



Guidelines

Diagnosis and management of infectious encephalitis in adults: Guidelines from the European Academy of Neurology and European Society of Clinical Microbiology and Infectious Diseases

Julia Granerod^{1,2}, Johann Sellner^{3,4}, Jean-Paul Stahl^{5,6}, Sylviane Defres^{1,6,7,8}, Alexandra Mailles^{6,9}, Erich Schmutzhard¹⁰, Elisabeth Aurelius¹¹, Thomas Whitfield¹, Luca Massacesi^{12,13}, Maarten J. Titulaer¹⁴, Pille Taba^{15,16}, Benedict D. Michael^{1,17,18}, Tehmina Bharucha^{6,19,20,21}, Lance Turtle^{1,7,22}, Brendan Sargent¹, Arina Tamborska¹, Jonathan Cattrall^{1,23}, Yun Huang¹, Eva Maria Hodel^{1,24,25}, Suzannah Lant¹, Glynn Webb¹, Rajish S.K. Shil¹, Shalley Dhar²⁶, Diederik van de Beek^{6,27}, Marie Studahl^{28,29}, Matthijs C. Brouwer^{6,27}, Uta Meyding-Lamade³⁰, Ava Easton^{1,31}, Bhagteshwar Singh^{1,6,7,22,32,†}, Tom Solomon^{1,6,18,22,33,*}

¹) Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK

²) Dr JGW Consulting AS, Sandefjord, Norway

³) Department of Neurology, Landeskrankenhaus Mistelbach, Mistelbach-Gänserndorf, Austria

⁴) Karl Landsteiner University of Health Sciences, Krems, Austria

⁵) Infectious Diseases, Grenoble Alps University, Grenoble, France

⁶) ESCMID Study Group for Infections of the Brain (ESGIB), Basel, Switzerland

⁷) Tropical and Infectious Diseases Unit, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

⁸) Faculty of Education, Liverpool School of Tropical Medicine, Liverpool, UK

⁹) Department of Infectious Diseases, French National Public Health Agency, Saint Maurice, France

¹⁰) Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

¹¹) Division of Infectious Diseases, Department of Medicine, Karolinska Institute, Stockholm, Sweden

¹²) Department of Neurosciences, University of Florence, Florence, Italy

¹³) Department of Neurology, Careggi University Hospital, Florence, Italy

¹⁴) Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands

¹⁵) Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

¹⁶) Clinic of Neurology, Tartu University Hospital, Tartu, Estonia

¹⁷) Liverpool Interdisciplinary Neuroscience Centre, University of Liverpool, Liverpool, UK

¹⁸) Department of Neurology, The Walton Centre for Neurology and Neurosurgery, Liverpool, UK

¹⁹) Department of Infectious Diseases, Imperial College Healthcare NHS Trust, London, UK

²⁰) Department of Infectious Diseases, Imperial College London, London, UK

²¹) The Francis Crick Institute, London, UK

²²) National Institute for Health and Care Research (NIHR) Health Protection Research Unit in Emerging and Zoonotic Infections, Liverpool, UK

²³) Department of Brain Sciences, Faculty of Medicine, Imperial College London, London, UK

²⁴) Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

²⁵) Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland

²⁶) Department of Neurovirology, National Institute of Mental Health and Neurosciences, Bangalore, India

²⁷) Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, the Netherlands

²⁸) Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

²⁹) Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden

³⁰) Department of Neurology and Epileptology, Hospital Nordwest Frankfurt, Frankfurt, Germany

³¹) Encephalitis International, Malton, UK

³²) Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

³³) The Pandemic Institute, Liverpool, UK

* Corresponding author: Tom Solomon, The Pandemic Institute, Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE, UK.

E-mail address: tsolomon@liverpool.ac.uk (T. Solomon).

† These authors contributed equally to this work.

ARTICLE INFO

Article history:

Received 1 December 2025

Received in revised form

23 February 2026

Accepted 7 March 2026

Available online xxx

Editor: L. Leibovici

Keywords:

Encephalitis

GRADE

Intervention

Neurology

Practice guidelines

ABSTRACT

Background: Encephalitis is difficult to diagnose and manage, posing a challenge to clinicians. Since the last European guidelines were published in 2010, novel causes have emerged, diagnostic processes have evolved and treatments assessed that need to be reflected in updated guidelines.

Objective: We aimed to produce recommendations for the diagnosis and management of infectious encephalitis in adults based on current evidence to equip clinicians to improve patient outcomes.

Methods: These guidelines were developed jointly with the support of two European specialist medical organizations. Clinical questions were prioritized and formulated in Population/Intervention/Comparison/Outcome format. A systematic literature search was conducted for each question, and the quality of evidence was assessed using standardized tools. Recommendations were developed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Where only indirect evidence was available, a good practice statement was made.

Results: Sixteen questions were considered, with two recommendations reached: for initiation of intravenous aciclovir as soon as possible upon suspicion of encephalitis and against replacing pathogen-specific PCR testing of cerebrospinal fluid (CSF) with multiplex CSF PCR panels for diagnosis of adult patients with suspected infectious encephalitis. For adults with proven herpes simplex virus encephalitis, we were unable to recommend for or against the use of corticosteroids. A further 13 good practice statements regarding when to clinically suspect infectious encephalitis, microbiological investigations, additional investigations, treatment, and ongoing care and rehabilitation were agreed.

Conclusions: Given the clinical severity and public health importance of this condition, the paucity of high-quality evidence is striking. Transnational, large-scale research in infective encephalitis is encouraged. **Julia Granerod, Clin Microbiol Infect 2026;■:1**

© 2026 The Authors. Co-published by European Academy of Neurology and Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Background

Encephalitis, or inflammation of the brain parenchyma, is a life-threatening condition associated with significant morbidity and mortality with survivors frequently experiencing serious ongoing sequelae [1]. The incidence of encephalitis varies around the world, ranging from 0.5 to 16 per 100 000 population [2–5]. Herpes simplex virus (HSV) is the most common cause of sporadic encephalitis among adults in Europe [6–8].

Encephalitis is difficult to diagnose and manage, posing a challenge to clinicians. Presenting symptoms, including fever and altered mental state, are nonspecific; only a minority of suspected cases actually have encephalitis [8]. Failure to consider encephalitis and instigate empirical treatment is common and associated with worse outcomes [9,10]. Many aetiologies are not immediately distinguishable but require different treatments [11,12]. The aetiology remains unexplained in a large fraction of cases; this varies from 20% to 70% in published studies [13]. Certain pathogens are more likely in individuals with altered immune status or chronic

medical conditions (Table 1), and some presenting clinical features are traditionally associated with specific pathogens. Whether clinical features or risk factors can be used to reliably predict encephalitis aetiology remains unresolved.

Cerebrospinal fluid (CSF) obtained through lumbar puncture (LP) is the cornerstone of diagnostic testing in encephalitis. LP is a minimally invasive procedure but requires procedural expertise and may be contraindicated [15–17]. It is important to clarify when imaging is required before LP, as over-reliance on computed tomography (CT) head imaging before LP may lead to unnecessary delays and negatively affect diagnostic yield and patient outcomes in central nervous system (CNS) infections [18,19]. Even with timely LPs, some patients remain undiagnosed. Potential reasons for this include a low concentration of pathogens in CSF, insufficient sample volume to perform the required tests, compromised sample integrity through delayed transport or processing, and limitations in the sensitivity of available tests [20]. A lack of CSF pleocytosis may result in wrongly excluding encephalitis as a diagnosis [21]. Repeat LP can be necessary for some diagnoses [22].

Table 1

Infectious causes of acute and subacute/chronic encephalitis in immunocompetent and immunocompromised adults.

Presentation	Immunocompetent	Immunocompromised ^a
Acute	Herpesviruses (HSV-1/2, VZV), enteroviruses, paramyxoviruses (measles, mumps), influenza viruses, adenovirus, parvovirus B19, LCMV, rubella virus, flaviviruses (WNV, JEV, TBEV, Dengue viruses), alphaviruses (WEEV, EEEV, VEEV), bunyaviruses (Lacrosse virus), coltivirus (Colorado tick fever virus), rhabdoviruses (rabies virus, other lyssaviruses, Chandipura virus), Henipah viruses (Nipah)	Herpesviruses (EBV, CMV, HHV-6 and -7, HSV-1/2, VZV), <i>Cryptococcus neoformans</i> , <i>Listeria monocytogenes</i> , <i>Toxoplasma gondii</i>
Subacute/chronic	Measles virus (SSPE), <i>Mycobacterium tuberculosis</i> , <i>Treponema pallidum</i> , <i>Borrelia burgdorferi</i>	Measles virus (inclusion body encephalitis), VZV (multifocal leukoencephalopathy), CMV, HSV (especially HSV-2), HHV-6, enteroviruses, JC/BK virus (PML), HIV (dementia), <i>C. neoformans</i> , <i>T. gondii</i>

CMV, cytomegalovirus; EBV, Epstein–Barr virus; EEEV, eastern equine encephalitis virus; HHV, human herpesvirus; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; PML, progressive multifocal leukoencephalopathy; SSPE, subacute sclerosing panencephalitis; TBEV, tick-borne encephalitis virus; VEEV, Venezuelan equine encephalitis virus; VZV, Varicella zoster virus; WEEV, western equine encephalitis virus; WNV, West Nile virus. Reference: [14].

^a These causes affect immunocompromised individuals in addition to the causes listed for immunocompetent individuals.

There is an increasing availability of multiplex PCR panels for pathogen detection in the CSF, which may use less CSF volume, and may reduce turnaround time and staff workload [23–25]. However, multiplex assays may be less sensitive than single-target assays and appropriate validation is essential [23]. Serological assays detecting intrathecal antibodies improve diagnostic yield but are insufficiently used in clinical practice [20]. Antibody tests are the mainstay for diagnosis of encephalitis caused by arboviruses, such as the flaviviruses West Nile virus and tick-borne, but are susceptible to false-positives and cross-reaction between antibodies to different flaviviruses after previous infection or immunization [26]. Serum and CSF testing frequently remain negative, and the cause of a suspected case can remain unclear [13]. Brain imaging using CT and magnetic resonance imaging (MRI) are often undertaken before CSF sampling and can reveal characteristic aetiological features (e.g., temporal lobe enhancement in HSV encephalitis) as well as exclude alternative diagnoses [27]. However, these are not usually relied on to distinguish causes of encephalitis. In patients remaining undiagnosed despite extensive diagnostics, a brain biopsy may be considered; however, the procedure has potential risks [28].

Treatment for encephalitis depends on the underlying cause. Common causes of encephalitis such as HSV and varicella zoster virus (VZV) are treated effectively with aciclovir [29]. Uncertainty remains regarding aciclovir duration and the necessity to demonstrate viral clearance from the CSF [11,30]. A long duration of genome detectability has been found to correlate with poor outcome in HSV encephalitis [31]. There is also significant interest in the benefit of immunomodulation with steroid therapy in HSV encephalitis [32,33]. Other infectious aetiologies have no proven treatment; therapies such as interferon, ribavirin, immunoglobulin, and steroids have been trialled with uncertain efficacy [34–38].

Critically, there are no recent European guidelines to advise on navigating these uncertainties in diagnosis and management of patients with suspected infectious encephalitis. The latest European guidelines were published in 2010 (focusing on ‘viral meningoencephalitis’); UK guidelines on viral encephalitis were published in 2012 and French guidelines on infectious encephalitis were published in 2017 [14,39,40]. Since this time, novel causes of encephalitis have emerged and diagnostic processes have evolved, which need to be reflected in updated guidelines.

Objectives and scope

We aimed to produce recommendations for the diagnosis and management of infectious encephalitis in adults based on current evidence and expert opinion to optimize diagnosis and treatment and improve patient outcome. The target audience of these guidelines includes all clinicians involved in diagnosis, treatment, and follow-up of encephalitis in adults in the context of hospital care, including hospital physicians, infectious disease specialists, neurologists, intensive care specialists, and microbiologists/virologists.

Methods

Development of this guideline followed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework and European Academy of Neurology recommendations on the development of neurological management guidelines [41,42]. A Task Force (TF) which consisted of 19 members was convened. TF members were experts in fields relevant to encephalitis (e.g., neurology, infectious disease, microbiology,

neurocritical care, rehabilitation, patient representative) or guideline development and represented all geographical areas of Europe. For detailed methodology, including TF composition, see the full guidelines protocol in the supplement.

Questions

TF members identified relevant clinical and scientific questions, using previous published guidelines, and their own practice and expertise [14]. Sixteen key questions were prioritized by the TF and formulated in Population/Intervention/Comparison/Outcome (PICO) format. Questions were grouped into five topics: when to clinically suspect infectious encephalitis; microbiological investigations; additional investigations; treatment; and ongoing care and rehabilitation. TF members were subdivided into Working Groups (WGs), each assigned to one of the five topics.

Search for studies

A predefined search strategy was devised for each question (see specific search strategies in the supplement) and used to search PubMed and the Cochrane Central Register of Controlled Trials for relevant studies from 1 January 2008 to 18 March 2021 (14 January 2022 for questions 1 and 2). January 2008 was chosen as the start date as the questions to be answered in these guidelines were informed by the previous UK guidelines which systematically searched the literature up until 2008 [14]. Relevant studies from the previous UK guidelines were included, and reference lists of included papers were reviewed for further relevant articles. A subsequent search was performed to identify new potentially relevant studies up to 26 January 2024.

To increase efficiency of the guidelines process, a number of approaches were taken, detailed in the study protocol in the supplement. One such approach was considering inclusion of systematic reviews alongside primary studies [43]. For searches yielding more than 1000 primary study results, the initial search was limited to systematic reviews. If a systematic review (assessed as moderate or high quality by Assessing the Methodological Quality of Systematic Reviews-2 [AMSTAR-2] or similar) was found, the search start date was reset to the latest search date of the systematic review.

Study selection and data extraction

Two independent reviewers screened the titles/abstracts and full texts of articles, where necessary, for eligibility. The inclusion criteria for studies were: (1) relevant to the question being addressed and (2) study design as defined by individual PICO criteria (see protocol in supplementary appendix; eligible case series must include ≥ 5 cases). Exclusion criteria included primary studies with < 5 cases; editorials, letters, and correspondence which did not report primary data; studies including only paediatric populations; studies in any language other than English for which reliable translation was not available; and animal-only studies.

Data from each included study were extracted into a structured data extraction form. The quality of included studies was assessed using standardized tools: the Cochrane Collaboration's tool for assessing risk of bias in randomized trials Risk of Bias-2 (RoB 2); Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies; Risk of Bias in Non-randomized Studies of Interventions; Joanna Briggs Institute & Newcastle–Ottawa Scale tools for noninterventional observational studies; and Assessing the Methodological Quality of Systematic

Reviews (AMSTAR)-2 [44–49]. All extracted data and quality assessments were verified by a second reviewer. Differences of opinion were resolved through discussion (with arbitration by a third reviewer if necessary).

Data synthesis and certainty in the evidence

After data extraction, the body of evidence for each question was summarized in tables. Where appropriate, a meta-analysis was conducted using standard Cochrane methodology [50]. All factors that might decrease (e.g., study limitations/risk of bias, inconsistency of results, indirectness of evidence, imprecision, publication bias) or increase (e.g., large effect sizes, out-of-sample validation of results, and dose–response) certainty in the evidence were considered, using the GRADE approach, with resulting labels of high, moderate, low, or very low certainty [42].

Formulation of recommendations

The GRADE approach was used to make recommendations based on the findings, using the Evidence to Decision framework [51]. Strength (strong or conditional) and direction (for or against) of recommendations were determined based on balance between desirable and undesirable effects, certainty in the evidence, values and preferences, required resources, cost effectiveness, equity, acceptability, and feasibility. A conditional recommendation was made when the balance was in favour or against a course of action, but this had the potential to vary substantially between different clinical situations, or the balance was not strongly in favour or against the action, such that it may be viewed differently by individual clinicians, patients or policymakers in a given scenario. Where a GRADE-based recommendation was not deemed appropriate by the WGs and overall TF, because of only indirect evidence being available, a good practice statement was made, in accordance with published guidance from the GRADE Working Group [52]. This lists criteria to be met to justify formulation of a good practice statement, and use of the Evidence to Decision process, outlining a structured process. The GRADE-ADOLOPMENT methodology was also considered, so that existing recommendations from previous guidelines were considered before embarking on a new recommendation process, to prevent duplication of effort where possible [53]. Consensus on recommendations and good practice statements was first achieved within WGs and then endorsed by all TF members at a meeting held at the European Society of Clinical Microbiology and Infectious Diseases Global conference in Barcelona, Spain on 28 April 2024. As none of the disagreements between the recommendations and statements proposed by the WGs and opinions from the TF remained unresolved after this meeting, a modified Delphi approach was not required to achieve consensus.

