Consensus Guidelines on Evaluation and Management of Suspected Acute Viral Encephalitis in Children in India

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Justification: Viral encephalitis is an important cause of mortality and morbidity in children. The etiological agents are varied, and physicians treating such children often feel limited by the lack of uniform guidelines on evaluation and management of these critically ill children in resource-constrained settings.

Process: An 'Expert Group Meeting on Viral Encephalitis in Children' was held on 19th January, 2012 in Gurgaon, Haryana (under the *aegis* of PEDICON 2012, the National Conference of Indian Academy of Pediatrics). The invited experts included pediatricians and microbiologists with expertise in the relevant field. Various issues related to the subject were discussed and it was decided to bring out recommendations on the topic. The final recommendations were produced after circulating the draft document, and incorporating/discussing all changes, by e-mail.

Objectives: To aid the pediatrician in the evaluation and management of children with suspected viral encephalitis and to assist the public health authorities in acute encephalitis surveillance. These guidelines do not cover viral encephalitis in the neonatal period and in immunocompromised children, Rabies encephalitis, and chronic viral encephalitis such as Subacute sclerosing panencephalitis (SSPE).

Recommendations: Recommendation for evaluation and management of suspected viral encephalitis in children are presented. In any acute encephalitis outbreak, pediatricians should be aware of the common viral causes of encephalitis in their area, what information and samples they should collect, and the contact details of the District Surveillance Unit. Pending specific diagnosis and therapy (which may or may not be possible), prompt empirical therapy and meticulous supportive care are important to prevent ongoing brain damage, and improve outcome.

Key words: *Child, Encephalitis, Guidelines, India, Investigations, Management.*

Viral encephalitis is an important cause of mortality and morbidity in children. It may be sporadic like herpes simplex encephalitis (HSE), or epidemic such as Japanese B encephalitis (JE). The etiological agents are varied, and physicians treating such children often feel limited by the lack of availability of diagnostic testing for most of these agents. There are numerous lacunae in our knowledge, problems in epidemiological investigations, lack of diagnostic facilities, as well as difficulties in managing these critically ill children in smaller centers in our country (***Box*1**). Pediatricians who treat these children should be aware of how to manage a child with suspected encephalitis, as specific antiviral therapy is lifesaving in some diseases and these should be diagnosed without delay. Moreover, optimum supportive care is of paramount importance in the management of these children. These guidelines have been developed to aid the pediatrician in the management of children with suspected viral encephalitis, in both sporadic and epidemic settings in India. These guidelines do not cover viral encephalitis in the neonatal period and in immunocompromised children, Rabies encephalitis, and chronic viral encephalitis such as Sub-acute sclerosing panencephalitis (SSPE).

Process

An 'Expert Group Meeting on Viral Encephalitis in Children' was held on 19th January, 2012 in Gurgaon, Haryana (under the aegis of PEDICON 2012, the National Conference of Indian Academy of Pediatrics). The invited experts included pediatricians and microbiologists with expertise in the relevant field (***Annexure* I**). Participants had been previously allotted specific topics for review. During the meeting, the problems related to managing these critically ill children in resource-constrained settings were identified (***Box* 1).** Subsequently, the experts deliberated on evaluation and management issues and a consensus reached on contentious topics. At the end of the meeting, it was decided to bring out recommendations on evaluation and management of suspected viral encephalitis in children,

BOX 1 PROBLEMS ENCOUNTERED IN THE MANAGEMENT OF CHILDREN WITH SUSPECTED VIRAL ENCEPHALITIS

- Paucity of data about the regional epidemiology and etiology of viral encephalitis
- Lack of easily available, low-cost microbiological testing for agents of viral encephalitis
- Lack of specific treatments for majority of the etiological agents
- High incidence of mimickers - pyogenic meningitis, cerebral malaria, tubercular meningitis, acute desseminated encephaloyelitis etc.
- Lack of facilities for intensive care in the periphery
- Lack of facilities for neuroimaging in the periphery.
- Inappropriate response during epidemics - what samples to take, how to store, whom to inform, etc.
- Patient delay in seeking health care
- Delay/not performing lumbar punctures
- Inappropriate supportive care

and a writing group identified for the purpose. Due to the lack of country-specific epidemiological information on the relative contribution of various etiologies to the burden of viral encephalitis, it was decided not to categorize the recommendations by either 'level of evidence' or 'strength of recommendation'. The draft was circulated by e-mail among all experts, and after incorporating all suggestions and review, the final document was produced.

EPIDEMIOLOGY AND DISEASE BURDEN

Definitions

The various definitions used in the document have been delineated in ***Box* 2.** Encephalopathy may be caused by many diverse causes including, systemic infection, metabolic derangement, inherited metabolic disorders, toxins, hypoxia, trauma, vasculitis, and central nervous system infection. Encephalitis means inflammation of the brain, which is difficult to decipher clinically and therefore, surrogate clinical markers are often used, including inflammatory changes in the cerebrospinal fluid or parenchymal inflammation on imaging [1]. Causes include viruses, small intracellular bacteria that directly infect the brain parenchyma and some parasites. It can also occur without direct brain infection, for example in acute disseminated encephalomyelitis (ADEM), or antibody-associated encephalitis. Acute encephalitis syndrome (AES) is a term used by WHO for syndromic surveillance in the context of Japanese encephalitis (JE) [2]. This definition includes not only viral encephalitis, but also all etiologies of fever and altered sensorium, such as bacterial meningitis, tubercular meningitis, cerebral malaria, and acute disseminated encephalomyelitis. Moreover, the duration of illness to classify as 'acute', has also not been clarified. After much discussion, a period of up to 14 days was considered by consensus to define 'acute'. Although the expert group felt this definition had problems and seemed complicated, and alternative terms such as 'acute febrile encephalopathy' and 'acute encephalitis-like syndrome' were considered, it was ultimately decided to continue with this definition for the sake of uniformity. Case definitions of suspected, probable and confirmed JE have previously been provided by the WHO [2].

