

ENCEPHALITIS
SOCIETY

The brain inflammation charity



Management of Suspected Viral Encephalitis in Adults

Professional Guidelines
Association of British Neurologists and
British Infection Association National Guidelines

Summary document produced on behalf of the National Encephalitis
Guidelines Development Group and the Encephalitis Society

Management of Suspected Viral Encephalitis in Adults

This is a synopsis produced for The Encephalitis Society. To read the full article please see: Solomon T, Michael BD (joint first), Smith PE, Sanderson F, Davies NWS, Hart IJ, Buckley C, Holland M, Easton A, Kneen R, Beeching NJ. On behalf of the National Encephalitis Guidelines Development Group. Management of suspected viral encephalitis in adults: Association of British Neurologists and British Infection Association National Guideline. **Journal of Infection** 2012; 64(4):347-73.

A separate parallel document has been produced for children: see page 15.

1. Introduction

Although Encephalitis is a relatively rare, its importance lies in that fact that for many forms treatment is effective if started promptly; in contrast, delays in treatment can be devastating. Encephalitis means inflammation of the brain parenchyma, and strictly speaking this is a pathological diagnosis. However, because of the obvious practical limitations of this, surrogate clinical markers of inflammation are used.

Classification of Encephalitis

The causes of Encephalitis can be defined as those due to direct infection of the Central Nervous System (CNS), para-, or post-infectious causes, and non-infectious causes. Infectious causes include numerous viruses, bacteria (especially intracellular bacteria such as *Mycoplasma pneumoniae*), parasites and fungi. Acute Disseminated Encephalomyelitis (ADEM) after measles is an example of a post-infectious Encephalitis. Non-infectious causes include antibody-associated Encephalitis, which may or may not be paraneoplastic. Most viral Encephalitis is acute, but sub-acute and chronic presentations are characteristic of particular pathogens, especially in the immunocompromised.

Epidemiology

The global reported incidence of Encephalitis varies according to the location, population studied, and differences in case definitions and research methods; however, the reported incidence in western settings ranges from 0.7-13.8 per 100,000 for all ages, being approximately 0.7-12.6 per 100,000 for adults and 10.5-13.8 per 100,000 children.¹⁻³

Herpes Simplex Virus (HSV) Encephalitis is the most commonly diagnosed viral Encephalitis in industrialised nations, with an annual incidence of 1 in 250,000 to 500,000.⁴ The age specific incidence is bimodal, with peaks in the young and the elderly. Most HSV Encephalitis is due to HSV-1, but about 10% is caused by HSV-2. The latter typically occurs in immunocompromised individuals and neonates, in whom it can cause a disseminated infection. Varicella Zoster Virus (VZV) is also a relatively common cause of viral Encephalitis, especially in the immunocompromised, whilst Cytomegalovirus (CMV) occurs almost exclusively in this group. Enteroviruses most often cause aseptic meningitis but can also be an important cause of Encephalitis. Among the other causes, Encephalitis associated with antibodies to the voltage-gated potassium channel complex, or N-Methyl-D-Aspartate Antibody (NMDA) receptors are increasingly recognised.⁵

Aims and Scope of this Guideline

In the 1980s the outcome of patients with HSV Encephalitis was shown to be dramatically improved with aciclovir treatment.^{6,7} Delays in starting treatment, particularly beyond 48 hours after hospital admission, are associated with a worse prognosis.^{8,9} Several comprehensive reviews of the investigation and management of Encephalitis have been published.¹⁰⁻¹² However, their impact on day-to-day clinical practice appears to be limited.^{2,13,14} The emergency management of meningitis in children and adults was revolutionised by the introduction of a simple algorithm as part of management guidelines.¹⁵

In February 2008 a group of clinicians met in Liverpool to begin the development process for clinical care guidelines based around a similar simple algorithm (See pages 14&15 - Algorithm for the Management of Patients with Suspected Viral Encephalitis), supported by an evidence base, whose implementation is hoped would improve the management of patients with suspected Encephalitis.

The scope of the guideline is to cover the initial management of all patients with suspected Encephalitis, up to the point of diagnosis, in an acute care setting such as acute medical unit or emergency department. They are thus intended as a ready reference for clinicians encountering the more common causes of Encephalitis, rather than specialists managing rarer causes. The guidelines also cover the specific treatments and further management of patients for whom a diagnosis of viral Encephalitis is made, particularly that due to HSV, VZV and enteroviruses. Encephalitis due to CMV is almost exclusively seen in the immunocompromised and is not covered in detail; its diagnosis and management is covered in HIV guidelines.^{16,17} At the end of the guidelines the special circumstances of returned travellers, immunocompromised patients and antibody-associated Encephalitis are discussed.