Results

Table 2 provides a summary of recommendations and good practice statements for each question. A brief justification is provided, along with notes that may support implementation of the guidelines in practice. The supplement provides a summary of the evidence, as well as detailed reports of the systematic reviews for each question, including flow diagrams for inclusion of studies,

characteristics of included studies, and quality/risk of bias assessments. For all questions, results from the studies are provided in evidence summaries and/or descriptive tables; where formal meta-analysis was deemed appropriate, forest plots and GRADE summary of findings tables are provided.

WHEN TO SUSPECT ENCEPHALITIS

Background question: What are the typical presenting clinical features of infectious encephalitis (including possible variations due to altered immune status)?

The classical clinical features of infectious encephalitis include fever and abnormal mental status, often with severe headache, nausea, and vomiting [14]. Altered mental state, seizures, fever, and aphasia have been identified as common features in HSV encephalitis, whereas focal neurological symptoms and rash were most commonly seen in VZV encephalitis in a UK prospective study [8,54–56]. A large Indian prospective cohort study reported seizures in three quarters of patients with HSV encephalitis [56]. Immunocompromised patients with infectious encephalitis are more likely to present with focal neurological deficits and confusion, and to have low CSF glucose concentration and high CSF neutrophil count than immunocompetent patients [57].

1. In adults with suspected encephalitis, how accurate are presenting clinical features in predicting an infectious aetiology compared to PCR?

Good practice statement

The presence or absence of specific clinical features (e.g., altered behaviour, seizures, coma, fever, focal neurological signs) should not be relied upon to guide management of patients with suspected infectious encephalitis.

Justification

Six relevant studies were found from which data for two studies could be pooled through meta-analysis [8,54–56,58,59]. As none of the studies were designed to primarily compare clinical features against a reference standard of PCR for a specific pathogen, the evidence was considered too indirect for a recommendation. The results, although of very low certainty, suggest suboptimal performance of the presence of altered behaviour, seizures, coma, fever, and focal neurological signs in predicting HSV and VZV as a causative pathogen (Tables S1.2 and S1.3).

Practical notes

Even though clinical features cannot definitively distinguish between aetiologies, some specific features may point towards a specific cause and prompt further investigation (Table 3) [60].

Subgroups

Clinical features for individual pathogens may differ between immunocompetent and immunocompromised individuals, although the evidence for specific pathogens is lacking.

Research needs

Studies should be conducted to compare presenting clinical features against a reference standard for diagnosis of common encephalitis pathogens, to support clinicians with decisions about diagnostics and empirical therapy.

Table 2
Summary of recommendations.

Question	Recommendations/good practice statements
When to suspect encephalitis	
1. Presenting clinical features – In adults with suspected encephalitis, how accurate are presenting clinical features in predicting an infectious aetiology compared to PCR?	The presence or absence of specific clinical features should not be relied upon to guide management of patients with suspected infectious encephalitis (good practice statement).
2. Presence of risk factors – In adults with infectious encephalitis, does the presence of risk factors (i.e., immune status, travel history, infectious contacts, pets, water exposure, past medical history) compared to their absence result in a higher risk of specific infectious aetiologies (as confirmed by PCR)?	A carefully taken history can reveal clues as to the cause of infectious encephalitis. Table 4 provides some risk factors suggestive of some specific aetiological agents of infectious encephalitis (good practice statement).
Microbiological investigations	
3. LP before imaging – In adults with suspected encephalitis, does LP before imaging result in deterioration or worse clinical outcome compared to no LP before imaging?	All patients with suspected encephalitis should have an LP as soon as possible after admission, unless contraindicated (good practice statement; Table 5). If there are clinical symptoms or signs of raised intracranial pressure with potential brain shift, a CT or MRI scan should be performed as soon as possible to evaluate for contraindications and potential features of the disease process (good practice statement; Table 5). There should be no delay in performing an LP following imaging unless contraindications are present. If imaging is not needed before LP, imaging (CT or MRI) should be performed after the LP (good practice statement; Table 5). There are absolute and relative contraindications for performing LP in patients receiving anticoagulant or antiplatelet therapy. Reversal, if needed, can be performed according to local guidelines (good practice statement; Table 5). In situations where an LP is not possible at first, the situation should be reviewed at least every 12–24 hours, and an LP performed when it is safe to do so (good practice statement).
3a. What are the contraindications for an immediate LP?	
4. Second LP – In adults with suspected encephalitis and a first non-diagnostic LP, does a second LP 48 hours later result in improved aetiological diagnosis?	If an initial LP is nondiagnostic and the LP was performed within the first 3 days after onset of the neurological features, a second LP should be performed 2–3 days later if there is an ongoing suspicion of encephalitis (good practice statement).
5. Multiplex PCR – In suspected sporadic infectious encephalitis, is individualized/specific CSF PCR better than standardized/multiplex CSF PCR panel for first-line detection of the causative pathogen? 5b. Are there additional specific testing panels for immunocompromised patients?	We conditionally recommend against replacing pathogen-specific PCR testing of CSF with multiplex CSF PCR panels for diagnosis of adults with suspected infectious encephalitis (conditional recommendation, low certainty in the evidence).
5a. Antibodies – Which CSF antibody testing is useful in the diagnosis of infectious encephalitis?	See Table 6 for guidance specific on CSF antibody testing by pathogen (good practice statement). Guidance from an infection specialist should be sought in deciding on and interpreting results from these investigations.
6. Brain biopsy – In patients with suspected infectious encephalitis and no aetiological diagnosis despite extensive investigation, who are deteriorating, does brain biopsy change patient management compared to no brain biopsy?	Brain biopsy has no place in the initial assessment of suspected acute infectious encephalitis (good practice statement). Biopsy may inform diagnosis and can influence management when there is no aetiological diagnosis despite extensive investigation, but the potential benefits should be balanced against the potential risks for the individual patient (good practice statement). Where possible, focal abnormalities on imaging should guide sampling using targeted stereotactic techniques (good practice statement). If imaging shows no focal abnormality, a blind biopsy may be considered (good practice statement).
Additional investigations	
7. CT/MRI – In adults with suspected encephalitis, what is the diagnostic accuracy of specific features on CT and MRI to predict an infectious aetiology compared to PCR?	It can be helpful to identify specific patterns of involvement of the brain on MRI to support suspicion of a particular pathogen pending PCR results (good practice statement). MRI (including contrast-enhanced diffusion-weighted imaging) is the preferred modality and should be performed as soon as possible in suspected infectious encephalitis; ideally within 24 hours of hospital admission, certainly within 48 hours (good practice statement). If the patient's condition precludes MRI scan, or MRI is not available, urgent CT scanning may help evaluate alternative causes of the patient's presentation, or potential contra-indications to immediate LP. However, diagnostic accuracy of CT is not comparable to MRI for making a diagnosis of infectious encephalitis, and CT is less accurate than clinical features for predicting potential complications from an LP (good practice statement).
8. EEG – In patients with suspected infectious encephalitis and psychiatric features, does EEG change the patient management compared to no EEG?	EEG need not be performed routinely in all patients with suspected infectious encephalitis (good practice statement). For patients with uncertainty whether there is a psychiatric or organic cause, an EEG should be performed to seek encephalopathic changes, as this may influence management (good practice statement). EEG should also be performed if subtle motor, or nonconvulsive seizures are suspected (good practice statement).
Treatment	
9. Treatment with aciclovir – In patients with suspected encephalitis, does treatment with aciclovir improve patient outcome compared to no aciclovir administration?	IV aciclovir should be started as soon as possible after suspicion of encephalitis (ideally within 6 hours from presentation to hospital). In some situations, other antimicrobial treatments should be considered alongside aciclovir (strong recommendation, low certainty in the evidence).
9a. If HSV is not confirmed when can aciclovir be stopped?	If there is a low clinical suspicion of HSV encephalitis, or a confirmed alternative diagnosis, aciclovir can be stopped if ALL of the following apply: (1) negative CSF PCR for HSV (if LP was >72 hours after onset of neurological illness), (2) normal CSF

(continued on next page)

Table 2 (continued)

Question	Recommendations/good practice statements
10. Duration of aciclovir treatment – In patients with proven HSV encephalitis (positive CSF PCR or intrathecal antibody production), does administering aciclovir for more than two weeks reduce morbidity compared to two-week aciclovir therapy?	white blood cell count (ignore if an alternative diagnosis would explain a raised count), and (3) no temporal lobe abnormality on MRI of the brain. If there is a high clinical suspicion of HSV encephalitis, aciclovir may be continued despite negative HSV PCR on CSF, absence of temporal lobe encephalitis on MRI brain, and despite an alternative diagnosis being made. In such cases, re-evaluation should be performed in consultation with an infection specialist and/or neurologist, including repeat CSF examination and brain imaging (good practice statement). In patients with proven HSV encephalitis, a minimum of 14 days of therapy with IV aciclovir should be administered (good practice statement). In patients who are improving, it is not necessary to repeat CSF examination before stopping therapy at 14 days (good practice statement). In patients who have not improved, are clinically worse, or who are immunocompromised, extension of therapy to 21 days, or even 28 days, can be considered. In this case, repeat CSF examination for leukocyte count and HSV PCR may be of benefit, with continuation of aciclovir until results are available (good practice statement).
10a. When should aciclovir resistance be suspected and what action should be taken?	Aciclovir resistance in encephalitis is very rare and should not be assumed to be the cause of progressive disease (good practice statement). In a patient with progressive disease despite 14 days of IV aciclovir therapy, assessment of the likelihood of aciclovir resistance must be performed alongside exclusion of alternative causes of deterioration. Switching therapy to foscarnet and testing for aciclovir resistance may be considered, in consultation with a neurologist or infection specialist (good practice statement). In patients who are immunosuppressed, and/or taking long-term aciclovir prophylaxis, there may be a lower threshold for considering aciclovir resistance, though it is still considered to be rare in the context of encephalitis (good practice statement).
11. Corticosteroids – In patients with proven HSV encephalitis, does the addition of corticosteroid therapy improve outcome compared to standard care alone?	For adults with proven HSV encephalitis, we are unable to recommend for or against the use of corticosteroids.
11a. If yes, when should corticosteroids be introduced?	
12. Aciclovir dose in VZV – In patients with proven VZV encephalitis (positive CSF PCR or intrathecal antibody production), does treatment with high dose aciclovir (usually 20 mg/kg three times per day) compared to 10 mg/kg aciclovir three times per day reduce mortality and morbidity?	Patients with proven VZV encephalitis should be treated with a standard dose of 10 mg/kg aciclovir three times daily (if renal function is normal). If an associated vasculitis is confirmed, corticosteroid therapy should be added; in the absence of evidence of vasculitis, empirical corticosteroids should not be started for this indication (good practice statement).
13. Prophylactic antiseizure therapy/medication – What is the impact on morbidity and mortality of prophylactic antiseizure treatment versus no prophylactic antiseizure treatment in patients with infectious encephalitis?	From the available indirect evidence, the balance between benefit and potential harm is against starting primary prophylaxis (without seizures as part of the illness). Management of seizures in the acute phase should be as per existing guidelines. A decision to continue the antiseizure medication after the acute hospital admission should be individualized based on various factors, including extent and location of abnormalities on brain imaging and number and timing of seizures, in discussion with the patient and the multidisciplinary team (good practice statement).
Ongoing care and rehabilitation	
14. Admission to intensive care – In patients with infectious encephalitis and deep/worsening coma score or status epilepticus, does admission to intensive care improve outcome and reduce mortality compared to no admission to intensive care?	Patients with infectious encephalitis and falling level of consciousness or status epilepticus (including nonconvulsive status epilepticus) require admission to an ICU, or a neurocritical care unit, if available, for assessment for airway protection and ventilatory support; management as needed of blood pressure, intracranial pressure, and cerebral perfusion pressure (using invasive monitoring where appropriate); and correction of metabolic imbalances, including electrolytes, carbon dioxide, and glucose (good practice statement).
15. HSV encephalitis relapse – In a patient with HSV encephalitis with recurrent/worsening symptoms, does autoantibody testing improve the chance of identifying the cause of relapse compared to not testing for autoantibodies?	In a patient with recent HSV encephalitis with recurrent or worsening symptoms, CSF should be tested for anti-NMDA receptor antibodies. Testing for other autoantibodies should also be considered (good practice statement).
16. Rehabilitation – In patients with infectious encephalitis, does follow-up care and rehabilitation reduce morbidity compared to no follow-up care and rehabilitation?	All patients with encephalitis should receive periodic assessment and rehabilitation at each stage of their encephalitis journey. This should be tailored to each patient, in terms of stage and severity of illness, its impact, and to their goals, values, and preferences (good practice statement). Patients (when conscious level permits) and their caregivers should be made aware of the support provided by the health and social care system of their country of residence, and also by nongovernmental organizations such as Encephalitis International (www.encephalitis.info) (good practice statement). Patients (and caregivers) should not be discharged from hospital without communication about their diagnosis and its potential impact on their life. Arrangements for outpatient follow-up and plans for on-going therapy and rehabilitation should be formulated prior to hospital discharge (good practice statement). All patients should be given access to assessment for rehabilitation (good practice statement).

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HSV, herpes simplex virus; ICU, intensive care unit; IV, intravenous; LP, lumbar puncture; MRI, magnetic resonance imaging; NMDA, N-methyl D-aspartate; VZV, Varicella zoster virus.

Table 3Clinical features suggestive of encephalitis aetiologies in adults^a.

Clinical feature	Pathogen/disease to consider ^b
Neurological	
Abnormal behaviour (new psychosis, mania, delirium, aggression, agitation, catatonia)	Autoimmune conditions ^c
Myoclonus	Measles virus/SSPE, <i>Tropheryma whipplei</i> , Prion disease, autoimmune conditions ^c
Brainstem features, including autonomic dysfunction, bulbar signs, and cranial neuropathies ^d	<i>Listeria monocytogenes</i> , <i>Brucella</i> species, <i>Mycobacterium tuberculosis</i> , and some viral CNS infections
Bulbar or ocular dysfunction	HHV-6, <i>L. monocytogenes</i> , <i>T. whipplei</i> , autoimmune conditions ^c
Rapid neurological decompensation ^d	Rabies virus
Parkinsonism or tremor	Flaviviruses (WNV, JEV, SLEV, TBEV, DENV), <i>Toxoplasma gondii</i> , <i>T. whipplei</i> , <i>Borrelia burgdorferi</i>
Acute flaccid paralysis	Polio virus, other enteroviruses, flaviviruses (e.g., tick-borne encephalitis virus, WNV), rabies virus
Cerebellar ataxia	VZV, mumps virus, <i>T. whipplei</i>
Other	
Skin rash, prior or current	VZV (vesicular/polymorphic), HHV-6, WNV, rubella virus, enteroviruses (palms and soles and/or oral ulcers), HIV, <i>Rickettsia</i> (palms and soles, papular), <i>Mycoplasma pneumoniae</i> , <i>Borrelia</i> species, <i>Treponema pallidum</i> (palms and soles, preceding genital ulcer), measles virus (papular), dengue virus (macular or petechial), <i>Neisseria meningitidis</i> (petechial)
Chronic skin ulcer	<i>Acanthamoeba</i> , <i>Balamuthia</i>
Eschar	<i>Orientia tsutsugamushi</i> , <i>Rickettsia</i> species
Lymphadenopathy	<i>Bartonella henselae</i> , HIV, EBV, CMV, measles virus, rubella virus, <i>T. pallidum</i> , <i>M. tuberculosis</i> , <i>Orientia tsutsugamushi</i>
Hepatitis	<i>Coxiella burnetii</i> , <i>O. tsutsugamushi</i> , DENV
Parotitis and/or epididymo-orchitis	Mumps virus, CMV
Pulmonary abnormalities	Influenza virus, <i>M. pneumoniae</i> , <i>C. burnetii</i> , <i>M. tuberculosis</i> , <i>Histoplasma capsulatum</i> , <i>Cryptococcus neoformans</i> , SARS-CoV-2, <i>Nocardia</i> species
Retinitis	CMV, HSV, VZV, <i>B. henselae</i> , <i>T. pallidum</i> , HIV, <i>Toxoplasma gondii</i>
Hydrophobia	Rabies virus

CMV, cytomegalovirus; CNS, central nervous system; DENV, dengue virus; EBV, Epstein–Barr virus; EV-71, Enterovirus-71; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; SLE, St. Louis encephalitis; SSPE, subacute sclerosing panencephalitis; TBEV, tick-borne encephalitis virus; VZV, Varicella zoster virus; WNV, West Nile virus.