Etiological Agents

Viral agents that have the potential of infecting the central nervous system in humans have previously been detailed [3]; the common causes of viral encephalitis reported from India are listed in ***Box* 3.** Agents that may be encountered in AES in an epidemic form include Japanese encephalitis, which is a major public health problem because of large endemic areas in the country, the high case fatality rate (20-30%) and frequent residual neuropsychiatric damage (50-70%) [2]; Enteroviruses, especially EV 71 [4], reported also from sporadic encephalitis cases [5]; Chandipura virus [6,7]; Nipah virus [8]; and, Chikangunya virus [9]. Another common viral agent of AES in the epidemic setting, being recognized more commonly now, is Dengue virus [10].

Viral agents responsible for sporadic encephalitis include Varicella zoster virus, Mumps, Human herpes virus 6 and 7, Epstein Barr virus, and most importantly, *Herpes simplex* virus. Herpse simplex virus encephalctis (HSE) is the most common cause of sporadic fatal viral encephalitis, with an incidence of 1-3/million in western countries [11] Not much information is available regarding proportion of AES cases due to HSE in the Indian setting. In untreated patients, mortality is high (70%), which is decreased to 30% in treated patients (risk

BOX 2 IMPORTANT DEFINITIONS

Encephalopathy

Encephalopathy describes a clinical syndrome of altered mental status, manifesting as reduced consciousness or altered behavior [1].

Encephalitis

Encephalitis means inflammation of the brain.

It is strictly a pathological diagnosis; but surrogate clinical/imaging markers may provide evidence of inflammation.

Acute Encephalitis Syndrome*

Clinically, a case of acute encephalitis syndrome is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures) [2].

Japanese B encephalitis (JE)

Laboratory-confirmed JE: A suspected case that has been laboratory-confirmed as JE [2].

Probable JE: A suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak [2].

***** *This definition includes not only viral encephalitis, but also all etiologies of fever and altered sensorium, such as bacterial meningitis, tubercular meningitis, cerebral malaria, acute disseminated encephalomyelitis etc. Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness.*

of sequelae of around 11%) [12]. Measles virus can cause acute encephalitis and has frequently been implicated in epidemic encephalitis, sometimes without rash [13]; although the evidence has been questioned [14,15].

Emerging Viral Agents and Changing Epidemiology

The changing epidemiology and newer viral agents causing AES worldwide have recently been reviewed [16,17]. Various other viral agents e.g., Human Parvovirus 4 [18], West Nile virus [19,20], Bagaza virus [21], Coxsackie virus [22] have been reported in sporadic AES cases from India. Various non-viral causes associated with encephalitis were recently described [23]. Some authors have also reported epidemic-like occurrence of AES due to non-infective causes in children from India e.g., plant toxins (*Cassia occidentalis*) [24], heat stroke [25], and Reye's syndrome [26-28]. The exact epidemiologic significance of some of these reports is difficult to elucidate from the available literature.

EVALUATION AND MANAGEMENT

Acute encephalitis syndrome is a medical and neurological emergency, requiring immediate consideration of key issues including immediate life support, identification of cause, and when available, institution of specific therapy. Management guidelines at the community level for a child with features suggestive of meningoencephalitis have previously been provided by PATH: Japanese Encephalitis Clinical Care Guidelines, 2005 [29], and by UNICEF and Government of India (Facility-based IMNCI Participants' Manual [30]. Our

BOX 3 AGENTS OF CLINICALLY IMPORTANT VIRAL ENCEPHALITIS IN INDIA*

Japanese encephalitis virus Enteroviruses

- Outbreak-2006, east UP (EV 89,76); 2008, Lucknow (EV 71)
- Sporadic-2004-06, AMU, UP (EV 71); 2007, Delhi (EV 71)

Herpes simplex virus 1 (HSV-1)

Dengue Virus (encephalopathy)

Measles virus

Chandipura

- Outbreak-Andhra Pradesh 2003; Gujarat 2004; Nagpur 2005; Nagpur 2007
- Sporadic-2005-06; Andhra Pradesh

Mumps virus

Chikungunya

Varicella zoster virus (VZV)

Epstein-Barr virus (EBV)

Human immunodeficiency virus (HIV)

Human herpesvirus 6 (HHV-6)

Nipah (Handra)

- Outbreak: 2001, Siliguri; 2007, West Bengal

West Nile virus[#]

Kyasanur Forest Disease

Rabies

***Cerebral malaria, pyogenic/tubercular meningitis and rickettsial diseases may mimic the clinical and/or laboratory characteristics of these agents, and may need to be excluded by appropriate tests; [#]Unconfirmed reports of recent outbreak in Kerala in October, 2011.*

guidelines reiterate the previously detailed initial stabilization and supportive management of a child with altered sensorium, and provide additional information on evaluation and management. The evaluation (clinical as well as investigations) and treatment have to proceed simultaneously (***Box* 4**). A step-wise management is described.

