Infective Encephalitis in Adults - Microbiology Full Hospital Guideline

Reference number: CG-ANTI/2023/019

Introduction

- Encephalitis is inflammation of the brain parenchyma with associated neurological dysfunction.
- Inflammation can be secondary to infection or non-infectious pathologies.
- 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.
- Bacteria, fungi, and parasites are other less common microbial causes (Appendix 1).
- 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.

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 may overlap, and meningoencephalitis can be diagnosed, investigated, and treated.
- The fever and altered mental status of encephalitis can also be secondary to non-infectious pathologies.
- 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.
- NB 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.
- Cerebrospinal fluid (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 (1 of 2) 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.
- Serum (2 of 2) for:
    - Storage.
        - 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

- 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 (WBC, RBC, Gram stain, acid-alcohol fast bacilli [AAFB] 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, human herpesvirus 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 (1 of 2) for:
    - Blood-borne virus (HIV, hepatitis B, and hepatitis C) screen.
    - If LFTs indicate hepatitis, add hepatitis A, hepatitis E, CMV, and EBV testing.
    - *Treponema* species/syphilis screen (if positive, CSF for syphilis investigation).
    - *Toxoplasma gondii*/toxoplasmosis screen (if positive, CSF for *Toxoplasma gondii* PCR).
- Serum (2 of 2) for:
    - Storage.
        - For possible future investigation, e.g. comparing acute and convalescent serology.
- 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 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:
    - Non-infectious pathologies; 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 antimicrobials

- 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 1), 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.

- [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)

Directed, intravenous antimicrobials

- 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:
        - Case by case – in collaboration with the physician/neurologist, ± virologist, ± microbiologist – consider repeating LP after 21 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.
    - NB Please note, HSV can be transmitted sexually. Therefore, please consider referral to a sexual health clinic to enable screening for other sexually transmitted infections and also to facilitate tracing of sexual contacts.

- Enterovirus:
    - Collaborate with the neurology, virology, and microbiology teams.

- VZV:
    - 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 VZV PCR negative, stop aciclovir.
            - If repeated and VZV PCR positive, continue aciclovir:
                - Consider repeating LP after further 7 days; if VZV PCR negative, stop aciclovir; if VZV PCR positive, continue aciclovir, and consider repeating LP after further 7 days.
    - Duration, with history of immunocompromise, ≥ 21 days:
        - Case by case – in collaboration with the physician/neurologist, ± virologist, ± microbiologist – consider repeating LP after 21 days:
            - If repeated and VZV PCR negative, stop aciclovir.
            - If repeated and VZV PCR positive, continue aciclovir:
                - Consider repeating LP after further 7 days; if VZV PCR negative, stop aciclovir; if VZV PCR positive, continue aciclovir, and consider repeating LP after further 7 days.

- CMV:
    - Collaborate with the neurology, virology, and microbiology teams.
- Bacterial, fungal, parasitic, and other viruses:
    - Collaborate with the neurology, virology, and microbiology teams.

Management of infective encephalitis (1 of 2)

Clinical concerns re encephalitis

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Assessment of airway, breathing, circulation, disability, and exposure (ABCDE)
In collaboration with the team senior, refer for level 2 (high dependency unit) or 3 (intensive care unit) management

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± Investigation with CT head – **before LP**

- Neuroimaging is indicated before LP in patients with: (i) focal neurological symptoms or signs; (ii) seizures; and/or, (iii) GCS ≤ 12

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± Investigation with LP

- Contraindications to LP include: (i) continuous or uncontrolled seizures; (ii) risk of cerebral herniation/'coning' identified on CT head scan, e.g. brain swelling or shift; (iii) infection at the site of LP; (iv) rapidly evolving rash; (v) respiratory or cardiac compromise; (vi) sepsis/septic shock; (vii) low platelet count/thrombocytopenia; (viii) clotting disorder; (ix) anticoagulant therapy

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If delay in LP > 6 hours, start aciclovir before LP

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Investigation – **without history of immunocompromise**