References: [39,60].

^a In Europe, HSV is the most likely pathogen with any presenting features above and therefore is only mentioned alongside presenting features that are particularly specific to HSV encephalitis.

^b This is not an exhaustive list.

^c Autoimmune encephalitis, such as anti-NMDAR encephalitis and others.

^d Some pathogens are prone to causing raised intracranial pressure, which may present with ‘false-localizing’ cranial nerve signs, most commonly abducens nerve palsy, or rapid neurological decompensation. These include *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, and *Histoplasma capsulatum*. Pyogenic meningitis (usually due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae*) can also present with such features, which is a major differential diagnosis of infectious encephalitis.

2. In adults with infectious encephalitis, does the presence of risk factors (i.e., immune status, travel history, infectious contacts, pets, water exposure, past medical history) compared to their absence result in a higher risk of specific infectious aetiologies (as confirmed by PCR)?

Good practice statement

Although evidence from well-conducted large studies is lacking, a carefully taken history can reveal clues as to the cause of infectious encephalitis. Table 4 provides some risk factors (e.g., immunocompromise, recent infection, travel, animal exposure) suggestive of some specific aetiological agents of infectious encephalitis.

Justification

Four potentially relevant studies were found from which data could not be pooled through meta-analysis, nor could a recommendation be made, because of missing data, indirectness, and not primarily performing a risk factor analysis for causative pathogens [8,55,58,61]. Two that aligned closely with the PICO suggested that older age may predict HSV as a causative pathogen, but the certainty in this was too low and overall, the evidence was too indirect to support a recommendation (Table S2.2) [8,61].

Practical notes

Even though risk factors cannot definitively distinguish between aetiologies, some specific risk factors may point towards

a specific cause and prompt further investigation (Table 4) [60,62–64]. Clinicians should remain informed about the spread of previously tropical or geographically restricted pathogens (e.g., TBEV, Chikungunya, dengue) as the epidemiology of infective encephalitis evolves because of population movements and climate change.

Subgroups

These are covered in Table 4.

Research needs

Large multicentre prospective studies are required to inform risk factors for specific infectious aetiologies.

MICROBIOLOGICAL INVESTIGATIONS

3. In adults with suspected encephalitis, does LP before brain imaging result in deterioration or worse clinical outcome compared to no LP before brain imaging?

3a. What are the contraindications for LP?

Good practice statements

- All patients with suspected encephalitis should have an LP as soon as possible after hospital admission, unless there is a contraindication.

Table 4
Risk factors suggestive of encephalitis aetiologies in adults^a.

Risk factor/exposure	Pathogen/disease to consider
Mosquito bites	WNV, SLEV, WEEV, JEV, La Crosse, MVEV, dengue virus, Usutu virus, Chikungunya virus, Zika virus
Tick bite	TBEV, Powassan virus, <i>Borrelia</i> species
Animal exposure	
Dog	Rabies virus
Bat	Rabies virus, Nipah virus
Bird	Usutu virus, WNV
Pig	Nipah virus, JEV
Cat	<i>Bartonella</i> species, <i>Toxoplasma gondii</i>
Rodent	LCMV, <i>Leptospira</i> species, Lassa virus, Hanta virus, <i>Francisella tularensis</i>
Macaque primate	Herpes B virus
Sheep/goat	<i>Coxiella burnetii</i>
Raccoon	<i>Baylisascaris procyonis</i>
Animal urine	<i>Leptospira</i> species
Travel	
Asia	JEV (China, Southeast Asia, Indian subcontinent), Nipah virus (Malaysia, Singapore, Bangladesh, India), TBEV (Russia, China, Japan), dengue virus (widespread), Chikungunya virus (widespread), <i>Orientia tsutsugamushi</i> (scrub typhus; widespread), Rabies virus
Europe	TBEV (central, eastern and northern countries), Toscana virus, WNV
Africa	Chikungunya, <i>Plasmodium falciparum</i> (malaria), dengue virus, Lassa virus (West Africa), Yellow fever virus
North America	WNV, EEEV, La Crosse virus, SLEV, WEEV
South America	Zika virus, Chikungunya virus, dengue virus, yellow fever virus, EEEV
Illness exposure	
Chickenpox	VZV
Measles	Measles virus
Respiratory infection	Mycoplasma, influenza virus, SARS-CoV-2, enterovirus, <i>Streptococcus pneumoniae</i>
Meningitis or sepsis	<i>Neisseria meningitidis</i>
Food exposure	
Unpasteurized milk and milk products	TBEV, <i>Listeria monocytogenes</i> , <i>Brucella</i> species, <i>C. burnetii</i>
Fresh water	<i>Naegleria fowleri</i> , <i>Leptospira</i> species, <i>Acanthamoeba</i> species
Soil	<i>Balamuthia mandrillaris</i> , <i>Acanthamoeba</i> species
Immunocompromise	HIV, <i>T. gondii</i> , <i>Cryptococcus neoformans</i> , <i>Mycobacterium tuberculosis</i> , CMV, JC virus, HHV-6, <i>L. monocytogenes</i>
Occupation	
Forest workers	TBEV, <i>Borrelia</i> species
Work with animals	Rabies virus, <i>Leptospira</i>

CMV, cytomegalovirus; EEEV, Eastern equine encephalitis virus; HHV-6, human herpesvirus 6; JEV, Japanese encephalitis virus; LCMV, lymphocytic choriomeningitis virus; MVEV, Murray Valley encephalitis virus; SLEV, St. Louis encephalitis virus; TBEV, tick-borne encephalitis virus; VZV, Varicella zoster virus; WEEV, Western equine encephalitis virus; WNV, West Nile virus.

References: [60,62–64].

^a It is important to note that this list is not complete and prioritizes pathogens of greatest importance in Europe.

Table 5
Contraindications for LP.

When to suspect raised intracranial pressure with potential brain shift, which indicates brain imaging should be performed before LP:
- Altered mental status (GCS <10) - New-onset seizures - Focal neurological signs, such as hemiparesis, aphasia, hemianopsia/hemianopia, and cranial nerve dysfunction^a - Presence of papilloedema^b - Severe immunocompromise (e.g., untreated HIV, transplant recipient, immunosuppressive therapy)
Situations which may prevent immediate LP, independent of imaging findings:
- Local infection at LP site - Severely abnormal coagulation tests, if performed^c - Low platelet count ($<40 \times 10^9/L$)^{c,d} - Anticoagulant or antiplatelet therapy (except for low-dose [75 mg once daily] aspirin/acetysalicylic acid, which can be continued)^e

GCS, Glasgow Coma Scale; INR, international normalized ratio; LP, lumbar puncture.

^a Although relative bradycardia with hypertension and abnormal 'doll's eye' movement are included as contraindications in other guidelines, they were felt to be unhelpful and rarely occur in the absence of other focal neurological signs. Although cranial nerve signs are excluded from focal neurological abnormalities when considering contraindications to lumbar puncture in the European meningitis guidelines [65], in the context of suspected encephalitis, cranial nerve signs are more likely to indicate a focal lesion which may predispose to the rare event of brain herniation during lumbar puncture.

^b If full visualization of the optic discs is not possible, or there is uncertainty, the inability to rule out papilloedema should not be the sole criterion for brain imaging before LP.

^c These thresholds vary between local and/or national guidelines and protocols, which should be consulted where available.

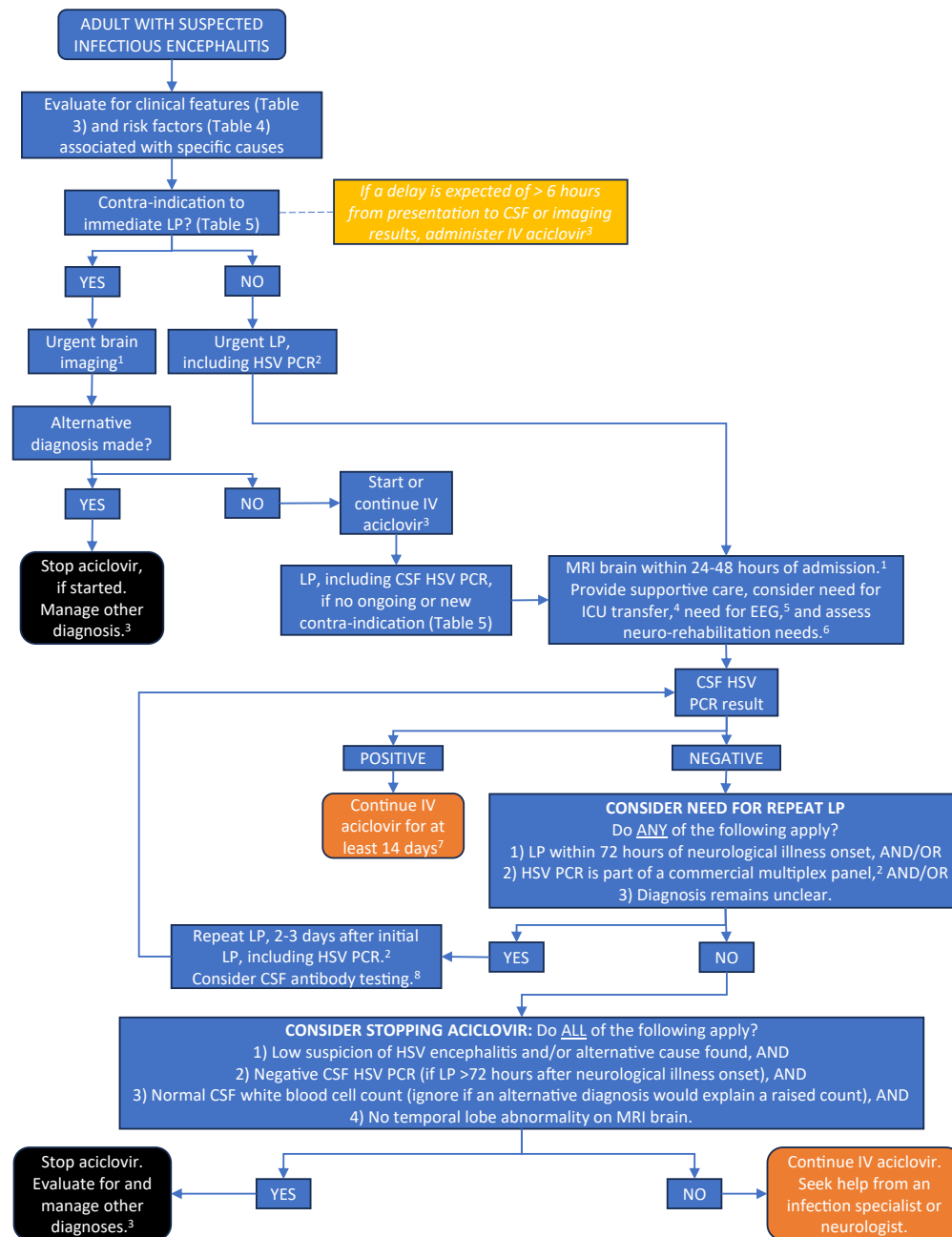
^d If there is evidence of platelet dysfunction, local expert input should be sought.

^e This should be guided by local and/or national guidelines and protocols, and a clinical assessment of benefit-versus-risk, for both performing-versus-deferring the lumbar puncture, and for stopping-versus-continuing the therapy. Key factors include the indication for and dose of the anticoagulant or antiplatelet agents, and the potential harm from delaying the lumbar puncture and therefore extending diagnostic uncertainty. An example of clinical guidelines on this, incorporating these factors, has been made by the Association of British Neurologists [66].

- If there are clinical symptoms or signs of raised intracranial pressure with potential brain shift (Table 5) [65,66], a brain CT or MRI scan should be performed as soon as possible to evaluate for contraindications and potential features of the disease

process. Aciclovir therapy should not be delayed awaiting imaging or LP [(Fig. 1) [67].

- There should be no delay in performing an LP after imaging unless contraindications are present (Table 5). If imaging is not



CSF, cerebrospinal fluid; CT, computed tomography; HSV, Herpes simplex virus; IV, intravenous; LP, lumbar puncture; MRI, magnetic resonance imaging; VZV, Varicella zoster virus

¹MRI is the preferred modality, but if the patient's condition precludes this or access to urgent MRI scanning is not available, CT scanning is of value. ²If the initial CSF HSV PCR is part of a commercial multiplex assay, then a negative result may be more likely to be a false-negative, in which case a dedicated singleplex HSV PCR should be used. If residual sample from the first LP is available, that could be used for a singleplex PCR, if LP was performed more than 72 hours since onset of neurological illness. ³See Table 8 for empirical treatments for suspected aetiologies other than HSV/VZV. ⁴See Question 14 for further details. ⁵See Question 8 for further details. ⁶See Question 16 for further details. ⁷Further details on duration can be found in Question 10. ⁸See Table 6 for further details.

Fig. 1. Algorithm for management of adults with suspected infectious encephalitis. Adapted from [14,67].

needed before LP, imaging (CT or MRI) should be performed after the LP.

- There are absolute and relative contraindications for performing LP in patients receiving anticoagulant or antiplatelet therapy. Reversal, if needed, can be performed according to local guidelines.
- In situations where an LP is not possible at first, the situation should be reviewed at least every 12–24 hours, and an LP performed when it is safe to do so.

Justification

No eligible studies were found which compare outcomes with LP before imaging to no LP before imaging; this meant a recommendation could not be justified. It has been shown in acute bacterial meningitis that LP without prior CT scan is associated with significantly earlier treatment and a favourable outcome [18]. Four studies were identified that reported on contraindications for LP [68–71]. Contraindications such as focal neurological signs and papilloedema were reported in most studies, whereas coagulation abnormalities for example were only mentioned in few. Suggestions regarding contraindications from the European Society of Clinical Microbiology and Infectious Diseases guideline on bacterial meningitis were also incorporated [65].

Practical notes

Potential contraindications not included in Table 5 may be included in local and national guidelines which should also be considered when making this decision. Ultimately, to arrive at the best possible decision a good healthcare organization is required which provides access to expertise and clinical experience at patient admission. Although the inability to obtain CSF should not delay intravenous (IV) aciclovir therapy, brain imaging may provide alternative diagnoses. Therefore, within the period of 6 hours after presentation to hospital (see question 9), it may be beneficial to wait for imaging before administering aciclovir.

Subgroups

The same contraindications should apply for immunocompromised as for immunocompetent individuals, although it is recognized that severe immunocompromise is itself a contraindication according to some authorities.

Research needs

Recent direct comparisons of outcomes after LP with and without prior imaging are required to inform clinical decision-making about use of imaging for patients presenting with suspected encephalitis.

4. In adults with suspected encephalitis and a first non-diagnostic LP, does a second LP 48 hours later result in improved aetiological diagnosis?

Good practice statement

If an initial LP does not confirm a diagnosis, and the LP was performed within the first 3 days after onset of the neurological features, a second LP should be performed 2–3 days later if there is an ongoing suspicion of encephalitis.

Justification

No article met the inclusion criteria; however, the WG decided that a good practice statement based on indirect evidence was necessary to ensure optimal care. In HSV encephalitis, it has been shown that a first PCR, usually within 3 days of onset of the neurological illness, may be negative whereas a repeat PCR is positive

[72–74]. In addition, evolution of CSF parameters such as differential leukocyte count may be useful in diagnosis of other pathogens, e.g. enteroviruses and *Mycobacterium tuberculosis* may cause an initial predominance of polymorphonuclear cells (polymorphs) which switches to mononuclear (lymphocyte) predominance later in the illness [75].