Step 1: Rapid Assessment and Stabilization

As in any emergency, initial steps should be directed to ensuring adequacy of airway, breathing and circulatory function. Airway management is of paramount importance in children with altered states of consciousness, as their protective reflexes are obtunded and they are more prone to aspiration. Children with Glasgow Coma Score less than 8 should preferably be intubated; mechanical ventilation should be provided in case the breathing efforts are not adequate. Appropriate oxygenation should be ensured.

The next important step is establishment of vascular access. If there is evidence of circulatory failure, fluid bolus (20 mL/kg-Normal saline) should be administered. Samples should be drawn for various investigations. If hypoglycemia is present, intravenous glucose should be administered. If the child is having seizures, or there is history of a seizure preceding the encephalopathy, anticonvulsant (intravenous benzodiazepine followed by

BOX 4 EVALUATION AND MANAGEMENT OF A CHILD WITH ACUTE ENCEPHALITIS SYNDROME

Step I: Rapid assessment and stabilization

- Establish and maintain airway: Intubate if GCS<8, impaired airway reflexes, abnormal respiratory pattern, signs of raised ICP, oxygen saturation <92% despite high flow oxygen, and fluid refractory shock
- Ventilation, Oxygenation
- Circulation: Establish IV access, take samples (CBC, Blood sugar, KFT, LFT, electrolytes, blood gas, lactate, PS and RDT for malarial parasite, serology for viruses), Fluid bolus if in circulatory failure (20 mL/kg NS), inotropes if required
- Identify signs of cerebral herniation or raised ICP
- Temperature: treat fever and hypothermia
- Treat ongoing seizures- Benzodiazepine, followed by phenytoin loading

Step II: Clinical evaluation: History and Examination

Step III: Investigation/Samples to be collected

- CSF
- Blood/serum, Urine
- MRI (CT, if MRI not available/possible), avoid sedation
- Throat swab, nasopharyngeal swab

Step IV: Empirical Treatment (must be started if CSF cannot be done/report will take time and patient sick)

- Ceftriaxone
- Acyclovir (use in all suspected sporadic viral encephalitis)

Artesunate (stop if peripheral smear and RDT are negative)

Step V: Supportive care and treatment

- Maintain euglycemia, Control fever, Maintain hydration
- Treat raised intracranial pressure, mild head-end elevation–15-30°
- Treat seizures; Give anticonvulsant if history of seizures or if GCS <8, or child has features of raised ICT
- Steroids: Pulse steroids (methylprednisolone or dexamethasone) must be given in children with suspected ADEM.

Step VI: Prevention/treatment of complications and rehabilitation

- Physiotherapy, posture change, Prevent bed sores and exposure keratitis
- Complications: aspiration pneumonia, nosocomial infections, coagulation disturbances
- Nutrition: early feeding
- Psychological support to patient and family

phenytoin loading 20 mg/kg) should be administered [31]. If there are features of raised intracranial pressure (asymmetric pupils, tonic posturing, papilledema, evidence of herniation), measures to decrease intracranial pressure should be rapidly instituted (head elevation, minimal disturbance, normothermia, pharmacotherapy, hyperventilation, etc.). Acid base and electrolyte abnormalities should be corrected. Normothermia should be maintained.

Step 2: Detailed History and Examination

A careful history should be taken with special emphasis on onset and duration, and other features such as fever, headache, vomiting, irritability, seizures, and rash (***Box* 5**). There may be a prodrome of upper respiratory illness, flu-like illness or diarrhea. Recent history or contact with a child having chicken pox or mumps must be enquired. The place of residence of the child (endemic area for any disease *e.g.,* JE), recent history of travel, or any occurrence of similar illness in the neighborhood must be noted.

A history of fever or recent illness suggests an acute infectious etiology, but other disorders in which encephalopathy maybe preceded by a febrile illness must also be considered. These include acute disseminated encephalomyelitis, Reye's syndrome, and mitochondrial and other inborn errors of metabolism [32]. History of trauma, drug/toxin exposure, dog bite, past medical illnesses, and family history must be elicited. Past history of similar illness may indicate the presence of an underlying inborn error of metabolism. Encephalitis associated with gastrointestinal symptoms include infections with enteroviruses, rotavirus and human parechovirus [1]. Encephalitis associated with respiratory illnesses may be due to influenza viruses, paramyxoviruses and the bacteria, *Mycoplasma pneumoniae* [1]; those with influenza associated encephalopathy may, in addition, have associated myositis [33].

The general physical examination may provide helpful etiological clues. Presence of pallor may indicate cerebral malaria, or intracranial bleed. Icterus could indicate leptospirosis, hepatic encephalopathy, or cerebral malaria. Skin rashes are common in meningococcemia, dengue, measles, varicella, rickettsial diseases, arboviral diseases, and enteroviral encephalitis. Petechiae are seen in meningococcemia, dengue and viral hemorrhagic fevers. Parotid swelling and orchitis point towards mumps as etiology. Mumps encephalitis, may, however, occur without parotitis [34]. In a study of 137 patients with mumps meningitis, parotitis was detected