Many patients with suspected viral Encephalitis ultimately prove to have another infectious or non-infectious cause for their illness. The further management and treatment of such patients is beyond the scope of this guideline, but we have included a section on follow-up and support for Encephalitis patients in both the healthcare and voluntary sectors after discharge from hospital. Finally, we have included some suggestions for audit standards to assess practice before and after implementation of the guidelines.



2. Diagnosing Encephalitis

Which clinical features should lead to suspicion of Encephalitis? How do they differ from other encephalopathies? And can they be used to diagnose the underlying cause?

Recommendations

- The constellation of a current or recent febrile illness with altered behaviour or consciousness, or new seizures, or new focal neurological signs, should raise the possibility of Encephalitis, or another CNS infection; and should trigger appropriate investigations (A, II)
- Metabolic, toxic, autoimmune and non-CNS sources of sepsis as causes for encephalopathy should be considered early in patients presenting with encephalopathy (B, III), especially if there are features suggestive of a non-encephalitic process, such as a past history of similar episodes, symmetrical neurological findings, myoclonus, asterixis, lack of fever, acidosis, or unexplained negative base excess (B, III)
- Clinical features, such as a sub-acute presentation (weeks-months), orofacial dyskinesia, choreoathetosis, faciobrachial dystonia, intractable seizures or hyponatraemia, may suggest an antibody-mediated Encephalitis, although these features are not all exclusive to antibody-mediated disease (B, II)
- The investigation priority is determined by the patient's clinical history and clinical presentation (C, III)

Which patients with suspected Encephalitis should have a lumbar puncture? And in whom should this be preceded by a computed tomography scan?

Recommendations

- All patients with suspected Encephalitis should have a Lumbar Puncture (LP) as soon as possible after hospital admission, unless there is a clinical contraindication (see figure, page 14) (A, II)
- If there is a clinical contraindication indicating possible raised intracranial pressure (ICP) due to or causing brain shift, a Computed Tomography (CT) scan should be performed as soon as possible (A, II). An immediate LP following this should ideally be considered on a case-by-case basis, unless the imaging reveals significant brain shift or tight basal cisterns due to or causing raised Intracranial Pressure, or an alternative diagnosis, or the patient's clinical condition changes (B, III)
- If a CT is not needed before a LP, imaging (CT or Magnetic Resonance Imaging (MRI)) should be performed as soon as possible afterwards (A, II)
- In anticoagulated patients, adequate reversal (with protamine for those on heparin and vitamin K, prothrombin complex concentrate, or fresh frozen plasma for those on warfarin) is mandatory before LP (A, II). In patients with bleeding disorders, replacement therapy is indicated (B, II). If unclear how to proceed, advice should be sought from a haematologist (B,III)

- In situations where a LP is not possible at first, the situation should be reviewed every 24 hours, and a LP performed when it is safe to do so (B, II)
- Lumbar punctures should be performed with needles that meet the standards set out by the National Patient Safety Agency (A, III)

What information should be gathered from the LP?

Recommendations

- Cerebrospinal Fluid (CSF) investigations should include:
 - Opening pressure (A, II)
 - Total and differential white cell count, red cell count, microscopy, culture and sensitivities for bacteria (2x2.5ml) (A, II)
 - If necessary, the white cell count and protein should be corrected for a bloody tap
 - Protein and glucose (1-2ml), which should be compared with a plasma glucose taken just before the LP (A, II)
 - A sample should be sent and stored for virological investigations or other future investigation as indicated in the next section (2ml) (A, II)
 - Mycobacterium tuberculosis (6ml) when clinically indicated (A, II)
- If an initial LP is non-diagnostic, a second LP should be performed 24-48 hours later (B, II)

What virological investigations should be performed?

Recommendations

- All patients with suspected Encephalitis should have a CSF polymerase chain reaction (PCR) test for HSV (1 and 2), VZV and enteroviruses, as this will identify 90% of cases due to viral pathogens (B, II)
- Further testing should be directed towards specific pathogens as guided by the clinical features, such as occupation, travel history and animal or insect contact (B, III)

What antibody testing should be done on serum and CSF?

Recommendations

- Guidance from microbiological, virological or infectious diseases specialist should be sought in deciding on these investigations (B, III)
- For patients with suspected Encephalitis where PCR of the CSF was not performed acutely, a later CSF and serum sample (taken approximately 10-14 days after illness onset) should be sent for HSV specific IgG antibody testing (B, III)
- In suspected flavivirus Encephalitis CSF should be tested for IgM antibody (B, II)
- Acute and convalescent blood samples should be taken as an adjunct to diagnostic investigation especially when Epstein Barr Virus (EBV), arboviruses, Lyme disease, brucellosis, rickettsioses, ehrlichiosis or mycoplasma are suspected (B, II)

What PCR/culture should be done on other samples (e.g. throat swab, stool, vesicle etc)?