Practical notes

Pending a second HSV PCR result, if the patient is considered to have a high likelihood of infectious encephalitis, aciclovir should be continued, unless an alternative diagnosis is established. The aim should be for LP to be repeated as close as possible to 48 hours after the initial LP, to avoid delay in making a diagnosis and informing management. In addition to repeating leukocyte count (total and differential), protein, glucose, and PCR for HSV and other viruses, further tests should be performed according to the clinical situation (e.g., larger volume sample for *M. tuberculosis*, or tests for other pathogens), in consultation with an infectious disease specialist and/or neurologist.

Subgroups

There was a lack of evidence for guidance focusing on specific subgroups.

Research needs

Studies are required to address this question specifically.

5/5b. In suspected sporadic infectious encephalitis is individualized/specific CSF PCR better than standardized/multiplex CSF PCR panel for first-line detection of the causative pathogen? Are there additional specific testing panels for immunocompromised patients?

Recommendation

We conditionally recommend against replacing pathogen-specific PCR testing of CSF with multiplex CSF PCR panels for diagnosis of adult patients with suspected infectious encephalitis (Conditional recommendation; low certainty in the evidence).

Justification

The main concern about current CSF multiplex PCR panels is the high risk of false-negative results for HSV-1, the most common cause of sporadic infectious encephalitis in adults in Europe. The corresponding Section 5 (Tables S5.2–S5.5) in the supplement provides the full Evidence to Decision which underpins the recommendation. Two cross-sectional studies met the inclusion criteria, and a further systematic review/meta-analysis was subsequently identified and included [22,76,77]. The most widely studied multiplex PCR panel used in suspected encephalitis is the BioFire FilmArray Meningitis/Encephalitis (ME) Panel. This includes targets for 14 pathogens with the potential to cause meningitis or encephalitis including HSV-1. However, in a meta-analysis of three studies (6883 participants) comparing the FilmArray ME against pathogen-specific 'single-plex' PCR, pooled sensitivity for HSV-1 PCR was 76% (see Table S5.7 for quality assessment using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist for diagnostic test accuracy). Although the certainty in this estimate was very low, this raised enough concerns about the ability of the FilmArray ME and other multiplex PCR panels to 'rule-out' the most important treatable viral pathogen. Although pooled sensitivity for other key encephalitis pathogens was better (VZV: 91%; HSV-2: 94%; enterovirus: 94%), and pooled specificity was 99–100% for all, the certainty in the evidence for these estimates was also low or very low.

In addition, false-positive results have been reported widely, especially for less common pathogens. Despite the potential for earlier results, and reduced need for human, consumable, and infrastructure resources in the laboratory, this prompted the WG to decide on a recommendation against use of multiplex PCR in place of pathogen-specific PCR for testing CSF in patients with suspected infectious encephalitis.

Practical notes

The WG considered that some laboratories have the BioFire FilmArray or other similar platforms in place for encephalitis as well as other syndromes. In such situations, if a negative PCR for HSV-1 on the multiplex panel can be followed by a dedicated single-plex HSV-1 PCR, that may be an adequate approach. However, it would mean that decision making for patient care may need to be deferred until that second PCR result. Communicating the initial negative result may be challenging to ensure this does not lead to premature cessation of antiviral therapy or other potential harmful effects.

Subgroups

The available evidence did not suggest a benefit for multiplex CSF PCR panels in specific subgroups of patients with suspected infectious encephalitis, for example immunocompromised individuals.

Monitoring and evaluation

All laboratories and their referring clinical units using multiplex PCRs for CSF testing in infectious encephalitis should perform a local evaluation to compare these against dedicated single-plex PCRs, as accuracy and impact of a positive or negative test may vary in different settings and for different patients.

Research needs

To inform the use of multiplex PCRs for encephalitis in adults, future studies should include more patients with HSV encephalitis, as well as disaggregated results for adults with suspected encephalitis (rather than combined with meningitis). The uncertainty in sensitivity estimates in recent systematic reviews highlights the urgent need for head-to-head clinical diagnostic test accuracy studies of single-plex versus multiplex HSV PCRs [23,78]. As a significant proportion of encephalitis cases remain undiagnosed, novel diagnostics are needed, particularly the development of untargeted approaches. Cost-effectiveness studies in microbiological diagnostics of infectious encephalitis would be beneficial, as would studies on metagenomics and proteomics to possibly

detect more aetiologies in encephalitis of hitherto unknown origin.

5a. Which CSF antibody testing is useful in the diagnosis of infectious encephalitis?

Good practice statement

See Table 6 for good practice statement by pathogen [79,80]. Guidance from a specialist in infectious diseases or clinical microbiology/virology should be sought in deciding on and interpreting results from these investigations.

Justification

Four suitable studies were found, although they were small and focused on specific pathogens, providing evidence that was too heterogeneous and indirect for a recommendation to be made [20,81–83]. CSF and serum testing for HSV-specific IgG antibodies can increase overall diagnosis of HSV encephalitis, including when PCR for HSV is negative [20], and diagnosis can be made long after the onset of HSV encephalitis because intrathecal antibodies can persist for many years [84]. Evidence for the value of anti-VZV IgG testing in addition to VZV CSF PCR is relatively lacking. A few studies have reported concurrent positivity by CSF PCR and VZV IgG antibodies in patients with VZV CNS infections [81,85]; however, another study failed to detect intrathecal production in CSF PCR positive patients [20]. Anti-TBEV IgM were detected in all and IgG antibodies in most CSF samples from patients infected in different areas of Europe who presented with neurological signs of TBE ($n = 5$) [82]. Diagnosis of subacute sclerosing panencephalitis is confirmed by demonstrating intrathecal production of measles-specific IgG [20,86].

Practical notes

Timing of testing, and, if relevant, re-testing, for antibodies in CSF should be decided with the help of a specialist in infectious diseases or clinical microbiology/virology. Testing for other pathogens, including flaviviruses such as dengue, Japanese encephalitis virus (JEV), and Toscana viruses, should be considered according to the geographical area in which the infection is thought to have been acquired.

Subgroups

Returning travellers from outside of Europe can have encephalitis because of various pathogens, each of which may require bespoke testing protocols which should be supported by an expert in imported infections.

Table 6

Good practice statements for CSF antibody testing by pathogen.

Pathogen	Good practice statements
Herpesviruses (HSV, VZV and others)	For patients with suspected encephalitis in whom HSV PCR of the CSF was not performed early in the illness, a paired CSF and serum sample taken 7–10 days from onset of the neurological illness should be sent for HSV-specific IgG antibody testing. For patients with suspected encephalitis in whom HSV PCR of the CSF was found to be repeatedly negative during the first week, and no other cause has been found, a CSF and a serum sample should be sent for HSV-specific IgG antibody testing. Testing for intrathecal antibodies ^a against other herpesviruses may be useful, but this should be decided on a case-by-case basis.
Flaviviruses (e.g., TBEV, JEV, WNV)	In suspected flavivirus encephalitis, CSF IgM antibody testing is diagnostic and should be repeated if initially negative, if the suspicion remains. If the individual is previously vaccinated IgM response may be delayed or ameliorated, and intrathecal CSF IgG antibodies ^a may be diagnostic.
SSPE	In patients with suspected SSPE, demonstration of intrathecal antimeasles antibodies ^a is diagnostic.
Borrelia	In patients with suspected neuroborreliosis, demonstration of intrathecal antibodies ^a is diagnostic.
Imported pathogens	For returning travellers where there may be suspicion of encephalitis acquired from the place of travel, CSF antibody testing can assist in making a diagnosis, but a specialist in imported infections should be consulted.

CSF, cerebrospinal fluid; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; SSPE, subacute sclerosing panencephalitis; TBEV, tick-borne encephalitis virus; VZV, Varicella zoster virus; WNV, West Nile virus.

^a This is the demonstration of antibody production within the central nervous system, rather than the antibodies having crossed into the CSF space from the blood [79,80].

Research needs

Updated direct evidence from larger studies designed to address this question is required to inform optimal specific tests, timing and samples for intrathecal antibody testing, and its potential pitfalls.

6. In adults with suspected infectious encephalitis and no aetiological diagnosis despite extensive investigation, who are deteriorating, does brain biopsy change patient management compared to no brain biopsy?

Good practice statement

- Brain biopsy has no place in the initial assessment of suspected acute infectious encephalitis.
- Biopsy may inform diagnosis and can influence management when there is no aetiological diagnosis despite extensive investigation (including direct and indirect evidence for infectious and autoimmune causes as well as MRI and functional imaging such as positron emission tomography), but the potential benefits should be balanced against the potential risks for the individual patient.
- Where possible, focal abnormalities on imaging should guide sampling using targeted stereotactic techniques.
- If imaging shows no focal abnormality, a blind biopsy may be considered.

Justification

Two suitable studies were identified [87,88]. Brain biopsy has been proposed to improve the diagnosis of encephalitis in these smaller case series or cohort studies, some of which focus on specific types of encephalitis (e.g., brainstem). However, not all studies report on change in management, and a comparison with those not having biopsy is not made in most studies making the evidence indirect and therefore requiring a good practice statement.

Practical notes

The balance of benefit versus potential harm needs to be weighed carefully, and by experts in the procedure as well as the potential causes of the illness, so decision to perform brain biopsy should ideally be discussed in a multidisciplinary team. This should include at least an infection specialist, neurologist, and neurosurgeon. This team should also decide on which tests should be performed on the brain tissue, which should be tailored to ongoing differential diagnoses, the type and amount of tissue obtained, which tests have already been performed, and accessibility of investigations in local and reference laboratories.

Subgroups

Specific patient subgroups, for example those with immunocompromise or other comorbidities, may require a tailored approach to timing and indications for biopsy.

Research needs

Studies seeking to assess the value of brain biopsy in diagnosis of encephalitis should be conducted prospectively and focus on the impact on patient management.

ADDITIONAL INVESTIGATIONS

Background question: What are the typical CT and MRI abnormalities in infectious encephalitis?

Patterns of imaging abnormalities are described in cohorts of more common encephalitis aetiologies (Table 7). HSV encephalitis typically exhibits bilateral asymmetrical involvement of the limbic system, including the medial temporal lobes, insular cortices and inferolateral frontal lobes, and cingulate gyri, on MRI [93,94]. In Japanese encephalitis, thalamic lesions on MRI are commonly seen, but the diagnosis is not excluded by their absence [89]. In TBE, a pathologic MRI is less common in the acute phase; however, with time lesions may appear in thalami, basal ganglia, and/or cerebellum [95].

7. In adults with suspected encephalitis, what is the diagnostic accuracy of specific features on CT and MRI to predict an infectious aetiology compared to PCR?

Good practice statement

- The diagnostic accuracy of brain imaging in predicting specific infectious aetiologies in encephalitis is unclear. It can be helpful to identify specific patterns of involvement of the brain on MRI to support suspicion of a particular pathogen pending PCR results.
- MRI (including contrast-enhanced diffusion-weighted imaging) is the preferred imaging modality and should be performed as soon as possible on patients with suspected infectious encephalitis; ideally this should be within 24 hours of hospital admission, but certainly within 48 hours.
- If the patient's condition precludes MRI scan, or MRI is not available, urgent CT scanning may help evaluate alternative causes of the patient's presentation, or potential contraindications to immediate LP. However, diagnostic accuracy of CT is not comparable with MRI for making a diagnosis of infectious encephalitis, and CT is less accurate than clinical features for predicting potential complications from a LP.

Table 7

Key MRI features suggestive of specific viral causes.

Virus	Key MRI findings	Typical distribution
HSV-1	T2 hyperintensity, restricted diffusion, sometimes haemorrhages are seen	Frontal and temporal lobes, rarely extratemporal
VZV	T2 hyperintensity with areas of restricted diffusion; vasculopathy, haemorrhage, and necrosis may occur	Cerebellum, thalami, cerebral cortex, basal ganglia
CMV	Nonspecific T2/FLAIR periventricular hyperintensities and/or ventriculitis, more prominent in HIV-associated cases	Periventricular, cerebral hemispheres
JEV	T2 hyperintensity, restricted diffusion. Sometimes haemorrhages are seen.	Thalami commonly involved. Basal ganglia, pons, midbrain, cerebellum are sometimes involved.
Dengue virus	T2 hyperintensity with areas of restricted diffusion. Sometimes petechial haemorrhages and diffuse cerebral oedema may be seen.	Bilateral thalami, pons, medulla
HIV	Diffuse cerebral atrophy. T2 hyperintensities in periventricular and deep white matter.	Periventricular and deep white matter

CMV, cytomegalovirus; HSV, herpes simplex virus; JEV, Japanese encephalitis virus; VZV, Varicella zoster virus.

References: [89–92].

Justification

Seven relevant studies were identified, none of which set out to make a direct comparison of the diagnostic accuracy of brain imaging versus PCR testing [27,54,55,58,59,91,96]. The presence of temporal lobe involvement in most patients with HSV encephalitis was reported in the majority of studies [27,55,56,59,60,96]. The sensitivity and specificity of CT imaging for HSV was 83% and 100%, respectively, in a UK study; MRI had a sensitivity of 85% and specificity of 100% for HSV [27]. For JEV in India, the commonest feature on MRI was thalamic hyperintensity, brainstem involvement, and basal ganglia involvement [91]. The included studies comprised a small number of participants, with substantial heterogeneity in terms of population and comparator diagnoses, so their results were not pooled using meta-analysis and a recommendation was not made.

Practical notes

Some features on an MRI scan of the brain may support continuation of therapy while awaiting PCR results, or when a PCR result is negative. For example, temporal lobe hyperintensity on MRI brain is suggestive of HSV encephalitis, so continuing aciclovir if the first PCR is negative, is advised. As CT is insensitive for establishing or excluding a diagnosis of encephalitis, it should not alone guide continuation or cessation of treatment. However, if an alternative diagnosis is established based on clinical features and CT, then cessation of presumptive encephalitis treatment can be considered (e.g., subdural haematoma in a patient on anticoagulation after a head injury), with the caveat that CT scans of patients with encephalitis may be reported as suggestive of an alternative pathology (e.g., ischaemic or haemorrhagic stroke or neoplasm). The timing of MRI can be of importance and repeated examinations might be necessary (especially if the patient continues to have features of encephalitis).

Subgroups

Patients may have potential alternative diagnoses that are better evaluated by CT imaging, or require urgent imaging, which may inform the decision on which modality to use.

Research needs

Direct comparisons of brain imaging versus pathogen-specific microbiological testing would inform relative accuracy of each.

8. In patients with suspected encephalitis and psychiatric features, does electroencephalography (EEG) change the patient management compared to no EEG?

Good practice statement

- The evidence is very uncertain about the impact of electroencephalography (EEG) on patient management. EEG need not be performed routinely in all patients with suspected infectious encephalitis.
- For patients with uncertainty whether there is a psychiatric or organic cause, an EEG should be performed to seek encephalopathic changes, as this may influence management.
- EEG should also be performed if subtle motor or nonconvulsive seizures are suspected.

Justification

One study reported that the majority of patients with probable limbic encephalitis of unknown aetiology (95%) referred from psychiatry for neurological assessment were diagnosed with organic rather than psychiatric disease after an abnormal EEG [97].

This was a small, single-centre study from outside of Europe and did not delineate what change in management was due to EEG results versus other aspects of the neurological evaluation [97]. However, various diagnoses were made more likely by the EEG results, EEG is known to be a useful test to discriminate features of an organic encephalopathy from a psychiatric diagnosis [14,98], and in suspected cases of non-convulsive status epilepticus, encephalitis may be one of the most common causes [99].

Practical notes and subgroups

An abnormal EEG result should be interpreted in the context of the pretest probability of infectious encephalitis, as EEG does not distinguish adequately between infectious encephalitis and other types of encephalopathy for example autoimmune encephalitis and hepatic encephalopathy. Patients with suspected encephalitis in whom there is a clinical suspicion of nonconvulsive or subleptomotor status epilepticus (Long and Koyfman's review of clinical features is helpful for nonexperts [100]) should be managed in clinical settings where EEG is available, ideally with capacity for continuous or prolonged monitoring. Patients at higher risk of seizures (e.g., HSV encephalitis, abnormal Glasgow Coma Scale, greater degree of temporal lobe oedema [101]), should be considered for transfer to settings with such capacity [102].