BOX 5 IMPORTANT POINTS IN THE HISTORY OF A CHILD WITH AES

- Fever, headache, vomiting, seizures, abnormal posturing
- Altered behavior, cognition, personality changes, altered consciousness
- Prodromal symptoms- flu-like illness, diarrhea
- Rash, vesicles, past history of chicken pox
- Residence of child: Rural/urban, endemic for cerebral malaria, any epidemic of AES in neighborhood
- History of animal contact, insect bite, dog bite
- Drug or toxin exposure- enquire for presence of any drugs at home
- Recent history of travel
- History of trauma
- Personal or family history of seizure disorder
- Recent immunizations
- History of recurrent episodes of encephalopathy: These are characteristic of some inborn errors of metabolism (urea cycle defects, organic acidemias and fatty acid oxidation defects), but may also be present in migraine, epilepsy, substance abuse, and Munchausen syndrome by proxy
- Other concurrent systemic illness e.g. jaundice (hepatic failure), pneumonia (hypoxic encephalopathy), diarrhea (dyselectrolytemia), dysentery (shigella encephalopathy)
- Past medical illness: Diabetes, congenital heart disease, chronic kidney or liver disease
- Family history of previous infant/child deaths
- Pre-morbid developmental/ neurological status of the child
- Risk factors for immunodeficiency- HIV risk factors, cancer treatment, steroid/immunosuppressant treatment

only in 37% of patients [35]. Labial herpes in young children may point towards herpes simplex virus encephalitis [36].

The neurological examination is targeted to document the level and localization of brain dysfunction. It may also provide information about the potential causes. The level of consciousness must be recorded in the form of an objective scale, such as the Glasgow Coma Scale (GCS). A modified GCS should be used for infants and young children [37]. While the GCS allows efficient, standardized communication of a child's state, a more detailed description of the child's clinical findings is often more useful for relaying detailed information and detecting changes over time.

Pupillary size, shape, symmetry and response to light provide valuable clues to brainstem and third nerve dysfunction. Topical administration of mydriatics must be avoided, but if done, should be documented to avoid confusion in interpretation. Unilateral pupillary dilatation in the comatose patient should be considered as evidence of oculomotor nerve compression from ipsilateral uncal herniation, unless proved otherwise [38]. Symptoms of progressive symmetrical external ophthalmoplegia suggest Bickerstaff brainstem encephalitis in association with *M. pneumoniae*, and can serve as a clue to the diagnosis, especially when associated with ataxia [39].

In HSE, neurological findings are mostly related to dysfunction of the fronto-temporal lobes *viz*., personality changes, confusion and disorientation. However, absence of herpes labialis, focal seizures or unilateral neurological findings does not rule out HSE. CT is usually normal in first 4-6 days of the disease [11]. MRI demonstrates high signal intensity lesions on T2-weighted, diffusion-weighted, and FLAIR images earlier in the course [13]. The MRI may rarely be normal in HSE. The optimum chance of obtaining a positive CSF PCR in HSE is between 2-10 days after the onset of illness [31].

The presence of oculocephalic (doll's eye), oculovestibular, corneal, cough and gag reflexes must be looked for to check brainstem function. Brainstem dysfunction is an important feature in some causes of viral encephalitis such as enterovirus 71, mumps, and rabies [1]. The trunk, limb position, spontaneous movements, and response to stimulation must be observed to look for any focal deficits, and posturing (decerebrate or decorticate). The power of the limbs and deep tendon reflexes must be checked. Brain tissue deforms intra-cranially and moves from higher to lower pressure when there is asymmetric, or generalized increased intracranial pressure [40]. This gives rise to the various herniation syndromes. Special attention should be given to posturing because it often signals a brainstem herniation syndrome [41]. The importance lies in recognition and prompt treatment, before the damage becomes irreversible. Associated acute flaccid paralysis along with encephalitis can be seen in enterovirus infections (anterior horn cell involvement), poliomyelitis (anterior horn cell involvement), acute disseminated encephalomyelitis (due to myelitis) and rarely in JE. The patient should be carefully observed for the presence of subtle seizures (twitching of fingers, mouth, eyelid etc). Myoclonic jerks are seen frequently in enterovirus encephalitis [42]. Dystonia or extrapyramidal movements signify extrapyramidal involvement which is very common in JE, seen in up to 1/3rd of children (43). Fundus examination must be performed to look for papilledema and retinal hemorrhages. Retinal hemorrhages are an important clue for cerebral malaria in endemic setting, being present in nearly a quarter of the patients [44]. Presence of signs of meningeal irritation (neck rigidity, Kernig's sign and Brudzinski's sign) must be looked for. Systemic examination must be performed to look for hepatosplenomegaly, pulmonary involvement such as pneumonia, pleural effusions, and cardiac involvement such as myocarditis. Myocarditis is an important complication of EV 71 encephalitis [42]. Children with EV 71 encephalitis may also develop neurogenic pulmonary edema.

Step 3: Investigations

Basic investigations: Basic blood investigations which should be obtained in all patients with AES include a complete blood count (including platelet count), blood glucose, serum electrolytes, liver and kidney function tests, blood culture, arterial blood gas, and lactate (if available). A peripheral smear for malarial parasite and rapid diagnostic test for malaria should be obtained. A chest *X*-ray should also be obtained.

Lumbar puncture: If the patient is hemodynamically stable, and no features of raised intracranial pressure, a lumbar puncture should be performed. If lumbar puncture is contraindicated, a neuroimaging study should be obtained prior to the lumbar puncture. Empirical treatment (Step 4) should be started pending the results of lumbar puncture and/or neuroimaging studies.