Recommendations

- Investigation should be undertaken through close collaboration between a laboratory specialist in microbiology or virology and the clinical team (B, III)
- In all patients with suspected viral Encephalitis throat and rectal swabs for enterovirus investigations should be considered (B, II); and swabs should also be sent from vesicles, if present (B, II)
- When there is a recent or concomitant respiratory tract infection, sputum (bacteria) or bronchial lavage or nose and throat swab/nasopharyngeal wash or aspirate (viruses) should be sent (B, III)
- When there is suspicion of mumps CSF PCR should be performed for this and parotid gland duct or buccal swabs should be sent for viral culture or PCR (B, III)

Which patients with Encephalitis should have a HIV test?

Recommendations

- A HIV test should be performed on all patients with Encephalitis or with suspected Encephalitis irrespective of interpretation of possible risk factors (A, II)

What is the role of magnetic resonance imaging (MRI) and other advanced imaging techniques in adults with suspected viral Encephalitis

Recommendations

- MRI (including diffusion weighted imaging), is the preferred imaging modality and should be performed as soon as possible on all patients with suspected Encephalitis for whom the diagnosis is uncertain; ideally this should be within 24 hours of hospital admission, but certainly within 48 hours (B, II)
- If the patient's condition precludes an MRI, urgent CT scanning may exclude structural causes of raised intracranial pressure, or reveal alternative diagnoses (A, II)
- The role of MR spectroscopy is uncertain; Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET) are not indicated in the assessment of suspected acute viral Encephalitis (B, II)

Which adults with suspected viral Encephalitis should have an electroencephalogram (EEG)?

Recommendations

- An Electroencephalogram (EEG) need not be performed routinely in all patients with suspected Encephalitis (A, II). However, for patients with mildly altered behaviour and uncertainty whether there is a psychiatric or organic cause, an EEG should be performed to seek encephalopathic changes (B, II)
- EEG should also be performed if subtle motor, or non-convulsive seizures are suspected (B, II)

What is the role of brain biopsy in adults with suspected viral Encephalitis?

Recommendations

- Brain biopsy has no place in the initial assessment of suspected acute viral Encephalitis. Stereotactic biopsy should be considered in patients with suspected Encephalitis in whom no diagnosis has been made after the first week, especially if there are focal abnormalities on imaging (B, II)
- If imaging shows nothing focal, an open biopsy, usually from the non-dominant frontal lobe, may be preferable (B, II)
- The biopsy should be performed by an experienced neurosurgeon and the histology should be examined by an experienced neuropathologist (B, III)



3. Treatment of Viral Encephalitis

For which patients should aciclovir treatment be started empirically?

Recommendations

- Intravenous aciclovir (10mg/kg three times daily) should be started if the initial CSF and/or imaging findings suggest viral Encephalitis, or within 6 hours of admission if these results will not be available, or if the patient is very unwell or deteriorating (A, II)
- If the first CSF microscopy or imaging is normal but the clinical suspicion of HSV or varicella zoster virus (VZV) Encephalitis remains, aciclovir should still be started within 6 hours of admission whilst further diagnostic investigations (as outlined) are awaited (A, II)
- If meningitis is suspected, patients should be treated in accordance with the British Infection Society (now British Infection Association) guideline (A, II)
- The dose of aciclovir should be reduced in patients with pre-existing renal impairment (A, II)
- Patients with suspected Encephalitis due to infection should be notified to the appropriate Consultant in Communicable Disease Control (A, III)

How long should aciclovir be continued in proven HSV Encephalitis, and is there a role for oral treatment?

Recommendations

- In patients with proven HSV Encephalitis, intravenous aciclovir treatment should be continued for 14-21 days (A, II), (see figure, page 14) and a repeat LP performed at this time to confirm the CSF is negative for HSV by PCR (B, II); if the CSF is still positive, aciclovir should continue intravenously, with weekly PCR until it is negative (B, II)

In patients who are HSV PCR negative when can presumptive treatment with aciclovir be safely stopped?

Recommendations

- Aciclovir can be stopped in immunocompetent patients, if:
 - An alternative diagnosis has been made, or
 - HSV PCR in the CSF is negative on two occasions 24-48 hours apart, and MRI is not characteristic for HSV Encephalitis
 - HSV PCR in the CSF is negative once >72 hours after neurological symptom onset, with unaltered consciousness, normal MRI (performed >72 hours after symptom onset), and a CSF white cell count of less than 5/mm³ (B, III)

What is the role of corticosteroids in HSV Encephalitis?

Recommendations

- Whilst awaiting the results of a randomised placebo-controlled trial corticosteroids should not be used routinely in patients with HSV Encephalitis (B, III)
- Corticosteroids may have a role in patients with HSV Encephalitis under specialist supervision, but data establishing this are needed and the results of a prospective RCT are awaited (C, III)

What should be the specific management of VZV Encephalitis?

