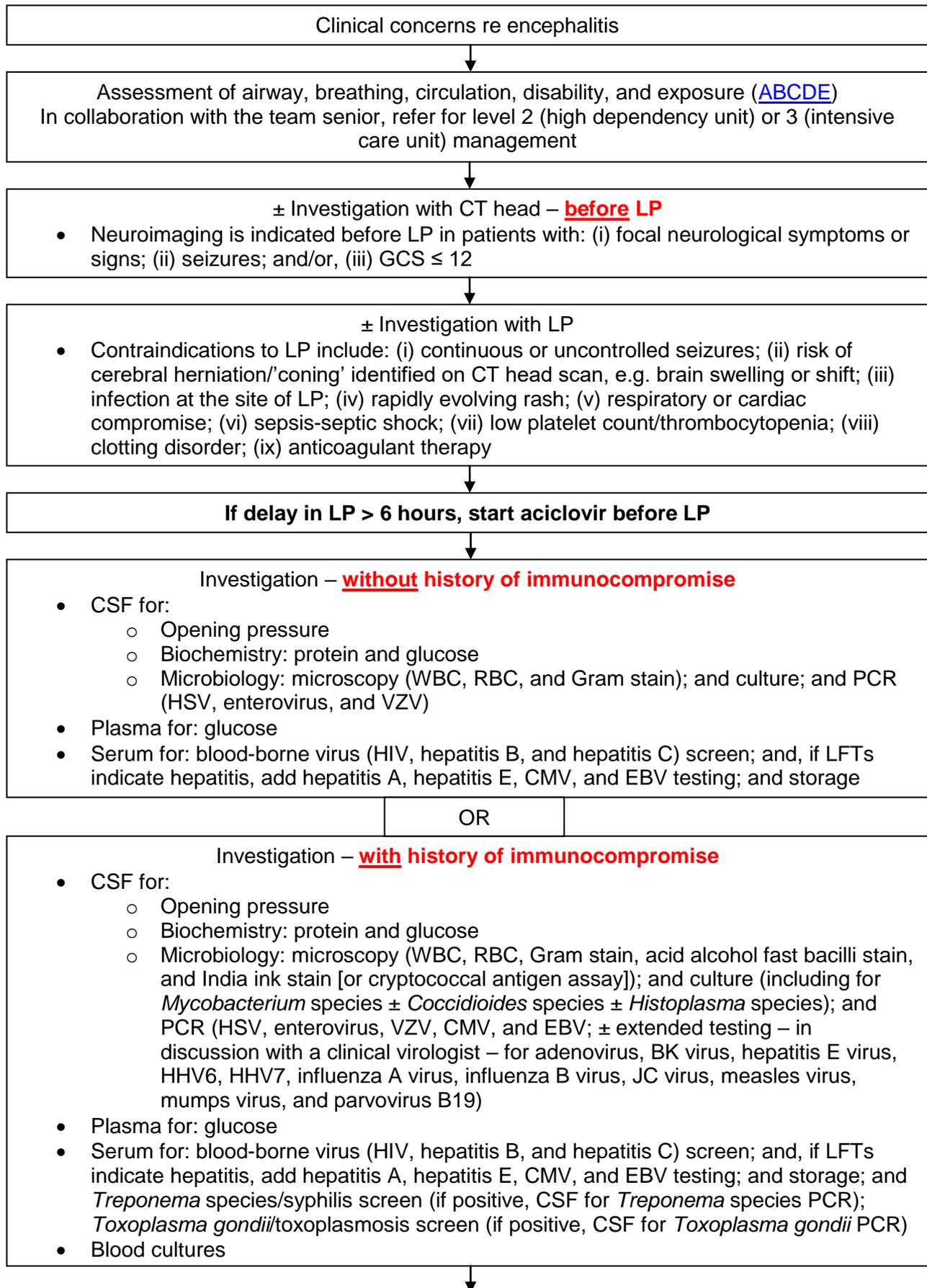
Treatment

Empiric, Intravenous Antivirals

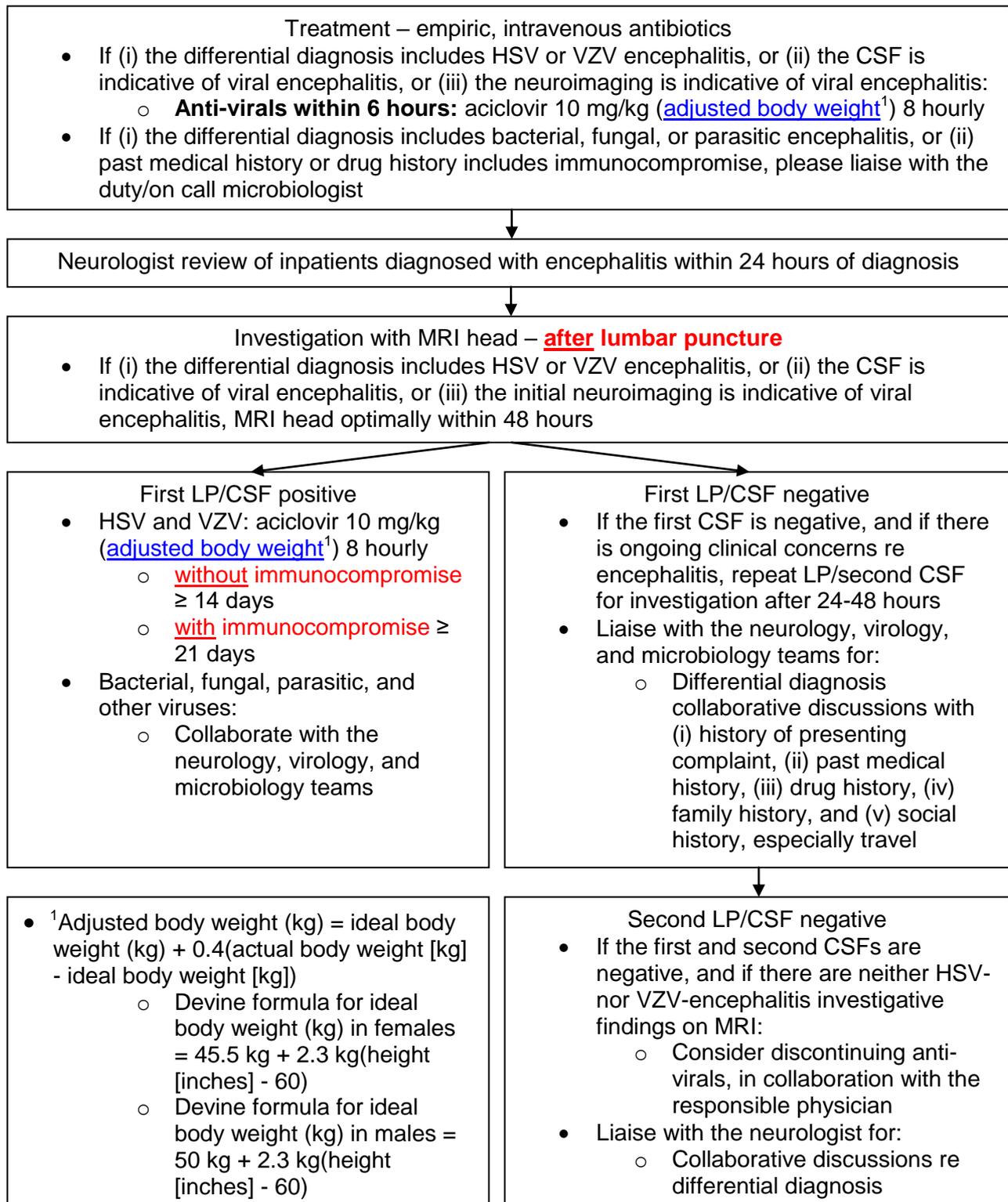
- If (i) the differential diagnosis includes HSV or VZV encephalitis, or (ii) the CSF is indicative of viral encephalitis, or (iii) the neuroimaging is indicative of viral encephalitis:
 - Empiric, intravenous anti-virals within 6 hours:
 - Aciclovir 10 mg/kg ([adjusted body weight](#)¹) 8 hourly.
- If the differential diagnosis includes bacterial, fungal, or parasitic encephalitis ([Appendix 2](#)), please liaise with the duty/on call microbiologist.
- If the past medical history or drug history includes immunocompromise, again, please liaise with the duty/on call microbiologist.
- ¹Adjusted body weight (kg) = ideal body weight (kg) + 0.4(actual body weight [kg] - ideal body weight [kg])
 - Devine formula for ideal body weight (kg) in females = 45.5 kg + 2.3 kg(height [inches] - 60)
 - Devine formula for ideal body weight (kg) in males = 50 kg + 2.3 kg(height [inches] - 60)

