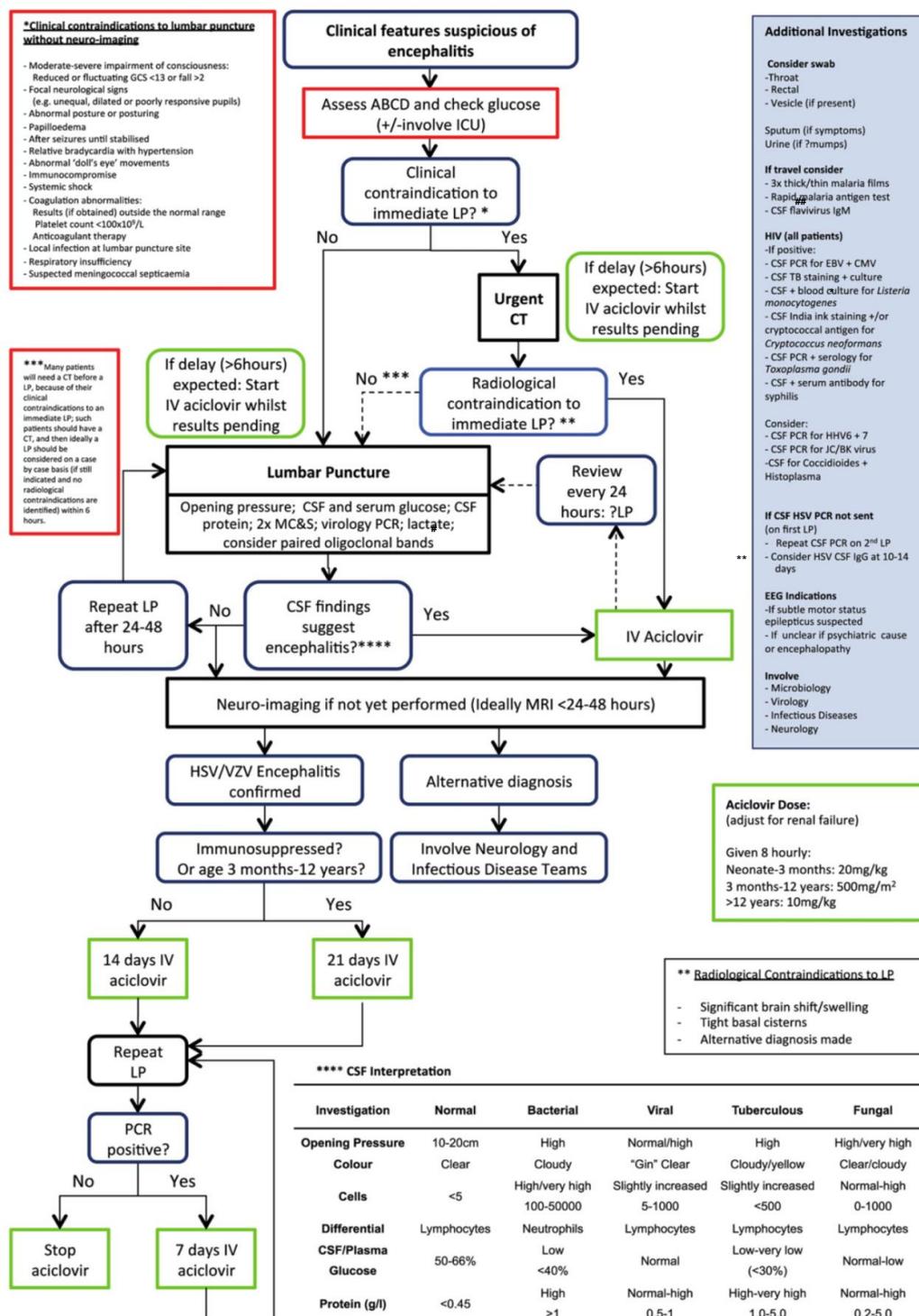


Wessex Regional Paediatric Neurology Guideline:

Management of Suspected Encephalitis

An algorithm summarising management is shown below (Figure 1). This must be read in conjunction with the text that follows and includes interpretation of it.



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)

Figure 1 Algorithm for the management of suspected acute encephalitis. From Kneen et al 2012¹ (with permission)

- Additional notes:
- See page 4 and Appendix 2 regarding contraindications to LP that may coexist with a 'normal' scan.
 - Suggested CSF volumes – 2ml if age <5 years, 4ml if age >5 years.
 - If CSF HSV serology sent, must be accompanied with paired serum HSV serology.
 - If travel history, discuss with local microbiology team +/- UHS paed ID team
 - If TB suspected, for interferon gamma release assay (Quantiferon / T-spot T)

Encephalitis - What is it? And why do we need a regional guideline?