Recommendations

- No specific treatment is needed for VZV cerebellitis (B, II).
- For VZV Encephalitis, whether due to primary infection or reactivation, intravenous aciclovir 10-15 mg/kg three times daily is recommended, with or without a short course of corticosteroids (B, II);
- If there is a vasculitic component, there is a stronger case for using corticosteroids (B, II)

What should be the specific management of enterovirus meningo-encephalitis?

Recommendations

- No specific treatment is recommended for enterovirus Encephalitis; in patients with severe disease pleconaril (if available) or intravenous immunoglobulin may be worth considering (C, III)

What acute facilities should be available and which patients should be transferred to a specialist unit?

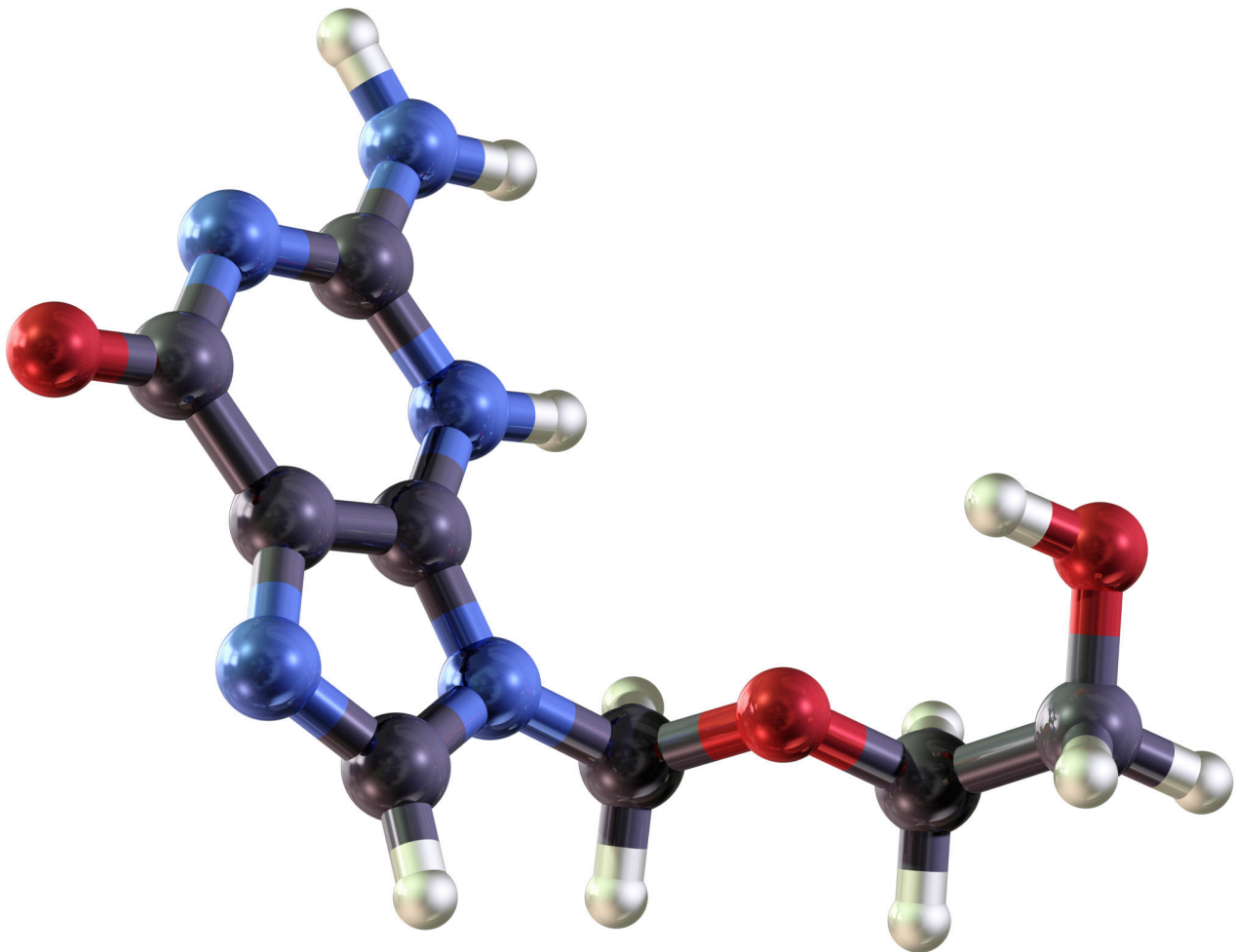
Recommendations

- Patients with suspected acute Encephalitis should have access to an immediate neurological specialist opinion and should be managed in a setting where clinical neurological review can be obtained as soon as possible and definitely within 24 hours of referral (B, III)
- There should be access to neuroimaging (MRI and CT), under general anaesthetic if needed, and neurophysiology (EEG), which may mean transfer to a specialist neuroscience unit (B, III)
- As CSF diagnostic assays are critical to confirming diagnosis, the results of CSF PCR assays should be available within 24-48 hours of a lumbar puncture being performed (B, III)
- When a diagnosis is not rapidly established or a patient fails to improve with therapy, transfer to a neurological unit is recommended. The transfer should occur as soon as possible and definitely within 24 hours of being requested (B, III)
- Patients with falling level of consciousness require urgent assessment by Intensive Care Unit staff for airway protection and ventilatory support, management of raised intracranial pressure, optimisation of cerebral perfusion pressure and correction of electrolyte imbalances (A, III)

What rehabilitation and support services should be available for adults affected by Encephalitis and their carers?