Directed, Intravenous Antivirals

- HSV:
 - Aciclovir 10 mg/kg ([adjusted body weight](#)) 8 hourly.
 - Duration, **without history of immunocompromise**, ≥ 14 days:
 - Case by case – in collaboration with the physician/neurologist, ± virologist, ± microbiologist – consider repeating LP after 14 days:
 - If repeated and HSV PCR negative, stop aciclovir.
 - If repeated and HSV PCR positive, continue aciclovir:
 - Consider repeating LP after further 7 days; if HSV PCR negative, stop aciclovir; if HSV PCR positive, continue aciclovir, and consider repeating LP after further 7 days.
 - Duration, **with history of immunocompromise**, ≥ 21 days:

Management of Infective Encephalitis (1 of 2)

Management of Infective Encephalitis (2 of 2)



NB Discharge from neurology (or liaise with neurologist on discharge) with:

- Formal cognitive assessment, e.g. Montreal Cognitive Assessment, ± occupational therapy
- Healthcare professional input re driving, employment, etc.
- Information re the Encephalitis Society, e.g. <https://www.encephalitis.info/>
- Neurology outpatient appointment

Appendix 1: HSV-1, Enterovirus, and VZV clinical disease and investigative/MRI findings

Virus	Clinical disease (from Venkatesan, <i>et al.</i>)	Investigative/MRI findings (from Venkatesan, <i>et al.</i>)
HSV-1	“Seizures, language, memory disturbance, and rarely brainstem involvement; SIADH”	“Asymmetric abnormalities in mesiotemporal lobes, orbitofrontal lobes, and insular cortex with oedema, possible restricted diffusion or haemorrhage (late stage)”
Enterovirus	“Rhombencephalitis, myelitis, and flaccid paralysis; hand, foot, and mouth disease; cardiac complications” (Enterovirus 70 and 71)	“Frequently normal MRI, although characteristic lesions of EV71 occur in dorsal brainstem, dentate nuclei of cerebellum, and anterior horns of spinal cord”
VZV	“Meningoencephalitis, cerebellitis, stroke, myelopathy, retinitis; can occur before, during, or after zoster rash or in absence of rash”	“Could affect temporal lobes, similar to HSV-1; lesions can occur in cerebellum and brainstem; ischaemic or haemorrhagic lesions in white matter or grey-white matter junction suggest vasculopathy”

Appendix 2: Bacterial, Fungal, and Parasitic Encephalitis

<p>Bacterial causative agents (and disease) include:</p> <ul style="list-style-type: none"> • <i>Bartonella henselae</i> (cat scratch disease); <i>Borrelia burgdorferi</i> (Lyme disease); <i>Legionella</i> spp (legionellosis); <i>Leptospira</i> spp (leptospirosis); <i>Listeria monocytogenes</i> (listeriosis); <i>Mycobacterium tuberculosis</i> complex (tuberculosis); <i>Mycoplasma pneumoniae</i>; <i>Rickettsia</i> spp (rickettsiosis); <i>Treponema pallidum</i> (syphilis); <i>Tropheryma whipplei</i> (Whipple’s disease)
<p>Fungal causative agents (and disease) include:</p> <ul style="list-style-type: none"> • <i>Coccidioides</i> spp (coccidioidomycosis); <i>Cryptococcus neoformans</i> (cryptococcosis); <i>Histoplasma capsulatum</i> (histoplasmosis)
<p>Parasitic causative agents (and disease) include:</p> <ul style="list-style-type: none"> • <i>Baylisascaris procyonis</i> (baylisascariasis); <i>Gnathostomas</i> spp (gnathostomiasis); <i>Taenia solium</i> (cysticercosis) • <i>Acanthamoeba</i> spp; <i>Balamuthia mandrillaris</i>; <i>Naegleria fowleri</i>; <i>Plasmodium</i> spp (malaria); <i>Toxoplasma gondii</i> (toxoplasmosis); <i>Trypanosoma</i> spp (trypanosomiasis)