- CSF for:
  - Opening pressure
  - Biochemistry: protein and glucose
  - Microbiology: microscopy (WBC, RBC, and Gram stain); and culture; and PCR (HSV, Enterovirus, and VZV)
- Plasma for: glucose
- Serum for: (i) blood-borne virus (HIV, hepatitis B, and hepatitis C) screen; (ii) if LFTs indicate hepatitis, hepatitis A, hepatitis E, CMV, and EBV testing; (iii) storage

or

Investigation – **with history of immunocompromise**

- CSF for:
  - Opening pressure
  - Biochemistry: protein and glucose
  - Microbiology: microscopy (WBC, RBC, Gram stain, AAFB 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, HHV6, HHV7, influenza A virus, influenza B virus, JC virus, measles virus, mumps virus, and parvovirus B19)
- Plasma for: glucose
- Serum for: (i) blood-borne virus (HIV, hepatitis B, and hepatitis C) screen; (ii) if LFTs indicate hepatitis, add hepatitis A, hepatitis E, CMV, and EBV testing; (iii) *Treponema* species/syphilis screen (if positive, CSF for *Treponema* species PCR); (iv) *Toxoplasma gondii*/toxoplasmosis screen (if positive, CSF for *Toxoplasma gondii* PCR); (v) storage
- Blood cultures

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Management of infective encephalitis (2 of 2)

Treatment – empiric, intravenous antimicrobials

- 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:
  - **Anti-virals within 6 hours:** aciclovir 10 mg/kg (adjusted body weight[1]) 8 hourly
- If (i) the differential diagnosis includes bacterial, fungal, or parasitic encephalitis, or (ii) past medical history or drug history includes immunocompromise, please liaise with the duty/on call microbiologist

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Neurologist review of inpatients diagnosed with encephalitis within 24 hours of diagnosis

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Investigation with MRI head – **after lumbar puncture**

- 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, MRI head optimally within 48 hours

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First LP/CSF positive

- HSV and VZV: aciclovir 10 mg/kg (adjusted body weight[1]) 8 hourly
  - without immunocompromise ≥ 14 days
  - with immunocompromise ≥ 21 days
- Bacterial, fungal, parasitic, and other viruses:
  - Collaborate with the neurology, virology, and microbiology teams

First LP/CSF negative

- 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
- Liaise with the neurology, virology, and microbiology teams for:
  - Differential diagnosis collaborative discussions with (i) history of presenting complaint, (ii) past medical history, (iii) drug history, (iv) family history, and (v) social history, especially travel

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Second LP/CSF negative

- If the first and second CSFs are negative, and if there are neither HSV- nor VZV-encephalitis investigative findings on MRI:
  - Consider discontinuing anti-virals, in collaboration with the responsible physician
- Liaise with the neurologist for:
  - Collaborative discussions re differential diagnosis

- [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)

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: bacterial, fungal, and parasitic encephalitis

Bacterial causative agents (and disease) include: • *Bartonella henselae* (cat scratch disease); *Borrelia burgdorferi* (Lyme disease); *Legionella* spp (legionellosis); *Leptospira* spp (leptospirosis); *Listeria monocytogenes* (listeriosis); *Mycobacterium tuberculosis* complex (tuberculosis); *Mycoplasma pneumoniae*; *Rickettsia* spp (rickettsiosis); *Treponema pallidum* (syphilis); *Tropheryma whipplei* (Whipple's disease)
Fungal causative agents (and disease) include: • *Coccidioides* spp (coccidioidomycosis); *Cryptococcus neoformans* (cryptococcosis); *Histoplasma capsulatum* (histoplasmosis)
Parasitic causative agents (and disease) include: • *Baylisascaris procyonis* (baylisascariasis); *Gnathostomas* spp (gnathostomiasis); *Taenia solium* (cysticercosis) • *Acanthamoeba* spp; *Balamuthia mandrillaris*; *Naegleria fowleri*; *Plasmodium* spp (malaria); *Toxoplasma gondii* (toxoplasmosis); *Trypanosoma* spp (trypanosomiasis)

Appendix 2: 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); 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 • GFR 25-50 ml/min • GFR 10-25 ml/min • GFR < 10 ml/min	 10 mg/kg IV 12 hourly 10 mg/kg IV 24 hourly 5 mg/kg IV 24 hourly
Hepatic impairment	No data
Therapeutic drug monitoring • Recommended • Sample • Level • Repeat	 Yes 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])
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Document control

Development of guidelines:	Version 2: Dr Nicola Cooper, Dr Jonathan Crookdake, Dr Cariad Evans, Dr Ravi Kothari Julia Lacey, Dr Peter Slovak, Dr Lalitha Vaithianathar Version 3: Kayleigh Lehal, Dr Peter Slovak
Consultation with:	Version 2: Acute Medicine Consultant, Antimicrobial Pharmacist, Microbiology Consultant, Neurology Consultant, Radiology Consultants, Virology Consultant Version 3: Lead Antimicrobial Pharmacist, Microbiology Consultant
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Key contacts:	Dr Peter Slovak, Microbiology Consultant p.slovak@nhs.net Kayleigh Lehal, Lead Antimicrobial Pharmacist kayleigh.lehal@nhs.net