Recommendations

- Patients (when conscious level permits) and their next-of-kin should be made aware of the support provided by voluntary sector partners such as the Encephalitis Society (www.encephalitis.info) (B, II)
- Patients should not be discharged from hospital without either a definite or suspected diagnosis. Arrangements for outpatient follow-up and plans for on-going therapy and rehabilitation should be formulated at a discharge meeting, and should include at least one follow-up appointment (A, II)
- All patients irrespective of age should have access to assessment for rehabilitation (A, III)



Molecule of Aciclovir

4. Special Circumstances

How does the management of suspected Encephalitis in the returning traveller differ?

Recommendations

- Patients returning from malaria endemic areas should have rapid blood malaria antigen tests and ideally three thick and thin blood films examined for malaria parasites (A, II). Thrombocytopenia, or malaria pigment in neutrophils and monocytes may be a clue to malaria, even if the films are negative.
- If cerebral malaria seems likely, and there will be a delay in obtaining the malaria film result, anti-malarial treatment should be considered and specialist advice obtained (A, III)
- The advice of regional and national tropical and infectious disease units should be sought regarding appropriate investigations and treatment for the other possible causes of Encephalitis in a returning traveller (Table 2) (A, III)

What differences are there in the management of suspected Encephalitis in the immunocompromised?

Recommendations

- Encephalitis should be considered in immunocompromised patients with altered mental status, even if the history is prolonged, the clinical features are subtle, there is no febrile element, or the CSF white cell count is normal (A, III)
- A CT head scan before LP should be considered in patients with known severe immunocompromise (B, III). If a patient's immune status is not known, there is no need to await the result of an HIV test before performing a LP
- MRI should be performed as soon as possible in all immunocompromised patients with suspected Encephalitis (A, II)
- Diagnostic microbiological investigations for all immunocompromised patients with suspected CNS infections include (B, II):
 - CSF PCR for HSV 1 & 2, VZV and enteroviruses
 - CSF PCR for EBV, and CMV
 - CSF acid fast bacillus staining and culture for Mycobacterium tuberculosis
 - CSF and blood culture for Listeria monocytogenes
 - Indian ink staining and/or cryptococcal antigen (CRAG) testing for Cryptococcus neoformans,
 - Antibody testing and if positive CSF PCR for Toxoplasma gondii,
 - Antibody testing of serum and if positive CSF for syphilis

Other investigations to consider, depending on the circumstances, include (C, III):

- CSF PCR for HHV6 and 7
 - CSF PCR for JC/BK virus
 - CSF examination for Coccidioides sp and Histoplasma sp
- Patients with HIV should be treated in an HIV centre (A, II)

- Immunocompromised patients with Encephalitis caused by HSV-1 or 2, should be treated with intravenous aciclovir (10mg/kg three times daily) for at least 21 days, and reassessed with a CSF PCR assay; following this long term oral treatment should be considered until the CD count is $>200 \times 10^6/L$ (A, II)
- Acute concomitant VZV infection causing Encephalitis should be treated with intravenous aciclovir (A, II)
- CNS CMV infections should be treated with ganciclovir, foscarnet or cidofovir (A, II)

What differences are there in the presentation and management of Encephalitis associated with antibodies?

Recommendations

- The diagnosis of antibody-mediated Encephalitis should be considered in all patients with suspected Encephalitis as they have a poor outcome if untreated. Moreover, the clinical phenotypes of these recently described disorders are still expanding (B, II)
- Clinical features, such as a sub-acute presentation, orofacial dyskinesia, choreoathetosis, faciobrachial dystonia, intractable seizures or hyponatraemia, may suggest an antibody-mediated Encephalitis, although these features are not exclusive to antibody-mediated disease (B, II)
- All patients with proven VGKC complex or NMDA receptor antibody-associated Encephalitis should have screening for neoplasm (B, II)
- Early immune suppression and tumour removal results in improved outcomes (B, II)

Guideline implementation and audit

We have included a table (see full published guidelines) of suggested clinical and operational issues that are relatively easy to audit in a standardised manner, and which can be adapted for local use.