The CSF analysis is an important investigation in children with AES. CSF should be examined for cytology, biochemistry, gram stain, Ziehl-Nielsen stain for acid fast bacilli, bacterial culture, latex agglutination, PCR for HSV 1 and 2, and IgM antibodies for JE and for Dengue virus (if suspected). Concurrent blood sugar must also be measured to look for the CSF to blood sugar ratio. 1-2 mL CSF should be stored for other virological studies, if needed. Usual CSF findings in viral encephalitis include

lymphocytic pleocytosis, mild to moderately elevated protein, and normal CSF sugar. Similar findings may occur in tubercular meningitis and partially treated pyogenic meningitis; however, the CSF sugar is likely to be low in these situations.

Neuroimaging: Only CT scan may be possible in the emergency situation but it may give valuable information such as presence of bleed, cerebral edema, temporal lobe hypodensities in herpes simplex encephalitis, thalamic abnormalities in JE, and basal exudates and hydrocephalus in tubercular meningitis. CT may also show brain herniation, effacement of cisterns, and infective collections such as brain abscesses and subdural empyema. If possible, an MRI should be obtained, as soon as the patient is stable. MRI is not needed if the etiology is clear by other investigations *e.g.*, cerebral malaria, pyogenic meningitis; or if suggestive changes are seen on CT; or in epidemic situations where the likely etiology is already known. In all other patients, MRI provides useful information regarding the etiology and alternative diagnoses. However, the availability, cost, and difficulties in transporting sick and unstable patients for MRI may be limiting factors. MRI sequences must include diffusion weighted imaging to detect early changes, and a gadolinium enhanced study.

Suggestive MRI findings are present in some etiologies of viral encephalitis such as Herpes simplex encephalitis, JE, enterovirus encephalitis **(*Table* I)**. MRI may show non-specific features of viral encephalitis such as cortical hyperintensities and cerebral edema. MRI is also useful for diagnosing alternative etiologies such as Acute disseminated encephalomyelitis, and antibody-associated encephalopathies.

Other microbiological investigations: When the etiology is not clear, other microbiological investigations must be obtained. These are also required in epidemic situations, where the etiology has not been established. The local health authorities must be informed, and a microbiologist should be consulted when taking the samples. These samples include urine, throat swab, nasopharyngeal aspirate, serum (acute, and convalescent after 2 weeks), and swab from vesicles or rash, if present. The duration of time the virus remains in the CSF may be brief; hence, CSF positivity for some viruses *e.g.*, enterovirus is very low. Therefore, it is important to collect and store these samples. The methods for collection, storage and transport of the samples are detailed in ***Table* II**. Details about the specific etiologies are given in ***Table* III.**

Tests for JE, HSV 1 and 2, dengue, poliovirus, measles, mumps and rubella are available in selected government and private laboratories. Tests for nipah virus, VZV, EBV, adenovirus and enterovirus are not easily available. There are commercially available tests, which test for a panel of viruses (HSV1, 2, VZV, HHV-6, Measles, Mumps, Rubella, Chandipura, Chikungunya, Nipah, Rabies, Enteroviruses, Japanese B, Dengue, West Nile virus) and bacteria with 1-2 mL CSF sample, using

TABLE I MRI FINDINGS IN VIRAL ENCEPHALITIS AND SOME MIMICKERS

Etiology	*MRI Finding*
Herpes simplex encephalitis [63]	Abnormal signal intensity in medial temporal lobe, cingulate gyrus, and orbital surface of frontal lobes
Japanese B encephalitis [64, 65]	Abnormal signal intensity in thalami (87-94%), substantia nigra, and basal ganglia
EV 71 [66]	Abnormal signal intensity in the dorsal pons, medulla, midbrain, and dentate nuclei of the cerebellum; gigh-signal lesions can also be found in the anterior horn cells of spinal cord in patients with acute flaccid paralysis
Chandipura virus *[67]	Normal
Nipah virus [68]*	Focal subcortical and deep white matter and gray matter lesions; small hyperintense lesions in the white matter, cortex, pons and cerebral peduncles have also been seen.
Varicella [69]	Multifocal abnormalities in cortex, associated cerebellitis, vasculitis and vasculopathy
Acute disseminated encephalomyelitis	Multifocal abnormalities in subcortical white matter; involvement of thalami, basal ganglia, and brainstem also seen
West Nile virus [70, 71]	Abnormalities in deep gray matter and brainstem (50%); white matter lesions mimicking demyelination may also be seen; meningeal involvement on contrast enhanced images.

Reports on small number of patients

TABLE II GUIDELINES FOR COLLECTION, STORAGE AND TRANSPORT OF SAMPLES

Type of sample	*Guidelines*
Blood	• Collect within 4 days after the onset of illness for isolation of virus and at least 5 days after the onset of illness for detection of IgM antibodies.
	• A second, convalescent sample should be collected at least 10-14 days after the first sample for serology.
	• Take clotted blood sample. Separate serum after clot retraction.
	• Serum should be shipped on wet ice within 48 hours or stored at for a maximum period of 7 days.
	• In case a delay is anticipated, sera must be frozen at -20°C and should be transported to the specified laboratory on frozen ice packs.
	• Repeated freezing and thawing can have detrimental effects on the stability of IgM antibodies.
Cerebrospinal fluid	• Send for cell count, bacteriology, biochemistry and virology -PCR, serology.
	• May be stored at +4°C if delays in processing for virus culture or viral PCR will be less than 24 hrs.
	• If greater delays are likely, CSF should be frozen at -80°C.
Swabs (naso-pharygeal, throat, vesicle)	• Dacron/ Nylon swabs should be used, and put into virus transport medium. Swabs may be utilized for a range of virus cultures and PCR.
Urine	10-20 mL of urine should be collected into sterile containers (without preservatives) for mumps virus culture and mumps PCR; store at -20°C.
Stool	Stool should be collected for enterovirus culture into clean containers; store at -20°C.
Brain biopsy	• Brain specimens should be collected unfixed into a sterile container. Brain smears can be used for viral antigen detection by immunofluorescent antibody staining, and for electron microscopy with negative staining.
	• Emulsified brain tissue is suitable for tissue culture and after proteinase K treatment for PCR.