Research needs

Larger prospective studies are needed to inform future recommendations on use of EEG in patients with suspected encephalitis.

TREATMENT

9. In patients with suspected encephalitis, does treatment with aciclovir improve patient outcome compared to no aciclovir administration?

Recommendation

Upon suspicion of encephalitis, we recommend initiation of IV aciclovir as soon as possible (ideally within 6 hours from presentation to hospital) (Strong recommendation; low certainty in the evidence). In some situations, other antimicrobial treatments should be considered alongside aciclovir (Table 8).

Justification

One eligible study was identified [103]. Data from an early randomized trial showed the superiority of aciclovir compared with vidarabine in terms of morbidity and mortality (19% versus 50%, p 0.04) for the treatment of HSV encephalitis [29,103]. Although randomized trials of aciclovir treatment have not been conducted for all patients with suspected encephalitis at presentation to hospital, the WG concluded that IV aciclovir should be started as soon as possible after suspicion of encephalitis based on HSV often being the most frequently reported aetiology of encephalitis in Europe [13]; high mortality and morbidity from HSV encephalitis [29,104]; benefit of early aciclovir administration in patients with HSV encephalitis [29,104–110]; and aciclovir also being active against VZV [13,96].

The TF agreed that the benefits of IV aciclovir administration far outweighed the risks; overall certainty in the evidence was moderate (as some of the evidence was indirect); and aciclovir is an easily affordable drug likely to be acceptable to patients, clinicians, and policymakers and feasible to implement for patients with suspected encephalitis. Taking the other supporting rationale into account, the TF decided to adopt a recommendation made by previous guidelines, in line with GRADE-ADOLOPMENT methodology [14,39,53,60]. In doing so, the TF acknowledged limited

Table 8
Available treatments for common causes of encephalitis^a.

Pathogen	Treatment
Viruses	
CMV	Ganciclovir or foscarnet
HIV	Antiretrovirals
HSV	IV aciclovir
VZV	IV aciclovir
Bacteria	
<i>Leptospira</i> species	Benzylpenicillin, ceftriaxone, or doxycycline
<i>Listeria monocytogenes</i>	Ampicillin/amoxicillin, co-trimoxazole, or meropenem
<i>Mycobacterium tuberculosis</i>	Regimens vary, for drug-susceptible disease most include rifampicin, isoniazid, pyrazinamide, and ethambutol or a fluoroquinolone, with dexamethasone
<i>Orientia tsutsugamushi</i> (Scrub typhus)	Doxycycline and/or azithromycin
<i>Streptococcus pneumoniae</i> (pneumococcus, usually causes meningitis)	Ceftriaxone (± vancomycin, depending on local risk of ceftriaxone resistance)
<i>Treponema pallidum</i> (syphilis)	Penicillin G, procaine penicillin, ceftriaxone, or doxycycline

CMV, cytomegalovirus; HSV, herpes simplex virus; IV, intravenous; VZV, Varicella zoster virus.

^a Adapted from [1,67].

evidence for the 6-hour target for initiating treatment, but felt this captured the balance of potential harm from delaying treatment, against the practicalities of performing clinical assessment, evaluating for alternative common differential diagnoses, and prescription and administration of an IV medication.

Practical notes

The initial clinical picture may include other differential diagnoses. Thus, broad treatment should be initiated according to the individual situation until test results are available. Available treatments for specific causes of encephalitis are displayed in Table 8.

Subgroups

The recommendation also applies to immunocompromised patients. Pregnancy is not considered an absolute contraindication for aciclovir initiation.

Research needs

There is interest in the potential use of high-dose oral valaciclovir as an alternative to IV aciclovir, which requires further investigation [1,111].

9a. If HSV is not confirmed, when can aciclovir be stopped?

Good practice statements

- If there is a low clinical suspicion of HSV encephalitis, or a confirmed alternative diagnosis, aciclovir can be stopped if ALL of the following apply: (1) negative CSF PCR for HSV (if LP was >72 hours after onset of neurological illness), (2) normal CSF white blood cell count (ignore if an alternative diagnosis would explain a raised count), and (3) no temporal lobe abnormality is found on MRI of the brain.
- If there is a high clinical suspicion of HSV encephalitis, aciclovir may be continued despite negative HSV PCR on CSF, the absence of temporal lobe encephalitis on brain MRI, and despite an alternative diagnosis being made. In such cases, re-evaluation should be performed in consultation with an infection specialist and/or neurologist, including repeat CSF examination and brain imaging.

Justification

No study met the inclusion criteria, so a recommendation was not formulated. As HSV is a common cause of infectious

encephalitis in adults in Europe (diagnosed in 10–20% of those with suspected encephalitis) [6,8,112,113], and HSV encephalitis can present with initial normal CSF leukocyte count, negative CSF HSV PCR, and normal MRI brain appearances, it was decided that empirical treatment should only be stopped if all of these are present, when the clinical probability is felt to be low [21,114,115].

Practical notes

Some PCR tests have suboptimal sensitivities and negative predictive values for HSV, so these may not be relied upon for meeting the above criteria for stopping treatment, as false-negatives may be common [23].

Subgroups

The good practice statement may not apply universally, and specific subgroups may require an alternative approach, for example, immunocompromised patients, and those with a differential diagnosis of VZV encephalitis (where aciclovir treatment may still be required).

Research needs

Conditions for stopping aciclovir treatment should be evaluated and refined in prospective studies of patients with suspected HSV encephalitis receiving aciclovir.

10. In patients with proven HSV encephalitis (positive CSF PCR or intrathecal antibody production), does administering aciclovir for more than 2 weeks reduce morbidity compared to 2-week aciclovir therapy?

Good practice statements

- In patients with proven HSV encephalitis, a minimum of 14 days of therapy with IV aciclovir should be administered.
- In patients who are improving, it is not necessary to repeat CSF examination before stopping therapy at 14 days.
- In patients who have not improved, are clinically worse, or who are immunocompromised, extension of therapy to 21 days, or even 28 days, can be considered. In this case, repeat CSF examination for leukocyte count and HSV PCR may be of benefit, with continuation of aciclovir until those results are available.

Justification

One observational study of infectious encephalitis from France suggests that longer durations of aciclovir (beyond 14 days) are not

associated with improved patient outcomes [109]. Our ability to provide a recommendation regarding the effect of treatment duration is limited, however, because of the retrospective nature of the study with unmeasured confounding, and no adjustments for known confounders. No randomized trials have been conducted to compare durations of aciclovir therapy for HSV encephalitis. Early trials of aciclovir versus vidarabine used 10 days of aciclovir for HSV encephalitis, but relapses were later reported [29,116–118]. Ongoing immune-mediated inflammation is thought to drive most relapses, although viral replication can persist. As a result, most clinicians now use at least 14–21 days IV treatment in confirmed cases.

Practical notes

If a patient is worsening despite IV aciclovir therapy for 14 days, alternative causes should be considered, such as coinfection with another pathogen or noninfective pathology including auto-immune. Because there is a risk of renal toxicity during aciclovir treatment, sufficient hydration is essential, and renal blood test monitoring should be performed at regular intervals.

Subgroups

Immunocompromised patients may require a different approach, as detailed in the good practice statements.

Research needs

Prospective, preferably randomized, head-to-head comparisons of durations of aciclovir therapy should be conducted. Pharmacokinetic studies of aciclovir and its metabolites might help to inform efficacy and safety of various durations, doses, and formulations.

10a. When should aciclovir resistance be suspected and what action should be taken?

Good practice statements

- Aciclovir resistance in encephalitis is very rare and should not be assumed to be the cause of progressive disease.
- In a patient with progressive disease despite 14 days of IV aciclovir therapy, assessment of the likelihood of aciclovir resistance must be performed alongside exclusion of alternative causes of deterioration. Switch of therapy to foscarnet and testing for mutations in HSV thymidine kinase gene may be considered, in consultation with a neurologist or infectious disease physician, and a microbiologist/virologist.
- In patients who are immunosuppressed, and/or taking long-term aciclovir prophylaxis, there may be a lower threshold for considering aciclovir resistance, although it is still considered to be rare in the context of encephalitis.

Justification

No studies were eligible for inclusion, although the body of indirect evidence available allowed a good practice statement to be formulated, which was deemed necessary to guide practice. Aciclovir resistance in encephalitis is described very rarely in the literature. Among non-neurological isolates from immunocompetent patients who are not taking long-term suppressive aciclovir therapy, resistance is also very rare [119–121]. Resistance, evidence for which comes mostly from nonencephalitis patients, is mostly described in individuals who are immunosuppressed and/

or taking long-term suppressive or preventative aciclovir therapy [122].

Practical notes

Phenotypic aciclovir resistance testing can be difficult to access, and there can be difficulties interpreting genotypic test results [123]. Turnaround times can also be long.

Subgroups

Immunocompromised patients may require a different approach, as detailed in the good practice statements.

Research needs

Systematic analysis of HSV genomes recovered from CSF would be valuable in determining the absolute risk of resistance in patients with HSV encephalitis.

11. In patients with proven HSV encephalitis, does the addition of corticosteroid therapy improve outcome compared to standard care alone?

11a. If yes, when should corticosteroids be introduced?

Recommendation

For adults with proven HSV encephalitis, we are unable to recommend for or against the use of corticosteroids.

Justification

Effectiveness of corticosteroids has not been demonstrated, but harm from corticosteroid use has also not been reported in trials, with moderate certainty in the evidence.

Three reports were eligible for inclusion [104,124,125]. A systematic review was deemed to be of low quality, so its results were not considered (Table S11.3) [124]. The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus Encephalitis terminated prematurely because of slow recruitment, but did not show any difference in outcome measures between adults with HSV encephalitis who received dexamethasone in addition to aciclovir compared with those who received aciclovir alone [104]. Dex-Enceph, a similar more recent trial in the UK, randomised 47 patients to aciclovir plus adjunctive dexamethasone and 47 to aciclovir alone, reporting no difference in primary or secondary outcomes between groups [125].

Further research may inform updates to this recommendation in the future. The corresponding Section 11 in the supplement provides the full Evidence to Decision documentation which underpins the decision. The summary of findings table (Table S11.2) contains only the primary outcome results for each trial (German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus Encephalitis and DexEnceph), as no significant difference was reported for any of the many secondary outcomes in either trial. The results of the two trials were not combined. The DexEnceph trial report was just published, and it was decided that a potentially premature meta-analysis would be unlikely to provide evidence for benefit or harm, as none of the outcomes had substantially different results between the groups in each trial.

Practical notes

Currently, in patients with suspected encephalitis where the aetiology may be HSV, another infection, or an autoimmune cause, corticosteroids are not usually given until HSV has been excluded. However, the evidence now suggests that corticosteroid therapy given as part of empirical treatment for other suspected brain

infections such as bacterial meningitis and CNS tuberculosis, or for suspected autoimmune encephalitis, is unlikely to be harmful in patients ultimately diagnosed with HSV encephalitis.

Subgroups

No subgroup analyses were performed in the German trial. Predefined subgroup analyses did not demonstrate benefit of corticosteroid use versus placebo within the UK-based trial.

Research needs

Future research should focus on the effect of early administration of corticosteroids alongside aciclovir therapy, compared against aciclovir therapy without corticosteroids. This was not fully addressed by the UK trial, in which there was a median of 7 days from presentation to starting corticosteroid therapy. This trial also reported in a *post-hoc* analysis, among patients receiving dexamethasone, that deterioration in the primary outcome (the Wechsler memory score) was associated with delay in administration of dexamethasone [125].

12. In patients with proven VZV encephalitis (positive CSF PCR or intrathecal antibody production), does treatment with high-dose aciclovir (usually 20 mg/kg three times per day) compared to 10 mg/kg aciclovir three times per day reduce mortality and morbidity?

Good practice statement

Patients with proven VZV encephalitis should be treated with a standard dose of 10 mg/kg aciclovir three times daily (if renal function is normal). If an associated vasculitis is confirmed, corticosteroid therapy should be added; in the absence of evidence of vasculitis, empirical corticosteroids should not be started for this indication.

Justification

No comparative studies investigating the use of 20 mg/kg per dose of aciclovir were identified; thus, there is insufficient evidence for a recommendation to be made regarding dosing of aciclovir in VZV encephalitis. The WG agreed to a standard dose of 10 mg/kg based on lack of evidence of potential benefit but well-established potential harm. Aciclovir has several potential adverse effects, including renal failure, which may be more common with higher doses [126,127]. When radiological evidence of CNS vasculitis in patients with VZV CNS infection is detected, corticosteroids might be considered, in addition to antiviral treatment, in accordance with treatment of other CNS vasculitides [98]. Although corticosteroids are used widely to treat post-infectious vasculitis [98], there is no evidence of benefit for patients with VZV encephalitis without vasculitis.

Practical notes and subgroups

The suggested dosing also applies to immunocompromised individuals. If renal insufficiency exists or develops, aciclovir dosing will require adjustment [127]. Concentrations of aciclovir and the metabolite 9-carboxymethoxymethylguanine, which correlates with toxicity symptoms, can be measured in serum and CSF [128,129]. There are no head-to-head studies comparing corticosteroid doses for vasculitis; thus, specific steroid dosing regimens remain unclear.

Research needs

Comparative studies are needed to inform optimal dosing of aciclovir therapy in VZV encephalitis.

13. What is the impact on morbidity and mortality of prophylactic antiseizure treatment versus no prophylactic antiseizure treatment in cases of infectious encephalitis?

Good practice statements

- Evidence for use of prophylactic antiseizure medication in patients with infectious encephalitis is lacking. From the available indirect evidence, the WG concluded that the balance between benefit and potential harm is against starting primary prophylaxis (without seizures as part of the illness).
- Management of seizures in the acute phase should be as per existing guidelines.
- A decision to continue the antiseizure medication after the acute hospital admission should be individualized based on various factors, including extent and location of abnormalities on brain imaging and number and timing of seizures, and should be made in discussion with the patient and the multidisciplinary team.

Justification

No studies were eligible for inclusion, so a recommendation could not be made. However, two cohort studies have shown that the number of antiseizure drugs was not significantly associated with terminal seizure freedom after the acute phase [130] and the risk of seizure relapse did not differ between patients on antiseizure drugs and those without [131].

Practical notes

The decision to continue/stop will depend on whether seizures are prolonged; whether seizures are recurrent; whether there are large areas of abnormality on MRI scan of the brain; whether specific areas are affected; and results of EEG. The antiseizure medication administered should be chosen as per usual epilepsy management guidelines.

Subgroups

The conclusions made by the WG also apply to specific subgroups, including immunocompromised patients.

Research needs

Studies should evaluate the benefits versus harms of primary prophylactic antiseizure medication, and the optimal timing of stopping antiseizure medication after encephalitis.

ONGOING CARE AND REHABILITATION

14. In patients with infectious encephalitis and deep/worsening coma score or status epilepticus, does admission to intensive care improve outcome and reduce mortality compared to no admission to intensive care?

Good practice statement

Patients with infectious encephalitis and falling level of consciousness or status epilepticus (including nonconvulsive status epilepticus) require admission to an intensive care unit (ICU), or a neurocritical care unit, if available, for assessment for airway protection and ventilatory support; management as needed of blood pressure, intracranial pressure, and cerebral perfusion pressure (using invasive monitoring where appropriate); and correction of metabolic imbalances, including electrolytes, carbon dioxide, and glucose.

Justification

One retrospective cohort study of consecutive adult patients admitted with HSV encephalitis reported that ICU admission was not associated with an unfavourable outcome at discharge in multivariate analysis when adjusting for other potential prognostic indicators, although its retrospective nature meant that it was not deemed suitable to inform a recommendation directly [108]. Relevant indirect evidence exists from other causes of coma and other neurological conditions (e.g., bacterial meningitis, stroke) which supports the use of critical care [132–134].