Encephalitis is a rare but potentially devastating disease involving inflammation of the brain parenchyma. There is often, but not always, CSF pleocytosis indicating concomitant inflammation of the meninges i.e. meningo-encephalitis. Other non-inflammatory encephalopathies may mimic encephalitis clinically. The aim of this guideline is to define clearly the clinical features suspicious of encephalitis, to provide a list of likely differential diagnoses, to guide appropriate investigations and treatment and to assist in decision making about starting and stopping aciclovir

This guidance is based on a current appraisal of the best evidence available and is consistent with current Association of British Neurologists and British Paediatric Allergy Immunology and Infection Group recommendations ^(1,2).

Incidence

In the UK, the rate of encephalitis is estimated at 2.8 cases/100,000 in the general childhood population, with the highest incidence in infants aged under 1 year of age, 8.7/100,000⁽³⁾. A typical DGH may see around 5 children/year with a diagnosis of encephalitis⁽⁴⁾. A prospective BPSU study conducted in Britain and Ireland over a 3 year period (1998-2001) identified 19 cases of HSV encephalitis in children aged 2-23 months of age⁽⁵⁾. A subsequent 2 year prospective study conducted in 3 regions of England identified 18 cases of HSV encephalitis (60% below 1 year of age, 35% between 1-4 years of age)⁽⁶⁾.

Presentation

Features suspicious of infective encephalitis:-

A. Fever > 38°C is usually but not invariably apparent at presentation

B. Persistently altered level of consciousness (LOC) or change in personality or behaviour for >24 hours and one or more features in two or more of the following groups:-

- 1) convulsions
emotional lability / psychiatric symptoms
focal neurology > 24 hours
- 2) CSF pleocytosis (>5 leucocytes/ μ L)
- 3) Characteristic neuroimaging findings (CT/MRI) associated with encephalitis such as changes in the cerebral cortex, or basal ganglia or at the grey-white matter junction, or, in ADEM, foci of demyelination in the white matter, basal ganglia and spinal cord. MRI may be insensitive for the detection of encephalitis early in the illness, especially in neonates.

Aetiology

1) Common causes of acute encephalitis in the UK include:-

Enterovirus, including parechoviruses, HSV, EBV, adenovirus, measles

2) Less common causes include:-

Viral - VZV, adenovirus, CMV, HHV6, parvovirus, mumps, rubella, influenza, para-influenza, arboviruses (including West Nile virus, Japanese B encephalitis and Colorado tick fever), HIV, and very rarely rabies, Ebola virus.

Bacterial– Borrelia (Lyme disease), mycoplasma pneumonia, Listeria, Bartonella (Cat scratch disease), mycobacterium tuberculosis, streptococcus pneumoniae, Gp A streptococcus, syphilis

Parasites – Malaria, toxoplasma

Rickettsia – Q fever, typhus, Rocky Mountain spotted fever

Children who are immunocompromised may have a more subacute course and have a far more extensive range of possible pathogens (please discuss with paediatric infectious diseases team, Southampton Children's Hospital).

3) Non-infectious causes of acute encephalitis include acute disseminated encephalomyelitis (ADEM), immune-mediated encephalitis (anti-NMDA, voltage gated K⁺ channel, anti-GAD etc), Hashimoto's encephalopathy, and neoplastic encephalomyelitis.

4) The differential diagnosis of non-inflammatory encephalopathies includes:-

- Trauma including non-accidental injury
- Vascular conditions, including venous sinus thrombosis as well as large middle cerebral and cerebellar stroke
- Drugs / toxins
- Metabolic disorders
- Malignancy
- Hypertensive encephalopathy and posterior reversible encephalopathy syndrome
- Status epilepticus
- Haemolytic-uraemic syndrome

Indicators in the history of possible aetiology (adapted from Thompson C et al, 2012²):

- Recent vaccination (ADEM), unvaccinated (Polio, Measles, Mumps, Rubella)
- History of rash - chicken pox (VZV), slapped cheek (parvovirus), roseola (HHV6), meningococcal, streptococcal
- Animal contact (cat scratch), insect contact (Lyme disease, malaria)
- History or presence of a cold sore or stomatitis (HSV). However, more often than not a child with HSV encephalitis does NOT have any perioral lesions.
- Parotitis, abdominal pain (pancreatitis) or testicular pain may be present in Mumps.
- Social History - may reveal Maternal HIV or previous residence in an endemic area.
- Travel History to exclude rabies (transmitted by bats or bite of an infected dog), arboviruses (transmitted by insect or tick in S. Asia and central Europe) and malaria.