DNA hybridization technique and very short turnaround time. However, these are prohibitively expensive at present. The sensitivity and specificity of these tests has also not been reported in published literature. Moreover, the flaviviruses WNV, DENV, and JEV share some common features, such as transmission via mosquitoes, and cross-react with each other in serological tests. These cross-reactive responses could confound the interpretation during serological testing, including neutralization tests and enzyme-linked immunosorbent assay (ELISA) [45,46].

In patients having unexplained encephalopathy with fever and rash, testing for rickettsial infections (Weil-Felix test, rickettsial serology) must be performed. HIV testing should be performed in children with unexplained encephalitis. Children with undiagnosed advanced HIV disease can present with CNS infections from rare causes, such as cytomegalovirus [1]; and rarely, meningoencephalitis may be a presenting feature of primary HIV infection.

Other tests: EEG is not routinely needed as it usually shows non-specific slowing in viral encephalitis. The presence of periodic lateralized epileptiform discharges may indicate underlying herpes simplex encephalitis, but their absence does not rule out the diagnosis. However, EEG must be performed in children with unexplained altered sensorium to look for suspected non-convulsive status epilepticus. EEG may also be helpful in patients with subtle and doubtful seizures, to guide anti-epileptic drug management.

If the diagnosis is not clear with the above mentioned tests, then alternative etiologies must be explored. In young children with unexplained altered sensorium, especially with pre-morbid developmental delay, investigations for inborn errors of metabolism (plasma ammonia, blood tandem mass spectroscopy, urine gas chromatography mass spectroscopy) must be carried out. In older children, the possibility of autoimmune disorders such as SLE (anti-nuclear antibodies, anti-ds-DNA antibodies), Hashimoto encephalopathy (anti-TPO antibodies), and anti-NMDA receptor and anti-VKGC antibody-mediated encephalitis may be considered. A urine toxicology screen should be performed. Finally, a brain biopsy may be needed to look for primary CNS vasculitis or neoplastic processes.

Step 4: Empirical Treatment

Empirical treatment must be started, pending the results of investigations. A broad spectrum antibiotic such as

TABLE III MICROBIOLOGICAL INVESTIGATIONS AVAILABLE IN ACUTE ENCEPHALITIS SYNDROME

Sample/ test	*Comment*
Japanese Encephalitis Virus	
Virus-specific IgM antibody in a single sample of cerebrospinal fluid (CSF) or serum, as detected by an IgM-capture ELISA specifically for JE virus	Further confirmatory tests (e.g. looking for cross-reactivity with other flaviviruses circulating in the geographical area) should be carried out: (*a*) when there is an ongoing dengue or other flavivirus outbreak; (*b*) when vaccination coverage is very high; or (*c*) in cases in areas where there are no epidemiological and entomological data supportive of JE transmission.^
Enteroviral encephalitis	
Detection of EV genome by RT-PCR or an equally sensitive and specific nucleic acid amplification test (real time) in CSF	Highly specific for EV encephalitis; however CSF, positivity rates are low
Isolation of virus from serum/stool/throat swab	Establishes carriage or systemic infection, but not necessarily the cause of the CNS disease; however, suggestive overall clinical picture and neuroimaging are useful pointers towards etiology
Dengue viral encephalitis	
Dengue virus-specific IgM antibody in a single sample of CSF[$], as detected by an IgM-capture ELISA	CSF positivity establishes the diagnosis of dengue encephalitis. serum positivity only confirms dengue infection.
HSV Encephalitis	
Detection of HSV DNA in CSF by PCR	Most sensitive method for early diagnosis of HSE; Sensitivity>95%, Specificity~100%
HSV specific antibody titres in serum and CSF	IgG preferable to IgM, Useful in cases where illness duration > 10-12 days, initial PCR not done or negative
Mumps virus encephalitis	
Detection of Mumps virus RNA in CSF by PCR	Sensitivity >95% in patients with a clinical diagnosis of viral CNS disease
Varicella zoster virus encephalitis	
Detection of VZV DNA by PCR in CSF	–
Nipah virus	
Detection of Nipah virus specific IgM antibodies in serum and CSF by IgM-capture ELISA	Sensitivity: Serum, 70%; CSF, <1/3rd of cases
PCR from CSF	–
Measles virus	
Appearance of measles virus specific IgM antibody in the CSF	Specificity of kit used should be checked; False positivity is a known issue
Chandipura virus	
PCR from CSF	–
Detection of specific IgM antibodies in CSF by ELISA	–

HI: hemagglutination inhibition; CF: complement fixation; PCR: Polymerase chain reaction; RT-PCR: Reverse transcriptase polymerase chain reaction; [$]Subject to availability; ^The large majority of JE infections are asymptomatic. Therefore, in areas that are highly endemic for JE, it is possible to have AES due to a cause other than JE virus and have JE virus-specific IgM antibody present in serum. To avoid implicating asymptomatic JE as the cause of other AES, sterile collection and testing of a CSF sample from all persons with AES are recommended when feasible.

ceftriaxone must be given, which can be stopped if no evidence of bacterial meningitis is forthcoming.