Practical notes and subgroups

The correction of simple precipitating factors, e.g. hypo-/hyperglycaemia or hypoxia or hypercapnia, should be attempted before planning transfer to ICU, or started if ICU care is needed anyway. Although most patients with infectious encephalitis and falling level of consciousness or status epilepticus require admission to an ICU, it should be noted that some patients may present with situations making ICU transfer less desirable, for example, those at a terminal stage of another disease at the time of onset of encephalitis. The decision for ICU care should be made through discussion between the treating clinicians, ICU team, and patient/relatives.

Research needs

Prospective studies including patients with a variety of causes of infectious encephalitis could help strengthen the evidence in this area.

15. In a patient with HSV encephalitis with recurrent/worsening symptoms, does autoantibody testing improve the chance of identifying the cause of relapse compared to not testing for autoantibodies?

Good practice statement

In a patient with recent HSV encephalitis with recurrent or worsening symptoms, CSF should be tested for anti-N-methyl-D-aspartate (anti-NMDA) receptor antibodies. Testing for other autoantibodies should also be considered.

Justification

No studies were eligible for inclusion, the lack of direct evidence precluding formulation of a recommendation. Other studies have found that a significant proportion (27–57%) of patients with relapsing symptoms post-HSV encephalitis have autoantibodies, predominantly anti-NMDA receptor antibodies [135–137].

Practical notes

The WG considered the few reports of other autoantibodies (apart from anti-NMDA receptor antibodies) that can be responsible for worsening or recurrent symptoms in patients with recent HSV encephalitis, including GAD65 and Caspr2 [138,139]. Because the body of literature is limited, exactly which other antibodies to test for should not be specified at this point, and this decision should be taken by a specialist, usually a neurologist. This may change as further knowledge accumulates.

Subgroups

There is insufficient evidence to inform how this good practice statement may apply differently to specific subgroups.

Research needs

There is a need for large prospective studies of patients with recurrent or worsening symptoms after HSV encephalitis, with systematic application of a variety of autoantibody and other tests.

16. In patients with infectious encephalitis, does follow-up care and rehabilitation reduce morbidity compared to no follow-up care and rehabilitation?

Good practice statements

- All patients with encephalitis should receive periodic assessment and rehabilitation at each stage of their encephalitis journey, from acute presentation to their return to the community. This should be tailored to the patient, in terms of their stage and severity of illness and its impact, and to their goals, values, and preferences.
- Patients (when conscious level permits) and their caregivers should be made aware of the support provided by the health and social care system of their country of residence, and also by nongovernmental organizations such as Encephalitis International (www.encephalitis.info).
- Patients (and caregivers) should not be discharged from hospital without communication about their diagnosis and its potential impact on their life. Arrangements for outpatient follow-up and plans for ongoing therapy and rehabilitation should be formulated before hospital discharge.
- All patients should be given access to assessment for rehabilitation.

Justification

Two studies were included [140,141]. A systematic review reported a potential beneficial effect of rehabilitation interventions in a variety of settings among paediatric and adult patients with infectious encephalitis, although only small studies with low methodological quality were included [140]. The other study conducted narrative interviews of people affected by HSV encephalitis and their caregivers, concluding that focused rehabilitation facilitated a more supported transition between the hospital and home [141]. Although the evidence did not directly address morbidity outcomes, a good practice statement was considered necessary, as the benefit of rehabilitation after similar illnesses far outweighs the potential harms and opportunity costs [142–144].

Practical notes

Neurorehabilitation should be started as early as possible, even if the patient is not capable of engaging with this actively, to avoid sequelae from loss of neurological function. Although patients with any critical illness benefit from rehabilitation, neurorehabilitation is preferred for patients with encephalitis. Neurorehabilitation teams integrate physical, cognitive, and behavioural issues, and have more experience in specific complications of injury to the brain such as epilepsy and painful hypertonia of limbs.

Patients and caregivers (i.e., person who provides regular support to someone who has an illness, disability, or long-term condition and needs help with daily life or health-related needs) should be involved in formulation of the rehabilitation objectives. Care should be taken to ensure that all patients with encephalitis should have an assessment for rehabilitation, even if they are determined to have mild disease or full recovery. Some needs may be subtle or masked, and the patient's perspective on impact of their illness on their life may differ from that of healthcare professionals.

Subgroups

The majority of studies focus on HSV encephalitis, limiting generalizability to all patients with encephalitis.

Research needs

Prospective studies of rehabilitation after encephalitis should be conducted, informed by work to determine patient-reported outcome measures and core outcome sets for postencephalitis rehabilitation, including morbidity, quality of life, and functional outcomes.

Discussion

Although prevention of encephalitis through targeted vaccination against infections such as measles and JEV is critical, these clinical practice guidelines focus on diagnosis and management. Recommendations and good practice statements are provided based on current evidence. It is hoped that this will help improve diagnostic and management practices for infectious encephalitis across Europe. Given the clinical severity and public health importance of this condition, the paucity of high-quality evidence is striking. Transnational, large-scale research in infective encephalitis is encouraged. Research should focus on novel treatments and diagnostics, the development of a core outcome set for use in future trials of interventions for acute care and postencephalitis rehabilitation, and other identified areas that have been highlighted under the relevant questions in this guideline. The search strategy for the guideline was limited to two databases for practical reasons; however, it is unlikely that important papers were missed as TF experts are also familiar with relevant literature. This guideline summarizes the available evidence and provides a comprehensive set of statements for use by clinicians, laboratory specialists, and policymakers to inform decisions around diagnosis and management of suspected and confirmed infectious encephalitis in adults.

CRedit authorship contribution statement

Julia Granerod: Methodology, Formal analysis (including evidence review and GRADE application), Investigation (including data collection), Data curation (including screening papers), Writing – original draft, Writing – review and editing, Supervision, Project administration. Johann Sellner: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Jean-Paul Stahl: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Sylviane Defres: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Alexandra Mailles: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Erich Schmutzhard: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Elisabeth Aurelius: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Thomas Whitfield: Formal analysis (including evidence review and GRADE application), Writing – review and editing, Funding acquisition. Luca Massacesi: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Maarten J. Titulaer: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Pille Taba: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Benedict D. Michael: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Tehmina Bharucha: Data curation (including screening papers), Writing – review and editing. Lance Turtle: Data curation (including screening papers), Writing – review and editing. Brendan Sargent: Data curation (including screening papers), Writing – review and editing. Arina Tamborska: Data curation (including screening papers), Writing – review and editing. Jonathan Catrall: Data curation (including screening papers), Writing

– review and editing. Yun Huang: Data curation (including screening papers), Writing – review and editing. Eva Maria Hodel: Data curation (including screening papers), Writing – review and editing. Suzannah Lant: Data curation (including screening papers), Writing – review and editing. Glynn Webb: Data curation (including screening papers), Writing – review and editing. Rajish S.K. Shil: Data curation (including screening papers), Writing – review and editing. Shalley Dhar: Data curation (including screening papers), Writing – review and editing. Diederik van de Beek: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Marie Studahl: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Matthijs C. Brouwer: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Uta Meyding-Lamade: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Ava Easton: Formal analysis (including evidence review and GRADE application), Writing – review and editing. Bhagteswar Singh: Methodology, Formal analysis (including evidence review and GRADE application), Investigation (including data collection), Data curation (including screening papers), Writing – original draft, Writing – review and editing, Supervision. Tom Solomon: Conceptualization, Methodology, Writing – review and editing, Supervision, Funding acquisition.

Transparency declaration

Potential conflict of interest

European Academy of Neurology (EAN) Register of Interest forms were collected from all TF members in May 2020 and submitted to the EAN in June 2020. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Conflict of Interest (COI) forms were collected also from TF members in 2020. Updated forms were collected upon submission of the draft manuscript in March 2025. For each WG, COI forms were reviewed by the guidelines management team: TS, JG, and BS (methodologist). For each potential COI, the Guidelines International Network principles were followed [145]. Specifically, all WG and TF members within the meetings were made aware of COIs relevant to the question being discussed, so that this was taken into account when that member spoke. It was not necessary to prevent voting on any recommendation for a specific COI. Data extraction and risk of bias/quality assessment were not performed by a group member who had been an author on a given study.

Financial report

The development of this guideline was funded jointly by ESCMID and EAN. EAN and ESCMID approval of the guideline was received on 13 and 28 November 2025, respectively.

Data availability

The data that support the findings of this study are available in the Supporting Information of this article. These data were derived from the following resources available in the public domain: PubMed at <https://pubmed.ncbi.nlm.nih.gov/> and the Cochrane Central Register of Controlled Trials at <https://www.cochranelibrary.com/central/about-central>.

Acknowledgements

These guidelines were presented at ESCMID Global in Vienna on 13 April 2025, EAN Congress in Helsinki on 22 June 2025, and

Encephalitis International conference on 4 December 2025. This article has been simultaneously co-published in European Journal of Neurology, and in Clinical Microbiology and Infection. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2026.03.009>.

References

- [1] Granerod J, Huang Y, Davies NWS, Sequeira PC, Mwapasa V, Rupali P, et al. Global landscape of encephalitis: Key priorities to reduce future disease burden. *Clin Infect Dis* 2023;77:1552–60. <https://doi.org/10.1093/cid/ciad417>.
- [2] Child N, Croxson MC, Rahnama F, Anderson NE. A retrospective review of acute encephalitis in adults in Auckland over a five-year period (2005–2009). *J Clin Neurosci* 2012;19:1483–5. <https://doi.org/10.1016/j.jocn.2012.03.010>.
- [3] Joshi R, Mishra PK, Joshi D, Santhosh SR, Parida MM, Desikan P, et al. Clinical presentation, etiology, and survival in adult acute encephalitis syndrome in rural Central India. *Clin Neurol Neurosurg* 2013;115:1753–61. <https://doi.org/10.1016/j.clineuro.2013.04.008>.
- [4] Lee SJ, Kim JM, Keum HR, Kim SW, Baek HS, Byun JC, et al. Seasonal trends in the prevalence and incidence of viral encephalitis in Korea (2015–2019). *J Clin Med* 2023;12:2003. <https://doi.org/10.3390/jcm12052003>.
- [5] Granerod J, Ellerington A, Davies NWS, Michael BD, Solomon T, Easton A. Encephalitis: An in-depth review and gap analysis of key variables affecting global disease burden. The Encephalitis Society 2022. <https://www.encephalitis.info/Handlers/Download.ashx?IDMF=8e46425e-745b-41cf-820e-bdf85f9ab3a>. [Accessed 2 August 2022].
- [6] de Ory F, Avellón A, Echevarría JE, Sánchez-Seco MP, Trallero G, Cabrerizo M, et al. Viral infections of the central nervous system in Spain: A prospective study. *J Med Virol* 2013;85:554–62. <https://doi.org/10.1002/jmv.23470>.
- [7] Mailles A, Argemi X, Biron C, Fillatre P, De Broucker T, Buzel R, et al. Changing profile of encephalitis: Results of a 4-year study in France. *Infect Dis Now* 2022;52:1–6. <https://doi.org/10.1016/j.idnow.2021.11.007>.
- [8] Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: A multicentre, population-based prospective study. *Lancet Infect Dis* 2010;10:835–44. [https://doi.org/10.1016/S1473-3099\(10\)70222-X](https://doi.org/10.1016/S1473-3099(10)70222-X).
- [9] McGrath N, Anderson NE, Croxson MC, Powell KF. Herpes simplex encephalitis treated with acyclovir: Diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 1997;63:321–6. <https://doi.org/10.1136/jnnp.63.3.321>.
- [10] Benson PC, Swadron SP. Empiric acyclovir is infrequently initiated in the emergency department to patients ultimately diagnosed with encephalitis. *Ann Emerg Med* 2006;47:100–5. <https://doi.org/10.1016/j.annemergmed.2005.07.019>.
- [11] Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: A clinician's guide. *Pract Neurol* 2007;7:288–305. <https://doi.org/10.1136/jnnp.2007.129098>.
- [12] Solomon T, Whitley RJ. Arthropod-borne viral encephalitis. In: Scheld M, Whitley RJ, Marra C, editors. *Infections of the Central Nervous system*. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004.
- [13] Boucher A, Herrmann JL, Morand P, Buzel R, Crabol Y, Stahl JP, et al. Epidemiology of infectious encephalitis causes in 2016. *Med Mal Infect* 2017;47:221–35. <https://doi.org/10.1016/j.medmal.2017.02.003>.
- [14] Solomon T, Michael BD, Smith PE, Sanderson F, Davies NWS, Hart IJ, et al. Management of suspected viral encephalitis in adults—Association of British Neurologists and British Infection Association National Guidelines. *J Infect* 2012;64:347–73. <https://doi.org/10.1016/j.jinf.2011.11.014>.
- [15] Costerus JM, Brouwer MC, van de Beek D. Technological advances and changing indications for lumbar puncture in neurological disorders. *Lancet Neurol* 2018;17:268–78. [https://doi.org/10.1016/S1474-4422\(18\)30033-4](https://doi.org/10.1016/S1474-4422(18)30033-4).
- [16] Ríos-Hernández M, Jacinto-Villegas JM, Zemiti N, Vilchis-González AH, Padilla-Castañeda MA, Debien B. Development of a lumbar puncture virtual simulator for medical students training: A preliminary evaluation. *Int J Med Robot* 2023;19:e2572. <https://doi.org/10.1002/rcs.2572>.
- [17] Mark DG, Horton BH, Reed ME. Shifts in diagnostic testing for headache in the emergency department, 2015 to 2021. *JAMA Netw Open* 2024;7:e247373. <https://doi.org/10.1001/jamanetworkopen.2024.7373>.
- [18] Michael B, Menezes BF, Cuniffe J, Miller A, Kneen R, Francis G, et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. *Emerg Med J* 2010;27:433–8. <https://doi.org/10.1136/emj.2009.075598>.
- [19] Glimåker M, Johansson B, Bell M, Ericsson M, Bläckberg J, Brink M, et al. Early lumbar puncture in adult bacterial meningitis—Rationale for revised guidelines. *Scand J Infect Dis* 2013;45:657–63. <https://doi.org/10.3109/00365548.2013.799289>.
- [20] Ambrose HE, Granerod J, Clewley JP, Davies NWS, Keir G, Cunningham R, et al. Diagnostic strategy used to establish etiologies of encephalitis in a prospective cohort of patients in England. *J Clin Microbiol* 2011;49:3576–83. <https://doi.org/10.1128/JCM.00862-11>.
- [21] Habis R, Kolchinski A, Heck AN, Bean P, Probasco JC, Hasbun R, et al. Absence of cerebrospinal fluid pleocytosis in encephalitis. *Clin Infect Dis* 2025;81:179–87. <https://doi.org/10.1093/cid/ciae391>.
- [22] de Montmollin E, Dupuis C, Jaquet P, Sarton B, Sazio C, Susset V, et al. Herpes simplex virus encephalitis with initial negative polymerase chain reaction in the cerebrospinal fluid: Prevalence, associated factors, and clinical impact. *Crit Care Med* 2022;50:e643–8. <https://doi.org/10.1097/CCM.0000000000005485>.
- [23] Trujillo-Gómez J, Tsokani S, Arango-Ferreira C, Atehortúa-Muñoz S, Jimenez-Villegas MJ, Serrano-Tabares C, et al. Biofire FilmArray Meningitis/Encephalitis panel for the aetiological diagnosis of central nervous system infections: A systematic review and diagnostic test accuracy meta-analysis. *EclinicalMedicine* 2022;44:101275. <https://doi.org/10.1016/j.eclinm.2022.101275>.
- [24] Humisto A, Antikainen J, Holma T, Jarva H, Toivonen A, Loginov R, et al. Evaluation of the novel CE-IVD-Marked multiplex PCR QIAstat-Dx Meningitis/Encephalitis panel. *Microbiol Spectr* 2023;11:e0514422. <https://doi.org/10.1128/spectrum.05144-22>.
- [25] Tseng YC, Lin PBC, Hsiao CT, Hsueh PR. Multiplex PCR rapid testing for meningitis/encephalitis. *J Infect* 2022;84:834–72. <https://doi.org/10.1016/j.jinf.2022.03.021>.
- [26] Holzmann H. Diagnosis of tick-borne encephalitis. *Vaccine* 2003;21(Suppl 1). [https://doi.org/10.1016/S0264-410X\(02\)00819-8](https://doi.org/10.1016/S0264-410X(02)00819-8). S36–40.
- [27] Granerod J, Davies NWS, Mukonoweshuro W, Mehta A, Das K, Lim M, et al. Neuroimaging in encephalitis: Analysis of imaging findings and interobserver agreement. *Clin Radiol* 2016;71:1050–8. <https://doi.org/10.1016/j.crad.2016.03.015>.
- [28] Mathon B, Pineton de Chambrun M, Bielle F, Amelot A, Le Joncour A. Encephalitis of unknown etiology? Not until the results of a brain biopsy. *Clin Infect Dis* 2021;72:e432. <https://doi.org/10.1093/cid/ciaa1093>.
- [29] Sköldenberg B, Forsgren M, Alestig K, Bergström T, Burman L, Dahlqvist E, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet Lond Engl* 1984;2:707–11. [https://doi.org/10.1016/S0140-6736\(84\)92623-0](https://doi.org/10.1016/S0140-6736(84)92623-0).
- [30] Cinque P, Cleator GM, Weber T, Monteyne P, Sindic CJ, van Loon AM. The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: A consensus report. The EU Concerted Action on Virus Meningitis and Encephalitis. *J Neurol Neurosurg Psychiatry*. 1996;61:339–45. <https://doi.org/10.1136/jnnp.61.4.339>.
- [31] Schloss L, Falk KI, Skoog E, Brytting M, Linde A, Aurelius E. Monitoring of herpes simplex virus DNA types 1 and 2 viral load in cerebrospinal fluid by real-time PCR in patients with herpes simplex encephalitis. *J Med Virol* 2009;81:1432–7. <https://doi.org/10.1002/jmv.21563>.
- [32] Martínez-Torres F, Menon S, Pritsch M, Victor N, Jenetzky E, Jensen K, et al. Protocol for German trial of Acyclovir and corticosteroids in Herpes-simplex-virus-encephalitis (GACHE): A multicenter, multinational, randomized, double-blind, placebo-controlled German, Austrian and Dutch trial [ISRCTN45122933]. *BMC Neurol* 2008;8:40. <https://doi.org/10.1186/1471-2377-8-40>.
- [33] Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. *J Neurol Neurosurg Psychiatry* 2005;76:1544–9. <https://doi.org/10.1136/jnnp.2004.049676>.
- [34] Wengse C, Ericsson J, Hallberg S, Ursing J. [Rapid improvement of tick-borne encephalitis after treatment with corticosteroids]. *Lakartidningen* 2017;114:ELAI. PMID: 28632298.
- [35] Hart JJ, Tillman G, Kraut MA, Chiang HS, Strain JF, Li Y, et al. West Nile virus neuroinvasive disease: Neurological manifestations and prospective longitudinal outcomes. *BMC Infect Dis* 2014;14:248. <https://doi.org/10.1186/1471-2334-14-248>.
- [36] Chowdhury MY, Lang R, Nassar F, Ben-David D, Giladi M, Rubinshtein E, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* 2001;7:675–8. <https://doi.org/10.3201/eid0704.010144>.
- [37] Kalil AC, Devetten MP, Singh S, Lesiak B, Poage DP, Bargerquast K, et al. Use of interferon-alpha in patients with West Nile encephalitis: Report of 2 cases. *Clin Infect Dis* 2005;40:764–6. <https://doi.org/10.1086/427945>.
- [38] Jackson AC, Warrell MJ, Rupprecht CE, Ertl HCJ, Dietzschold B, O'Reilly M, et al. Management of rabies in humans. *Clin Infect Dis* 2003;36:60–3. <https://doi.org/10.1086/344905>.
- [39] Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, et al. Viral meningoencephalitis: A review of diagnostic methods and guidelines for management. *Eur J Neurol* 2010;17:999–e57. <https://doi.org/10.1111/j.1468-1331.2010.02970.x>.
- [40] Stahl JP, Azouvi P, Bruneel F, De Broucker T, Duval X, Fantin B, et al. Guidelines on the management of infectious encephalitis in adults. *Med Mal Infect* 2017;47:179–94. <https://doi.org/10.1016/j.medmal.2017.01.005>.
- [41] Leone MA, Keindl M, Schapira AH, Deuschl G, Federico A. Practical recommendations for the process of proposing, planning and writing a