Acknowledgements

In addition to the authors listed, the following are currently members of the National Encephalitis Guidelines Development Group: *Solomon Almond, Enitan Carrol, Mehrengise Cooper, Cheryl Hemmingway, Paul Klapper, Ming Lim, Jean-Pierre Lin, Hermione Lyall, Kevin Mackway-Jones, Nick Makwana, Anthony Marson, Bimal Mehta, Esse Menson, Isam Osman, Andrew Riordan, Delane Shingadia, Aman Sohal, David Stoeter, Ed Wilkins*

This article presents independent work funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0108-10048). Additional funding was provided by the Association of British Neurologists, the British Infection Association, The Encephalitis Society and University of Liverpool; these organisations contributed members to the guideline development team, but have no conflicts of interests to declare.

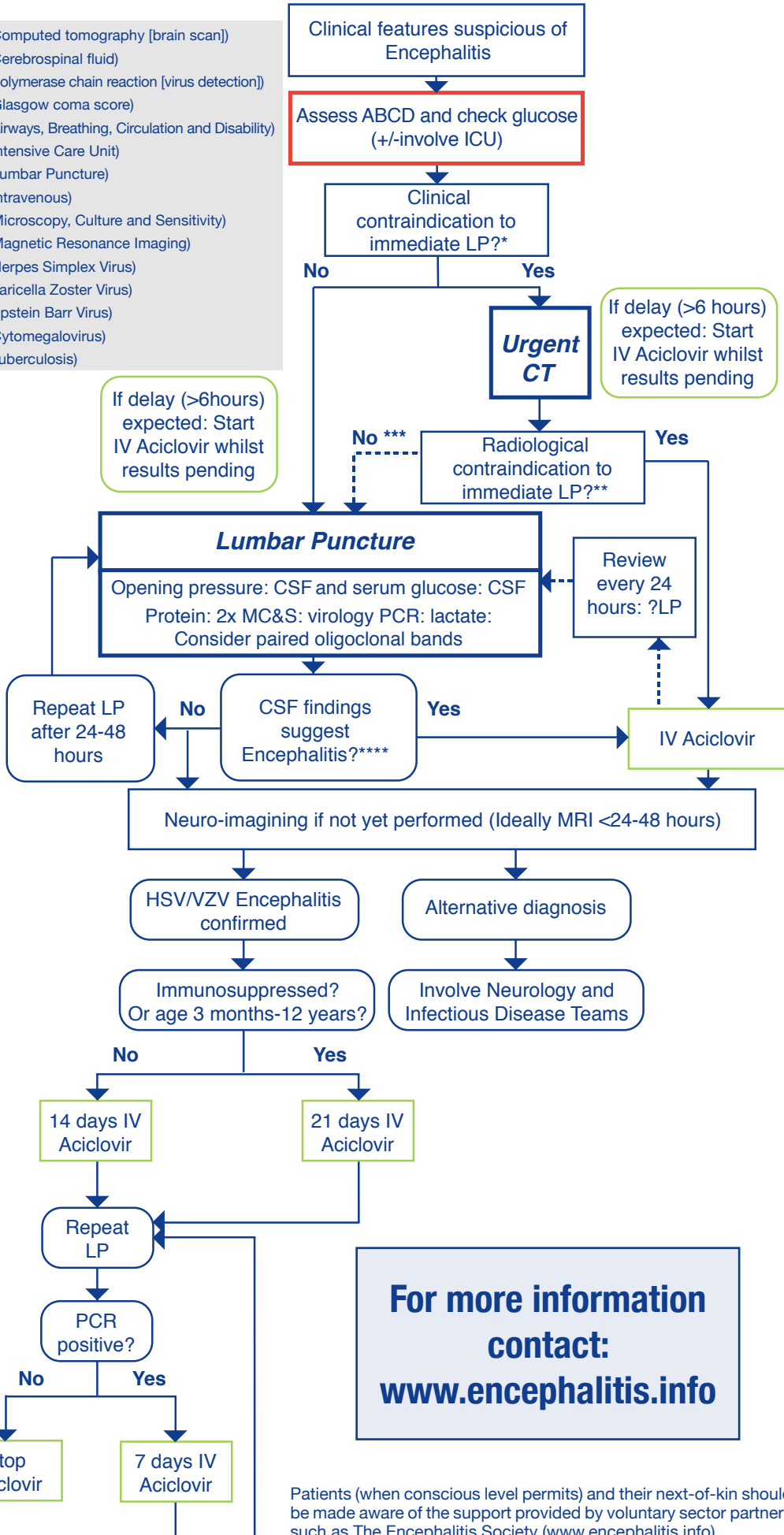
References

1. Jmor, F, Emsley H C A, Fisher M, Solomon T, Lewthwaite P. The incidence of acute Encephalitis syndrome in Western Industrialised and Tropical Countries. *Virology* 2008; 5: 134, doi:10.1186/1743-422X-5-134
2. Michael B D, Sidhu M, Stoeter D, Roberts M, Beeching N J, Wilkins E, et al. The Epidemiology and Management of Adult Suspected Central Nervous System Infections - a retrospective cohort study in the NHS Northwest Region. *Q J Med* 2010; 103: 749-5, doi:10.1093/qjmed/hcq121
3. Granerod J, Tam C C, Crowcroft N S, Davies N W S, Borchert M, Thomas S L. Challenge of the unknown. A systematic review of acute Encephalitis in non-outbreak situations. *Neurology* 2010; 75: 924-32.
4. Whitley RJ. Herpes simplex Encephalitis: adolescents and adults. *Antiviral Res* 2006; 71: 141-8.
5. Granerod J, Ambrose H E, Davies N W S, Clewley J P, Walsh A L, Morgan D, et al. The aetiology of Encephalitis in England: A multi-centre prospective study. *Lancet Infect Dis* 2010;10: 835-44.
6. Skoldenberg B, Forsgren M, Alestig K, Burman L, Dahlqvist E, Forkman A, et al. Acyclovir versus vidarabine in herpes simplex Encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet* 1984; 2: 707-11.
7. Whitley R J, Alford C A, Hirsch M S, Schooley R T, Luby J P, Aoki F Y, et al. Vidarabine versus acyclovir therapy in herpes simplex Encephalitis. *N Eng J Med* 1986; 314: 144-9
8. McGrath N, Anderson N E, Croxson M C, Powell K F. Herpes simplex Encephalitis treated with acyclovir: Diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 1997; 63: 321-6.
9. Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, et al. Outcome of and prognostic factors for herpes simplex Encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* 2002; 35: 254-60.
10. Klapper P E, Cleator G M. European guidelines for diagnosis and management of patients with suspected herpes simplex Encephalitis. *Clin Microbiol Infect* 1998; 4: 178-180.
11. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, et al. Viral Encephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol* 2005; 12: 331-43.
12. Tunkel A R, Glaser C A, Bloch K C, Sejvar J J, Marra C M, Roos K L, et al. The management of Encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 47: 303-27.
13. Bell DJ, Suckling R, Rothburn MM, Blanchard T, Stoeter D, Michael BD et al. Management of suspected herpes simplex virus Encephalitis in adults in a UK teaching hospital. *Clin Med* 2009; 9: 231-5.
14. Kneen R, Jakka S, Mithyantha R, Riordan A, Solomon T. The management of infants and children treated with aciclovir for suspected viral Encephalitis. *Arch Dis Child* 2010; 95: 100-6, doi: 10.1136/adc.2008.14499
15. British Infection Society. Early Management of Suspected Bacterial Meningitis and Meningococcal Septicaemia in Adults Algorithm, 2003; accessed 5th February 2005, www.britishinfectionsociety.org/drupal/sites/default/files/MeningitisAlgorithm03.pdf.
16. British HIV Association and British Infection Association guidelines in press 2011
17. Mofenson L M, Brady M T, Danner S P, Dominguez K L, Hazra R, Handelsman E, et al. Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America; Pediatric Infectious Diseases Society; American Academy of Pediatrics. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. 2009; 58:1-16

The Management of suspected viral Encephalitis

KEY:

CT	(Computed tomography [brain scan])
CSF	(Cerebrospinal fluid)
PCR	(Polymerase chain reaction [virus detection])
GCS	(Glasgow coma score)
ABCD	(Airways, Breathing, Circulation and Disability)
ICU	(Intensive Care Unit)
LP	(Lumbar Puncture)
IV	(Intravenous)
MC&S	(Microscopy, Culture and Sensitivity)
MRI	(Magnetic Resonance Imaging)
HSV	(Herpes Simplex Virus)
VZV	(Varicella Zoster Virus)
EBV	(Epstein Barr Virus)
CMV	(Cytomegalovirus)
TB	(Tuberculosis)



Additional Investigations

Consider swab

- Throat
- Rectal
- Vesicle (if present)

Sputum (if symptoms)
Urine (if mumps)

If travel consider

- 3x thick/thin malaria films
- Rapid malaria antigen test
- CSF flavivirus igM

HIV (all patients)

If positive:

- CSF PCR for EBV + CMV
- CSF TB staining + culture
- CSF + blood culture for Listeria monocytogenes
- CSF india ink staining +/- cryptococcal antigen for Cryptococcus neoformans
- CSF PCR + serology for Toxoplasma gondii
- CSF + serum antibody for syphilis

Consider:

- CSF PCR for HHV6 + 7
- CSF PCR for JC/BK virus
- CSF for Coccidioides + Histoplasma

If CSF HSV PCR not sent

(on first LP)

- Repeat CSF PCR on 2nd LP
- Consider HSV CSF IgG at 10-14 days

EEG Indications

- If subtle motor status epilepticus suspected
- If unclear if psychiatric cause or encephalopathy

Involve

- Microbiology
- Virology
- Infectious Diseases
- Neurology

Aciclovir Dose:

(adjust for renal failure)