Appendix 3: Encephalitis and Aciclovir

Treatment regimens in adults	Viral encephalitis: 10 mg/kg (adjusted body weight ¹) IV 8 hourly.
Cautions	BNF: "Elderly (risk of neurological reactions) (in adults); maintain adequate hydration (especially with infusion or high doses)."
Interactions	Please review the BNF for an up-to-date and comprehensive list of interactions.
Common or very common side effects	BNF: "Nausea. Photosensitivity reaction. Skin reactions. Vomiting." Please review BNF for uncommon and rare or very rare.
Renal impairment <ul style="list-style-type: none"> • GFR 25-50 ml/min • GFR 10-25 ml/min • GFR < 10 ml/min 	10 mg/kg IV 12 hourly 10 mg/kg IV daily 5 mg/kg IV daily
Hepatic impairment	No data.
Therapeutic drug monitoring <ul style="list-style-type: none"> • Recommended • Sample • Level • Repeat 	Yes, if clinical concerns re side effects or therapeutic failure 1-2 ml serum, pre dose Pre dose CMMG, ≤ 2.6 mg/l 6-8 days
Dose and frequency advice	Within the working day, discuss with the ward pharmacist or antimicrobial pharmacist. Out-of-hours, discuss with the on call pharmacist.

¹ Adjusted body weight (kg) = ideal body weight (kg) + 0.4(actual body weight [kg] - ideal body weight [kg])

Devine formula for ideal body weight (kg) in females = 45.5 kg + 2.3 kg(height [inches] - 60)

Devine formula for ideal body weight (kg) in males = 50 kg + 2.3 kg(height [inches] - 60)

References

Bennett, J. E., Dolin, R., and Blaser, M. J. 2015. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 8th Edition. Elsevier.

British National Formulary. 2020. BNF. Available at: <https://www.medicinescomplete.com/#/> (accessed April 2020).

Encephalitis Society. Management of Suspected Viral Encephalitis in Adults. Available at: <https://www.encephalitis.info/management-of-viral-encephalitis-guidelines> (accessed April 2020).

Johns Hopkins ABX Guide. 2020. Encephalitis. Available at: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540190/all/Encephalitis (accessed April 2020).

Gluckman, S. J. 2019. Viral encephalitis in adults. UpToDate. Available at: https://www.uptodate.com/contents/viral-encephalitis-in-adults?search=viral%20encephalitis%20adult&source=search_result&selectedTitle=1~80&usage_type=default&display_rank=1 (accessed July 2019).

The Renal Drug Database. 2020. Available at: <https://renaldrugdatabase.com/> (accessed April 2020).

Sanford Guide Antimicrobial Therapy. 2020. Encephalitis, Encephalopathy. Available at: <https://www.sanfordguide.com/products/digital-subscriptions/> (accessed April 2020).

Venkatesan, A., Michael, B. D., Probasco, J. C., Geocadin, R. G., and Solomon, T. 2019. Acute encephalitis in immunocompetent adults. Lancet.

Document Control

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Version:	3
Approval date:	Antimicrobial Subgroup - 21/10/2020 Medical Division - 28/10/2020
Changes from previous version:	Introduction, Differential Diagnosis, Investigation, Treatment, Management, Appendices, References
Date uploaded:	30/10/2020
Next review date:	November 2023
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