- neurological management guideline by EAN task forces. *Eur J Neurol* 2015;22:1505–10. <https://doi.org/10.1111/ene.12818>.
- [42] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction–GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94. <https://doi.org/10.1016/j.jclinepi.2010.04.026>.
- [43] Woolf S, Schünemann HJ, Eccles MP, Grimshaw JM, Shekelle P. Developing clinical practice guidelines: Types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. *Implement Sci* 2012;7:61. <https://doi.org/10.1186/1748-5908-7-61>.
- [44] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>.
- [45] Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36. <https://doi.org/10.7326/0003-4819-155-8-201110180-00009>.
- [46] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. <https://doi.org/10.1136/bmj.i4919>.
- [47] Joanna Briggs Institute. JBI critical appraisal tools. <https://jbi.global/critical-appraisal-tools>. [Accessed 9 September 2024].
- [48] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008. <https://doi.org/10.1136/bmj.j4008>.
- [49] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. 2000.
- [50] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 (updated August 2024). Cochrane, 2024. Available from www.cochrane.org/handbook.
- [51] Rehfuess EA, Stratiol JM, Scheel IB, Portela A, Norris SL, Baltussen R. The WHO-INTEGRATE evidence to decision framework version 1.0: Integrating WHO norms and values and a complexity perspective. *BMJ Glob Health* 2019;4(Suppl 1):e000844. <https://doi.org/10.1136/bmjgh-2018-000844>.
- [52] Guyatt GH, Alonso-Coello P, Schünemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: Guidance from the GRADE Working Group. *J Clin Epidemiol* 2016;80:3–7. <https://doi.org/10.1016/j.jclinepi.2016.07.006>.
- [53] Schünemann HJ, Wiercioch W, Brozek J, Etkeandia-Ikoltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *J Clin Epidemiol* 2017;81:101–10. <https://doi.org/10.1016/j.jclinepi.2016.09.009>.
- [54] Jordan B, Kösling S, Emmer A, Koch A, Müller T, Kornhuber M. A study on viral CNS inflammation beyond herpes encephalitis. *J Neurovirol* 2016;22:763–73. <https://doi.org/10.1007/s13365-016-0452-5>.
- [55] Çiftçi Kavaklıoğlu B, Çoban E, Şen A, Söylemezoglu E, Aldan MA, Ataklı D, et al. Review of viral encephalitis cases seen at a tertiary care center in Turkey: Focus on Herpes Simplex Type 1. *Noro Psikiyatri Ars* 2017;54:209–15. <https://doi.org/10.5152/npa.2016.12540>.
- [56] Misra UK, Kalita J. Seizures in encephalitis: Predictors and outcome. *Seizure* 2009;18:583–7. <https://doi.org/10.1016/j.seizure.2009.06.003>.
- [57] Kolchinski A, Li M, Habis R. Encephalitis in the immunocompromised: Clinical presentation, diagnostic findings, treatment, and comparison of infectious and autoimmune etiologies. 2024. <https://doi.org/10.1093/ofid/ofaf332>.
- [58] Basaran S, Yavuz SS, Bali EA, Cagatay A, Oncul O, Ozsut H, et al. Hyponatremia is predictive of HSV-1 encephalitis among patients with viral encephalitis. *Tohoku J Exp Med* 2019;247:189–95. <https://doi.org/10.1620/tjem.247.189>.
- [59] Pleumpanupat P, Danchaivijitr N, Danchaivijitr C. Retrospective study of patients with herpes simplex encephalitis and positive CSF PCR. *J Med Assoc Thai* 2009;92(Suppl 2): S95–100. PMID: 19562992.
- [60] Bloch KC, Glaser C, Gaston D, Venkatesan A. State of the art: Acute encephalitis. *Clin Infect Dis* 2023;77. <https://doi.org/10.1093/cid/ciad306>. e14–33.
- [61] Hansen MA, Samannodi MS, Castelblanco RL, Hasbun R. Clinical epidemiology, risk factors, and outcomes of encephalitis in older adults. *Clin Infect Dis* 2020;70:2377–85. <https://doi.org/10.1093/cid/ciz635>.
- [62] Lewis P, Glaser CA. Encephalitis. *Pediatr Rev* 2005;26:353–63. <https://doi.org/10.1542/pir.26-10-353>.
- [63] Granerod J. Encephalitis in England: Incidence and cause. London, UK: London School of Hygiene and Tropical Medicine; 2011.
- [64] T AM, Singh B, Rupali P. Central nervous system infections in the tropics. *Curr Opin Infect Dis* 2024;37:201–10. <https://doi.org/10.1097/QCO.0000000000001015>.
- [65] van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. *Clin Microbiol Infect* 2016;22(Suppl 3). <https://doi.org/10.1016/j.cmi.2016.01.007>. S37–62.
- [66] Dodd KC, Emsley HCA, Desborough MJR, Chhetri SK. Periprocedural antithrombotic management for lumbar puncture: Association of British Neurologists clinical guideline. *Pract Neurol* 2018;18:436–46. <https://doi.org/10.1136/practneurol-2017-001820>.
- [67] Singh B, Lipunga G, Thangavelu P, Dhar S, Cronemberger L, Abhilash K, et al. A multifaceted intervention to improve diagnosis and early management of hospitalised patients with suspected acute brain infections in Brazil, India, and Malawi: An international multicentre intervention study. *Lancet* 2025;405:991–1003. [https://doi.org/10.1016/S0140-6736\(25\)00263-6](https://doi.org/10.1016/S0140-6736(25)00263-6).
- [68] Gaieski DF, Nathan BR, Weingart SD, Smith WS. Emergency neurologic life support: Meningitis and encephalitis. *Neurocrit Care* 2012;17(Suppl 1). <https://doi.org/10.1007/s12028-012-9751-8>. S66–72.
- [69] Bell DJ, Suckling R, Rothburn MM, Blanchard T, Stoeter D, Michael B, et al. Management of suspected herpes simplex virus encephalitis in adults in a U.K. teaching hospital. *Clin Med Lond Engl*. 2009;9:231–5. <https://doi.org/10.7861/clinmedicine.9-3-231>.
- [70] Michael BD, Powell G, Curtis S, Bailey L, Almond S, McGill F, et al. Improving the diagnosis of central nervous system infections in adults through introduction of a simple lumbar puncture pack. *Emerg Med J* 2013;30:402–5. <https://doi.org/10.1136/emered-2012-201248>.
- [71] Ellul M, Solomon T. Acute encephalitis – diagnosis and management. *Clin Med (Lond)*. 2018;18:155–9. <https://doi.org/10.7861/clinmedicine.18-2-155>.
- [72] Aurelius E, Johansson B, Sköldenberg B, Forsgren M. Encephalitis in immunocompetent patients due to herpes simplex virus type 1 or 2 as determined by type-specific polymerase chain reaction and antibody assays of cerebrospinal fluid. *J Med Virol*. 1993;39:179–86. <https://doi.org/10.1002/jmv.1890390302>.
- [73] Studahl M, Bergström T, Hagberg L. Acute viral encephalitis in adults—a prospective study. *Scand J Infect Dis* 1998;30:215–20. <https://doi.org/10.1080/00365549850160828>.
- [74] Davies NWS, Brown LJ, Gonde J, Irish D, Robinson RO, Swan AV, et al. Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections. *J Neurol Neurosurg Psychiatry* 2005;76:82–7. <https://doi.org/10.1136/jnnp.2004.045336>.
- [75] Jereñ T, Beus I. Characteristics of cerebrospinal fluid in tuberculous meningitis. *Acta Cytol* 1982;26:678–80.
- [76] Broadhurst MJ, Dujari S, Budvytiene I, Pinsky BA, Gold CA, Banaei N. Utilization, yield, and accuracy of the FilmArray Meningitis/Encephalitis panel with diagnostic stewardship and testing algorithm. *J Clin Microbiol* 2020;58:e00311–20. <https://doi.org/10.1128/JCM.00311-20>.
- [77] Govekar SR, Lakshman LP, Reddy V, Mani RS, Mahadevan A, Susarla SK, et al. Syndrome evaluation system for simultaneous detection of pathogens causing acute encephalitic syndrome in India, Part-2: Validation using well characterized clinical samples. *Front Neurol* 2018;9:1193. <https://doi.org/10.3389/fneur.2018.01193>.
- [78] Vaughn E, Mircescu A, Caya C, Yao M, Gore G, Dendukuri N, et al. Diagnostic accuracy of rapid one-step PCR assays for detection of herpes simplex virus-1 and -2 in cerebrospinal fluid: A systematic review and meta-analysis. *Clin Microbiol Infect* 2022;28:1547–57. <https://doi.org/10.1016/j.cmi.2022.06.004>.
- [79] Granerod J, Cunningham R, Zuckerman M, Mutton K, Davies NWS, Walsh AL, et al. Causality in acute encephalitis: Defining aetiologies. *Epidemiol Infect* 2010;138:783–800. <https://doi.org/10.1017/S0950268810000725>.
- [80] Reiber H, Lange P. Quantification of virus-specific antibodies in cerebrospinal fluid and serum: Sensitive and specific detection of antibody synthesis in brain. *Clin Chem*. 1991;37:1153–60.
- [81] Gregoire SM, van Pesch V, Goffette S, Peeters A, Sindic CJM. Polymerase chain reaction analysis and oligoclonal antibody in the cerebrospinal fluid from 34 patients with varicella-zoster virus infection of the nervous system. *J Neurol Neurosurg Psychiatry* 2006;77:938–42. <https://doi.org/10.1136/jnnp.2006.090316>.
- [82] Reusken C, Boonstra M, Rugebregt S, Scherbeijn S, Chandler F, Avšič-Zupanc T, et al. An evaluation of serological methods to diagnose tick-borne encephalitis from serum and cerebrospinal fluid. *J Clin Virol* 2019;120:78–83. <https://doi.org/10.1016/j.jcv.2019.09.009>.
- [83] Forsgren M, Sköldenberg B, Jeansson S, Grandien M, Blomberg J, Juto P, et al. Serodiagnosis of herpes encephalitis by indirect enzyme-linked immunosorbent assay, experience from a Swedish antiviral trial. *Serodiagn Immunother Infect Dis*. 1989;3:259–71.
- [84] Vandvik B, Sköldenberg B, Forsgren M, Stjernstedt G, Jeansson S, Norrby E. Long-term persistence of intrathecal virus-specific antibody responses after herpes simplex virus encephalitis. *J Neurol* 1985;231:307–12. <https://doi.org/10.1007/BF00313707>.
- [85] Grahñ A, Studahl M, Nilsson S, Thomsson E, Bäckström M, Bergström T. Varicella-zoster virus (VZV) glycoprotein E is a serological antigen for detection of intrathecal antibodies to VZV in central nervous system infections, without cross-reaction to herpes simplex virus 1. *Clin Vaccine Immunol* 2011;18:1336–42. <https://doi.org/10.1128/CLV.05061-11>.
- [86] Wendorf KA, Winter K, Zipprich J, Schechter R, Hacker JK, Preas C, et al. Subacute sclerosing panencephalitis: The devastating measles complication that might be more common than previously estimated. *Clin Infect Dis* 2017;65:226–32. <https://doi.org/10.1093/cid/cix302>.
- [87] Tan IL, Mowry EM, Steele SU, Pardo CA, McArthur JC, Nath A, et al. Brainstem encephalitis: Etiologies, treatment, and predictors of outcome. *J Neurol* 2013;260:2312–9. <https://doi.org/10.1007/s00415-013-6986-z>.