Given 8 hourly:

- Neonate-3 months: 20mg/kg
- 3 months-12 years: 500mg/m²
- >12 years: 10mg/kg

Reference:

Journal of Infection
2012; 64(4):347-73

For more information contact:
www.encephalitis.info

* } Tables associated with this algorithm are on the next page.
**

Patients (when conscious level permits) and their next-of-kin should be made aware of the support provided by voluntary sector partners such as The Encephalitis Society (www.encephalitis.info)

*** Clinical contraindications to lumbar puncture without neuro-imaging**

- Moderate-severe impairment of consciousness: Reduced or fluctuating GCS<13 or fall >2
- Focal neurological signs (e.g. unequal, dilated or poorly responsive pupils)
- Abnormal posture or posturing
- Papilloedema
- After seizures until stabilised
- Relative bradycardia with hypertension
- Abnormal 'doll's eye' movements
- Immunocompromise
- Systemic shock
- Coagulation abnormalities:
 - Results (if obtained) outside the normal range
 - Platelet count <100x10⁹ /L
 - Anticoagulant therapy
- Local infection at lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicaemia

Tables associated with the algorithm on page 14

**** Radiological Contraindications to LP**

- Significant brain shift/swelling
- Tight basal cisterns
- Alternative diagnosis made

Many patients will need a CT before a LP, because of their clinical contraindications to an immediate LP; such patients should have a CT, and then ideally a LP should be considered on a case by case basis (if still indicated and no radiological contraindications are identified) within 6 hours.

****** CSF Interpretation**

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10-20cm	Highly Cloudy	Normal/high	High	High/very high
Colour	Clear	Cloudy	"Gin" clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100-50000	Slightly increased 5-1000	Slightly increased <500	Normal-high 0-1000
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/Plasma Glucose	50-66%	Low<40%	Normal	Low-very low (30%)	Normal-low
Protein (g/l)	<0.45	High >1	Normal-high 0.5-1	High-very high 1.0-5.0	Normal-high 0.2-5.0

GRADE rating system for the strength of the guidelines recommendations and the quality of the evidence.

Strength of recommendation		Quality of evidence	
A	Strongly recommended	I	Evidence from randomised controlled trials
B	Recommended, but other alternatives may be acceptable	II	Evidence from non-randomised studies
C	Weakly recommended: seek alternatives	III	Expert opinion only
D	Never recommended		

Atkins D, Best D, Briss P A, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490.

References:

Solomon T, Michael BD (joint first), et al. On behalf of the National Encephalitis Guidelines Development Group. Management of suspected viral encephalitis in adults: Association of British Neurologists and British Infection Association National Guideline. *Journal of Infection* 2012; 64(4):347-73. If you would like to read the article in full, it is available on the following website:
[www.journalofinfection.com/article/S0163-4453\(11\)00563-9/fulltext](http://www.journalofinfection.com/article/S0163-4453(11)00563-9/fulltext)

Kneen R, Michael BD (joint first), et al. On behalf of the National Encephalitis Guidelines Development Group. Management of suspected viral encephalitis in children: Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guideline. *Journal of Infection* 2012; 64(5):449-77. If you would like to read the article in full, it is available on the following website:
[www.journalofinfection.com/article/S0163-4453\(11\)00562-7/fulltext](http://www.journalofinfection.com/article/S0163-4453(11)00562-7/fulltext)

ENCEPH UK

Understanding and Improving the Outcome of Encephalitis

In this NIHR Programme Grants for Applied Research award led by Professor Tom Solomon at the Institute of Infection and Global Health, at the University of Liverpool, over the next five years we will:

- Study the clinical predictors of Encephalitis, and of poor outcome
- Better understand those outcomes in terms of cognitive function, quality of life, and cost
- Develop the means of intervening to improve the outcome, including implementation of these guidelines.

Studies

This programme grant consists of a series of inter-related studies; a retrospective study looking back at previous patients, a prospective study investigating new patients and an Intervention study to change practice; the over-arching aim is to better understand and improve the outcomes of encephalitis for the benefit of patients.

The research will be based around three patient populations:

- A cohort of patients who had Encephalitis previously, who were recruited between 2005 and 2008 during the Department of Health-funded Health Protection Agency study of the Aetiology of Encephalitis in England (the HPA cohort)
- A new large 4-year multi-centre prospective cohort study of adults and children with suspected encephalitis across the UK which will recruit in 60 hospitals
- Patients with suspected encephalitis, on whom data will be collected through a cluster randomised controlled trial of implementation of these guidelines which will be conducted in 20 hospitals.

For more information and to get involved visit:

www.encephuk.org



ENCEPHALITIS
SOCIETY

The brain inflammation charity

Encephalitis Society

32 Castlegate, Malton, North Yorkshire YO17 7DT
United Kingdom

Support Team: +44(0)1653 699599
support@encephalitis.info