Even though epidemiological data on HSE from India is lacking, the consensus recommendation of the expert group is that acyclovir must be started in all cases of sporadic viral encephalitis, as HSE is a treatable disease. Acyclovir should be stopped if an alternative diagnosis has been made, or HSV PCR in the CSF is negative and MRI is normal. However, if the CSF PCR for HSV or MRI have been performed very early after symptom

onset (within 48 hours), these may be falsely negative. Hence, these studies should be repeated before stopping acyclovir if the clinical suspicion of HSE continues to be high. The dose and duration of acyclovir therapy is given in ***Box* 6**.

Empirical anti-malarial (artemisin-based combination therapy) must be started if there is a suspicion of cerebral malaria. This should be stopped if the peripheral smear and rapid diagnostic tests are negative.

Step 5: Supportive Care

After stabilization of airway, breathing and circulation, other supportive care measures must be instituted along with the empirical treatment as mentioned above. Timely and appropriate supportive care is of paramount importance to reduce the mortality and morbidity associated with viral encephalitis. Patients with GCS< 8, having features of raised intracranial pressure, status epilepticus and shock should ideally be managed in an intensive care unit; however, this may not always be possible in resource-constrained settings. The following are the components of supportive care:

(*a*) *Maintenance intravenous fluids*: Fluid therapy should be targeted to maintain euvolemia and normoglycemia, and to prevent hyponatremia. Children with acute viral encephalitis should receive fluids at the normal daily requirement. Increased fluid and fluid boluses may be indicated for dehydration and hypotension. Isotonic fluids are preferred, and hypotonic fluids (e.g. 0.18% saline in 5% dextrose, Isolyte P) must be avoided, especially in the presence of raised intracranial pressure. Serum sodium should be monitored, and abnormalities of serum sodium should be corrected slowly. If there are features of syndrome of inappropriate secretion of anti-diuretic hormone, only then fluids should be restricted to two-thirds of the daily maintenance.

BOX 6 DOSE AND DURATION OF ACYCLOVIR IN CHILDREN WITH ENCEPHALITIS^

Dose*
3 mo to 12 y: 500mg/m^2 8 hourly
>12 y: 10mg/Kg 8 hourly
Duration
Confirmed cases: 14-21 d intravenous treatment; Minimum 21 d for those aged 3mo-12y$^{\#}$
Where therapy was started empirically; Stop acyclovir, if an alternative diagnosis is confirmed, or if HSV PCR in the CSF is negative on two occasions (24-48 h apart) and MRI imaging does not suggest HSE.

*^Based on reference [50]; *Dose to be reduced in those with pre-existing renal failure; $^{\#}$CSF-PCR for HSV may be done at 14-21 days and treatment continued till CSF is negative.*

(*b*) *Management of raised intracranial pressure*: Raised intracranial pressure is a common cause of death in children with viral encephalitis. It is important to recognize and promptly manage signs of raised ICP. A common mistake in the emergency departments is to mistake decerebrate posturing for seizures, and inappropriately treat with anti-epileptic drugs. Intracranial pressure monitoring is available in very few centers. Therefore, clinical parameters have to be used to guide the treatment. Attempt should be made to maintain the cerebral perfusion pressure (CPP), which is the major factor that affects cerebral blood flow and hence, adequate oxygenation. CPP depends on the mean arterial pressure and the ICP (CPP= MAP– ICP). CPP can reduce as a result of reduced MAP or raised ICP or combination of these two. Therefore, adequate mean arterial pressure should be maintained.

The following steps are used in the management of raised intracranial pressure [47]. The patient should undergo intubation if the GCS is less than 8, or if there is evidence of herniation, or if the patient has irregular respirations and inability to maintain airway. If there are signs of impending herniation, then the patient should be hyperventilated to a target $PaCO_2$ of 30-35 mm Hg. Mannitol should be given at a dose of initial bolus of 0.25 g/kg, then 0.25 g/kg, q 6 h as per requirement, up to 48 hours. Hypertonic (3%) saline is preferable to mannitol in the presence of hypotension, hypovolemia, and renal failure. The dose is 0.1–1 mL/kg/hr by infusion; the serum sodium should be targeted to a level of 145-155 meq/L [48]. The patient should have adequate sedation and analgesia. Noxious stimuli should be avoided; nebulized lignocaine should be administered prior to endotracheal tube suctioning.

(*c*) *Maintain euglycemia:* Identify and treat hypoglycemia with intravenous dextrose (2 mL/kg 10% dextrose, then glucose infusion rate of 6–8 mg/kg/min). Blood glucose should be monitored and both hypo- and hyper-glycemia should be avoided.

(*d*) *Treatment and prevention of seizures:* If the child is having seizures, or has history of seizures, anticonvulsant should be administered. A benzodiazepine should be given (Lorazepam 0.1 mg/kg, diazepam 0.3 mg/kg, or midazolam 0.1 mg/kg) followed by phenytoin loading (20 mg/kg). Even if there is no history or clinical evidence of seizures, empirical anticonvulsant therapy may be considered in children with GCS <8, and features of raised intracranial pressure [47, 49]. This is because seizures may further raise the intracranial pressure and thus worsen the outcome.