- [88] Abdullah KG, Li Y, Agarwal P, Nayak NR, Thawani JP, Balu R, et al. Long-term utility and complication profile of open craniotomy for biopsy in patients with idiopathic encephalitis. *J Clin Neurosci* 2017;37:69–72. <https://doi.org/10.1016/j.jocn.2016.11.013>.
- [89] Dung NM, Turtle L, Chong WK, Mai NT, Thao TT, Thuy TT, et al. An evaluation of the usefulness of neuroimaging for the diagnosis of Japanese encephalitis. *J Neurol* 2009;256:2052–60. <https://doi.org/10.1007/s00415-009-5249-5>.
- [90] Jayaraman K, Rangasami R, Chandrasekharan A. Magnetic resonance imaging findings in viral encephalitis: A pictorial essay. *J Neurosci Rural Pract* 2018;9:556–60. https://doi.org/10.4103/jnrp.jnrp_120_18.
- [91] Misra UK, Kalita J, Phadke RV, Wadwekar V, Boruah DK, Srivastava A, et al. Usefulness of various MRI sequences in the diagnosis of viral encephalitis. *Acta Trop* 2010;116:206–11. <https://doi.org/10.1016/j.actatropica.2010.08.007>.
- [92] Beutler T, Vijaywargiya D, Bashir R, Mangla R. Cytomegalovirus (CMV) encephalitis presenting with ring-enhancing lesions in a solid organ-transplant (SOT) recipient. *Neurology* 2025;104(Number 7 Supplement 1). P12–10.003.
- [93] McCabe K, Tyler K, Tanabe J. Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis. *Neurology* 2003;61:1015–6. <https://doi.org/10.1212/01.wnl.0000082387.97051.f5>.
- [94] Sener RN. Herpes simplex encephalitis: Diffusion MR imaging findings. *Comput Med Imaging Graph* 2001;25:391–7. [https://doi.org/10.1016/S0895-6111\(01\)00005-2](https://doi.org/10.1016/S0895-6111(01)00005-2).
- [95] Abbuehl LS, Branca M, Ungureanu A, Federspiel A, Leib SL, Bassetti CLA, et al. Magnetic resonance imaging in acute meningoencephalitis of viral and unknown origin: Frequent findings and prognostic potential. *Front Neurol* 2024;15:1359437. <https://doi.org/10.3389/fneur.2024.1359437>.
- [96] Le Maréchal M, Mailles A, Seigneurin A, Tattévin P, Stahl JP, Épaulard O. A prospective cohort study to identify clinical, biological, and imaging features that predict the etiology of acute encephalitis. *Clin Infect Dis* 2021;73:264–70. <https://doi.org/10.1093/cid/ciaa598>.
- [97] Chandra SR, Seshadri R, Chikabasaviah Y, Issac TG. Progressive limbic encephalopathy: Problems and prospects. *Ann Indian Acad Neurol* 2014;17:166–70. <https://doi.org/10.4103/0972-2327.132616>.
- [98] Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The management of encephalitis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008;47:303–27. <https://doi.org/10.1086/589747>.
- [99] Mitchell JW, Valdeiros SR, Jefferson S, Hywel B, Solomon T, Marson AG, et al. Autoimmune encephalitis as an increasingly recognised cause of non-convulsive status epilepticus: A retrospective, multicentre evaluation of patient characteristics and electroencephalography (EEG) results. *Seizure* 2020;80:153–6. <https://doi.org/10.1016/j.seizure.2020.06.020>.
- [100] Long B, Koyfman A. Nonconvulsive status epilepticus: A review for emergency clinicians. *J Emerg Med* 2023;65:e259–71. <https://doi.org/10.1016/j.jemermed.2023.05.012>.
- [101] Alam AM, Chen JPK, Wood GK, Facer B, Bhojak M, Das K, et al. Correction: Increased volume of cerebral oedema is associated with risk of acute seizure activity and adverse neurological outcomes in encephalitis – Regional and volumetric analysis in a multi-centre cohort. *BMC Neurol* 2022;22:451. <https://doi.org/10.1186/s12883-022-02995-6>.
- [102] Wood GK, Babar R, Ellul MA, Thomas RH, Van Den Tooren H, Easton A, et al. Acute seizure risk in patients with encephalitis: development and validation of clinical prediction models from two independent prospective multicentre cohorts. *BMJ Neurol Open* 2022;4:e000323. <https://doi.org/10.1136/bmjno-2022-000323>.
- [103] Hjalmarsson A, Granath F, Forsgren M, Brytting M, Blomqvist P, Sköldenberg B. Prognostic value of intrathecal antibody production and DNA viral load in cerebrospinal fluid of patients with herpes simplex encephalitis. *J Neurol* 2009;256:1243–51. <https://doi.org/10.1007/s00415-009-5106-6>.
- [104] Meyding-Lamadé U, Jacobi C, Martinez-Torres F, Lenhard T, Kress B, Kieser M, et al. The German trial on Aciclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE): a multicenter, randomized, double-blind, placebo-controlled trial. *Neurol Res Pract* 2019;1:26. <https://doi.org/10.1186/s42466-019-0031-3>.
- [105] Poissy J, Champenois K, Dewilde A, Melliez H, Georges H, Senneville E, et al. Impact of Herpes simplex virus load and red blood cells in cerebrospinal fluid upon herpes simplex meningo-encephalitis outcome. *BMC Infect Dis* 2012;12:356. <https://doi.org/10.1186/1471-2334-12-356>.
- [106] Kataoka H, Saeki K, Kobayashi Y, Kiriya T, Sugie K, Ueno S. Predictors of outcomes in acyclovir-treated limbic encephalitis. *J Infect* 2013;66:201–5. <https://doi.org/10.1016/j.jinf.2012.10.007>.
- [107] Sheybani F, Arabikhan HR, Naderi HR. Herpes Simplex Encephalitis (HSE) and its outcome in the patients who were admitted to a tertiary care hospital in mashhad, Iran, over a 10-year period. *J Clin Diagn Res* 2013;7:1626–8. <https://doi.org/10.7860/JCDR/2013/5661.3221>.
- [108] Singh TD, Fugate JE, Hocker S, Wijedicks EFM, Aksamit AJJ, Rabinstein AA. Predictors of outcome in HSV encephalitis. *J Neurol* 2016;263:277–89. <https://doi.org/10.1007/s00415-015-7960-8>.
- [109] Stahl JP, Mailles A, De Broucker T. Herpes simplex encephalitis and management of acyclovir in encephalitis patients in France. *Epidemiol Infect* 2012;140:372–81. <https://doi.org/10.1017/S0950268811000483>.
- [110] Tan IL, McArthur JC, Venkatesan A, Nath A. Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. *Neurology* 2012;79:2125–32. <https://doi.org/10.1212/WNL.0b013e3182752ceb>.
- [111] Pouplin T, Pouplin JN, Van Toi P, Lindegardh N, Rogier van Doorn H, Hien TT, et al. Valacyclovir for herpes simplex encephalitis. *Antimicrob Agents Chemother* 2011;55:3624–6. <https://doi.org/10.1128/AAC.01023-10>.
- [112] Mailles A, Stahl JP. Infectious encephalitis in france in 2007: a national prospective study. *Clin Infect Dis* 2009;49:1838–47. <https://doi.org/10.1086/648419>.
- [113] Rohani H, Arjmand R, Mozghani SH, Shafiee A, Amini MJ, Forghani-Ramandi MM. The Worldwide prevalence of herpes simplex virus encephalitis and meningitis: A systematic review and meta-analysis. *Turk Arch Pediatr* 2023;58:580–7. <https://doi.org/10.5152/TurkArchPediatr.2023.23007>.
- [114] Saraya AW, Wacharapluesadee S, Petcharat S, Sittidethoripat N, Ghai S, Wilde H, et al. Normocellular CSF in herpes simplex encephalitis. *BMC Res Notes* 2016;15(9):95. <https://doi.org/10.1186/s13104-016-1922-9>.
- [115] Sartori B, Jaquet P, Belkacemi D, de Montmollin E, Bonneville F, Sazio C, et al. Assessment of magnetic resonance imaging changes and functional outcomes among adults with severe herpes simplex encephalitis. *JAMA Netw Open* 2021;4:e2114328. <https://doi.org/10.1001/jamanetworkopen.2021.14328>.
- [116] Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986;314:144–149. DOI: <https://doi.org/10.1056/NEJM198601163140303>.
- [117] VanLandingham KE, Marsteller HB, Ross GW, Hayden FG. Relapse of herpes simplex encephalitis after conventional acyclovir therapy. *JAMA*. 1988;259:1051–1053.
- [118] Dennett C, Klapper PE, Cleator GM. Polymerase chain reaction in the investigation of 'relapse' following herpes simplex encephalitis. *J Med Virol* 1996;48:129–32. [https://doi.org/10.1002/\(SICI\)1096-9071\(199602\)48:2%3C129::AID-JMV2%3E3.0.CO;2-B](https://doi.org/10.1002/(SICI)1096-9071(199602)48:2%3C129::AID-JMV2%3E3.0.CO;2-B).
- [119] Schulte EC, Sauerbrei A, Hoffmann D, Zimmer C, Hemmer B, Mühlau M. Acyclovir resistance in herpes simplex encephalitis. *Ann Neurol* 2010;67:830–3. <https://doi.org/10.1002/ana.21979>.
- [120] Fujii H, Harada S, Yoshikawa T, Yamada S, Omura N, Shibamura M, et al. Differences in the likelihood of acyclovir resistance-associated mutations in the thymidine kinase genes of herpes simplex virus 1 and varicella-zoster virus. *Antimicrob Agents Chemother* 2019;63:e00017–19. <https://doi.org/10.1128/AAC.00017-19>.
- [121] Schalkwijk HH, Snoeck R, Andrei G. Acyclovir resistance in herpes simplex viruses: Prevalence and therapeutic alternatives. *Biochem Pharmacol* 2022;206:115322. <https://doi.org/10.1016/j.bcp.2022.115322>.
- [122] Kuo JY, Yeh CS, Wang SM, Chen SH, Wang JR, Chen TY, et al. Acyclovir-resistant HSV-1 isolates among immunocompromised patients in southern Taiwan: Low prevalence and novel mutations. *J Med Virol* 2023;95:e28985. <https://doi.org/10.1002/jmv.28985>.
- [123] Glasgow HL, Zhu H, Xie H, Kenkel EJ, Lee C, Huang ML, et al. Genotypic testing improves detection of antiviral resistance in human herpes simplex virus. *J Clin Virol*. 2023;167:105554. <https://doi.org/10.1016/j.jcv.2023.105554>.
- [124] Ramos-Estebanez C, Lizarraga KJ, Merenda A. A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy? *Antivir Ther* 2014;19:133–9. <https://doi.org/10.3851/IMP2683>.
- [125] Solomon T, Hooper C, Easton A, Rosala-Hallas A, Facer B, Moore P, et al. Safety and efficacy of adjunct dexamethasone in adults with herpes simplex virus encephalitis in the UK (DexEnceph): a multicentre, observer-blind, randomised, phase 3, controlled trial. *Lancet Neurol* 2026;25:136–46. [https://doi.org/10.1016/S1474-4422\(25\)00454-5](https://doi.org/10.1016/S1474-4422(25)00454-5).
- [126] Martinot M, Klein A, Demesmay K, Groza M, Mohseni-Zadeh M, Tebacher-Alt M, et al. Acute renal failure related to high doses of acyclovir (15 mg/kg/8 h) during treatment of varicella zoster virus encephalitis. *Antivir Ther* 2019;24:309–12. <https://doi.org/10.3851/IMP3313>.
- [127] Lee EJ, Jang HN, Cho HS, Bae E, Lee TW, Chang SH, et al. The incidence, risk factors, and clinical outcomes of acute kidney injury (staged using the RIFLE classification) associated with intravenous acyclovir administration. *Ren Fail* 2018;40:687–92. <https://doi.org/10.1080/0886022X.2018.1487866>.
- [128] Berry L, Venkatesan P. Aciclovir-induced neurotoxicity: Utility of CSF and serum CMMG levels in diagnosis. *J Clin Virol* 2014;61:608–10. <https://doi.org/10.1016/j.jcv.2014.09.001>.
- [129] Heildén A, Odar-Cederlöf I, Diener P, Barkholt L, Medin C, Svensson JO, et al. High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir-related neuropsychiatric side effects: an observational study. *Nephrol Dial Transplant* 2003;18:1135–41. <https://doi.org/10.1093/ndt/gfg119>.
- [130] Leng X, Yuan F, Zhao J, Song C, Zhao Z, Zhang Y, et al. Long-term seizure outcome in patients with status epilepticus due to acute encephalitis. *Seizure* 2019;69:70–5. <https://doi.org/10.1016/j.seizure.2019.04.005>.
- [131] Peng A, Lai W, Li W, Qiu X, Zhang L, He S, et al. Antiepileptic drugs for acute encephalitic patients presented with seizure. *Epilepsy Res* 2020;164:106347. <https://doi.org/10.1016/j.eplepsyres.2020.106347>.
- [132] Chalfin DB, Trzeciak S, Likourezos A, Baumann BM, Dellinger RP. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. *Crit Care Med* 2007;35:1477–83. <https://doi.org/10.1097/01.CCM.0000266585.74905.5A>.

- [133] Rincon F, Mayer SA, Rivolta J, Stillman J, Boden-Albala B, Elkind MSV, et al. Impact of delayed transfer of critically ill stroke patients from the Emergency Department to the Neuro-ICU. *Neurocrit Care* 2010;13:75–81. <https://doi.org/10.1007/s12028-010-9347-0>.
- [134] Helbok R, Olson DM, Le Roux PD, Vespa P. Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. *Neurocrit Care* 2014;21(Suppl 2). <https://doi.org/10.1007/s12028-014-0040-6>. S85–94.
- [135] Armangue T, Spatola M, Vlagea A, Mattozzi S, Cárceles-Cordon M, Martinez-Heras E, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol* 2018;17:760–72. [https://doi.org/10.1016/S1474-4422\(18\)30244-8](https://doi.org/10.1016/S1474-4422(18)30244-8).
- [136] Armangue T, Moris G, Cantarín-Extremuera V, Conde CE, Rostasy K, Erro ME, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology* 2015;85:1736–43. <https://doi.org/10.1212/WNL.00000000000002125>.
- [137] Nosadini M, Mohammad SS, Corazza F, Ruga EM, Kothur K, Perilongo G, et al. Herpes simplex virus-induced anti-N-methyl-D-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. *Dev Med Child Neurol* 2017;59:796–805. <https://doi.org/10.1111/dmcn.13448>.
- [138] Berek K, Beer R, Grams A, Helbok R, Lindner A, Pflauser B, et al. Caspr2 antibodies in herpes simplex encephalitis: an extension of the spectrum of virus induced autoimmunity? - A case report. *BMC Neurol* 2022;22:131. <https://doi.org/10.1186/s12883-022-02637-x>.
- [139] Armangué T, Olivé-Cirera G, Martínez-Hernández E, Rodes M, Peris-Sempere V, Guasp M, et al. Neurologic complications in herpes simplex encephalitis: clinical, immunological and genetic studies. *Brain J Neurol* 2023;146:4306–19. <https://doi.org/10.1093/brain/awad238>.
- [140] Christie S, Chan V, Mollayeva T, Colantonio A. Systematic review of rehabilitation intervention outcomes of adult and paediatric patients with infectious encephalitis. *BMJ Open* 2018;8:e015928. <https://doi.org/10.1136/bmjopen-2017-015928>.
- [141] Cooper J, Kierans C, Defres S, Easton A, Kneen R, Solomon T. Care beyond the hospital ward: understanding the socio-medical trajectory of herpes simplex virus encephalitis. *BMC Health Serv Res* 2017;17:646. <https://doi.org/10.1186/s12913-017-2608-2>.
- [142] Rahayu UB, Wibowo S, Setyopranoto I, Hibatullah Romli M. Effectiveness of physiotherapy interventions in brain plasticity, balance and functional ability in stroke survivors: A randomized controlled trial. *Neuro-Rehabilitation* 2020;47:463–70. <https://doi.org/10.3233/NRE-203210>.
- [143] Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2016;47. <https://doi.org/10.1161/STR.0000000000000098>. e98–169.
- [144] Corini C, Gervasoni E, Perini G, Cosentino C, Putzolu M, Montesano A, et al. Mobility and balance rehabilitation in multiple sclerosis: A systematic review and dose-response meta-analysis. *Mult Scler Relat Disord* 2023;69:104424. <https://doi.org/10.1016/j.msard.2022.104424>.
- [145] Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, et al. Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. *Ann Intern Med* 2015;163:548–53. <https://doi.org/10.7326/M14-1885>.