Indicators of aetiology based on presentation:

Clinical Presentation	Possible Aetiological Agent
Seizures	HSV, immune-mediated encephalitis
Cranial nerve abnormality	HSV, EBV, Listeria, TB, Lyme Disease
Cerebellar Ataxia	VZV, EBV, Mumps
Dementia	HIV, Measles, syphilis
Poliomyelitis-like flaccid paralysis	poliovirus, enteroviruses
Retinitis	CMV, Cat scratch, syphilis
Rash	VZV, HHV-6, Rubella, Lyme Disease, Enteroviruses, Mycoplasma, HIV
Respiratory tract findings	Influenza, Adenovirus, Mycoplasma, tuberculosis. ADEM is commonly preceded by a respiratory illness.
Parotitis	Mumps
Lymphadenopathy	HIV, EBV, CMV, Measles, Rubella, Cat Scratch
Hepatitis	Q Fever

Investigations and management

After other non-infectious causes of encephalopathy have been excluded, investigation and management of encephalitis aims to identify the causative pathology and manage complications of infection. Despite extensive investigation, a microbiological/virological diagnosis is obtained in less than 1/3 of children presenting with a presumed infective encephalitis.

CSF: CSF analysis is a highly useful investigation in all suspected cases of encephalitis and where possible should be done on presentation to confirm diagnosis before starting antiviral therapy. However, in an acute setting there may be contraindications to Lumbar Puncture (See Appendix 2). If lumbar puncture is not performed on admission, it should be reconsidered every day until performed. Any decision to proceed with LP (or not) will need to take clinical features that might indicate raised intracranial pressure into account, whether or not recent cranial imaging is available. The decision to proceed to LP in a child who is either sedated or has had clinical signs that are suggestive (but not confirmatory) of raised ICP should only be made by a consultant paediatric neurologist or neurosurgeon.

CSF should be sent for M,C+S, PCR for HSV types 1 &2, VZV and enterovirus (store a sample for further possible analysis if needed), glucose (with paired plasma glucose), lactate and consider oligoclonal bands (paired with serum sample). The opening pressure should also be measured. If CSF findings are not indicative of *Herpes simplex* encephalitis, yet the clinical suspicion is high, urgent neuroimaging (MRI) should be performed and the LP repeated within 24-48 hrs. An adequate volume of CSF is required to perform the required investigations:-

Age < 5 years 2 ml

Age > 5 years 4 ml

Microbiological investigations: Blood culture and CSF sampling are essential investigations in encephalitis. Sampling from other sites (eg nasopharynx, urine, stool, throat) should be guided by clinical features. Testing for specific infectious agents should be guided by the history, particularly of immunocompromise, travel and vaccinations.

Neuroimaging: Essential, as can identify complications of encephalitis and is often used to diagnose non-infectious alternatives of encephalopathy CT should be obtained as soon as possible after admission for any child with reduced level of consciousness. If despite a normal CT scan, the child continues to deteriorate/doesn't start to improve within 48 hours, the case should be discussed with the neurology team at SCH to decide whether an urgent MRI is required. MRI scans should be reviewed by experienced neuroradiologists and paediatric neurologists at the tertiary centre.

EEG: Useful for identifying underlying seizure activity even in those patients who have no clinical features of seizures. It is also a sensitive indicator of cerebral dysfunction, and is of particular value in children with HSV encephalitis, where the typical pattern of periodic lateralising epileptiform discharges are seen arising from the temporal lobes.

Treatment

Treatment should be guided according to likely aetiology. Empirical treatment should include broad spectrum antibiotics (third generation cephalosporin). The diagnosis of *herpes simplex* encephalitis should be considered in any patient who meets the criteria for infective encephalitis and IV aciclovir should be initiated. There is insufficient data to recommend antimicrobial therapy for mycoplasma encephalitis. A macrolide such as azithromycin should only be used empirically if the patient presents with respiratory symptoms. Once the aetiology is discovered, treatment should be rationalised accordingly.

Monitoring the child admitted with encephalitis

Neuro obs should be performed every 30 minutes for the first 2 hours, then hourly whilst required. Standardised early warning systems such as PEWS should also be utilised.

Aciclovir treatment in children ⁽²⁾

When to start aciclovir treatment in children with suspected HSV encephalitis

Although HSV encephalitis accounts for approximately 20% of all cases of encephalitis, it accounts for 40% of encephalitis morbidity⁽⁶⁾. The diagnosis of *herpes simplex* encephalitis should be considered in any patient who meets the criteria for infective encephalitis. In this situation, IV aciclovir (500mg/m² tds) should be started pending results. Children with encephalitis and CSF pleocytosis should also be started empirically on aciclovir, awaiting viral PCR results. If the initial LP is performed in the 1st 24 hours of the illness, consider repeating an LP 24-48 hours later and performing urgent neuroimaging (MRI) before considering stopping aciclovir.

When to stop aciclovir in children treated for suspected HSV encephalitis

If there is no ongoing clinical suspicion of HSE (a definitive alternative diagnosis becomes apparent, or it seems very unlikely that the patient has viral encephalitis).

Aciclovir can be stopped if CSF collected >72 hrs but <10 days following onset of neurological symptoms is HSV PCR negative AND there is a low clinical suspicion of HSE (eg, a clinical recovery and normal level of consciousness, normal neuroimaging and <5 cells/mm³ in CSF).

If symptoms persist or abnormal neuroimaging, despite CSF HSV PCR being negative, consider discussing the case with paediatric neurology or paediatric infectious diseases team, SCH.

If HSV encephalitis is confirmed, please discuss the case with SCH neurology team and repeat LP at end of treatment course. If HSV PCR remains positive, continue IV aciclovir followed by a repeat LP 7 days later.

When NOT to start aciclovir in children with neurological symptoms/signs

Children with simple febrile convulsions who recover fully.

Seizures without documented fever or history of fever (unless immunocompromised)

Other obvious cause for symptoms, eg blocked VP shunt, drug overdose.

CSF and clinical picture are highly suggestive of bacterial meningitis

Presumed infective encephalitis but negative PCRs for herpes viruses on a CSF sample obtained between 72 hours and 10 days from onset of neurological illness.

Immunomodulatory treatment

A randomised controlled trial of the use of steroids in adults is underway in Europe and UK, but steroids are not currently indicated in children with a suspicion or proven viral encephalitis.⁽⁸⁾ However, there is evidence that steroids helps adults with VZV reactivation encephalitis, and it may be reasonable to consider this in children with the same diagnosis.⁽⁸⁾ Expert neurological advice should always be sought in children with VZV reactivation encephalitis.

Steroids are the mainstay of treatment in ADEM and other antibody-mediated encephalitides e.g. anti-NMDA antibody encephalitis. Liaison with tertiary neurological services is a necessity in these circumstances, where IV immunoglobulin, plasma exchange and other immunosuppressants may be considered.

Prognosis

There is limited literature on long-term outcome following encephalitis. The prognosis depends on the underlying aetiology. One retrospective study of 93 children admitted to hospital with encephalitis between 2000-2004 found that focal neurological findings at presentation was a negative prognostic indicator, however, seizures at presentation were not predictive of symptoms at discharge.⁽⁹⁾ Long-term morbidity (neurological sequelae) rates in children with *Herpes Simplex* Encephalitis range between between 63-67%^(10,11), with patients under 3 years of age more severely affected. Similar rates of neurological morbidity have been documented post enterovirus encephalitis and VZV encephalitis.⁽¹²⁾ A Glasgow coma score of less than 6 and presence of disease for longer than 4 days prior to starting treatment is a predictor of poor outcome.

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Appendix 1 - CSF interpretation

Investigation	Normal	Bacterial	Viral	TB	Fungal
Opening pressure	10-20 cm H ₂ O	High	Normal/high	high	High/very high
Colour	clear	Cloudy	“gin” clear	Cloudy/yellow	Clear/cloudy
Cells	<5	100-50000	5-1000	<500	0-1000
Differential	lymphocytes	Neutrophils	lymphocytes	lymphocytes	Lymphocytes
CSF/Plasma glucose	50-66%	<40%	normal	<30%	Normal/low
Protein (g/l)	<0.45	>1	0.5-1	1.0-5.0	0.2-5.0

Appendix 2 – contraindications to LP without neuroimaging ⁽¹⁾

Imaging needed before lumbar puncture (to exclude brain shift, swelling, or space occupying lesion)

- Moderate to severe impairment of consciousness (GCS < 13)^a or fall in GCS of >2
- Focal neurological signs (including 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

Other contraindications

- Systemic shock
- Coagulation abnormalities:
 - Coagulation results (if obtained) outside the normal range
 - Platelet count <100 × 10⁹/L
 - Anticoagulant therapy
- Local infection at the lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicaemia (extensive or spreading purpura)

^aThere is no agreement on the depth of coma that necessitates imaging before lumbar puncture; some argue Glasgow coma score < 12, others Glasgow coma score < 9.

- Patients on warfarin should be treated with heparin instead, and this stopped before lumbar puncture.
- Consider imaging before lumbar puncture in patients with known severe immunocompromise (e.g. advanced HIV).
- A lumbar puncture may still be possible if the platelet count is 50 × 10⁹/L; Seek haematological advice.