(*e*) *Other drugs*

Corticosteroids: The role of corticosteroids in the treatment of viral encephalitis is not established. However, corticosteroids may be considered along with acyclovir in patients with marked cerebral edema, brain shift or raised intracranial pressure. Their role remains controversial because steroids may theoretically increase viral replication [1]. However a retrospective analysis of 45 adults with HSV encephalitis showed that lack of administration of corticosteroids was a significant independent predictor of a poor outcome [50]. Trials of adjunctive corticosteroid treatment in herpes simplex encephalitis are in progress [51]. Steroids have not shown to be of benefit in JE [52]. Steroids are indicated in ADEM, Hashimoto encephalopathy, and autoimmune encephalitis.

Antiviral treatment, i.e., Acyclovir is effective against encephalitis caused by Varicella Zoster virus. The dosage is same as that for herpes simplex encephalitis [53]. Pleconaril has been found to be useful in Enterovirus encephalitis and aseptic meningitis, but in not in EV 71 encephalitis [42,54]. IVIG has been used in EV 71 encephalitis, but the evidence of clinical benefit is not well established [42, 55]. Oral ribavirin was not found to be useful in children with Japanese B encephalitis in a randomized controlled trial [56]. There is experimental evidence of benefit of minocycline in JE [57]. Movement disorders such as dystonia may need treatment with trihexyphenidyl.

(*f*) *Other measures:* Acid-base and electrolyte abnormalities should be corrected. Any concurrent bacterial infections e.g., pneumonia should be treated with appropriate antibiotics. The patient should be monitored for changing level of consciousness, fever, seizures, autonomic nervous system dysfunction, increased intracranial pressure, and speech and motor disturbances. Nosocomial infections are important complications during hospitalization, and must be prevented and treated promptly.

Step 6: Prevention/treatment of complications and rehabilitation

Nosocomial infections, aspiration pneumonia, and coagulation disturbances may occur as complications, and should be detected and treated. Myocarditis and pulmonary edema are important complications of EV 71 encephalitis. Milrinone has been shown to be of benefit in these patients. Regular posture change must be done to prevent the development of bed sores. The patient should be started on early physiotherapy, to prevent the development of contractures.

PREVENTIVE STRATEGIES

Prevention and/or control of AES require a multi-pronged strategy which should consist of (*i*) Surveillance for cases of AES; (*ii*) Vector control; (*iii*) Reduction in man-vector contact; and (*iv*) Vaccination. Control of vectors and prevention of man-vector contact are key non-vaccination strategies, but are beyond the scope of the present communication.

AES Surveillance and Role of Pediatrician in Outbreak Situations

The purpose of AES surveillance is to estimate disease burden, to understand disease pattern, and its influence on mortality and morbidity. Surveillance helps in documenting the burden of the disease and also helps in proper utilization of scarce resources. The first and foremost requirement is establishing a proper "case definition", which can be applied in the field. The same has been provided here and also by the WHO [2]. Strengthening of surveillance is urgently needed throughout the country, more so in endemic states where frequent outbreaks are reported. Sentinel site hospitals should be identified for disease surveillance and case management, both in endemic and non-endemic areas. Mechanisms should be developed for AES reporting both by institutions and individual practitioners. It could even be a web-based system, as is being done for infectious diseases surveillance by IAP through IDsurv (http://www.idsurv.org/).

In any AES outbreak, pediatricians will see affected patients. They should be aware of what information and samples they should collect, and whom to inform. All pediatricians need to be aware of the case definition of AES. They should be aware of the common viral etiologies in their area, and should be alert if there is a clustering of cases. The cases should be notified to the District Surveillance Unit. All cases of AES should be notified to the local health authorities (the IDSP District surveillance unit). The concerned officer may be informed by telephone, fax, or e-mail. The requisite forms are available on the IDSP Portal (www.idsp.nic.in). The minimum data to be collected has been published (58). The samples that need to be collected, their timing and methods have already been detailed (***Table* II**).

Immunization

Human vaccination is the only effective, long-term, cost-effective measure against AES. At-risk population should receive a safe and efficacious vaccine as part of the national immunization program. Although vaccines are under development against many viral agents responsible for AES in children, but primarily it is JE against which vaccines are

available for routine use. Vaccines are currently under development against Dengue, Enteroviruse 71, and other flaviviruses like West Nile virus.

JE vaccination

The most effective immunization strategy in JE endemic settings is a one-time campaign in the primary target population, as defined by local epidemiological data, followed by incorporation of the JE vaccine in to the routine immunization program [59]. This approach has a greater public health impact than either strategy separately.

The JE vaccines include; a mouse brain derived inactivated vaccines (high incidence of sometime fatal complications, currently not available in India); Cell culture-derived, inactivated JE vaccine based on the Beijing P-3 strain (available only in China); and Cell culture-derived, live attenuated vaccine based on the SA14-14-2 strain [60]. Some newer JE vaccines are on the horizon (Chimeric vaccine -IMOJEV by Sanofi Pasteur, Inactivated SA-14-14-2 vaccine (IC51) - IXIARO by Intercel, Inactivated vero-cell derived JE vaccine-Beijing-1 JE strain by Biken and Kaketsuken) [61], but would not be discussed further here. The IAP Guidelines on Immunization provide recommendations on JE vaccination in India [62].

Cell culture-derived, live attenuated vaccine: Currently, this is the only JE vaccine available in India. This vaccine is based on the genetically stable, neuro-attenuated SA 14-14-2 strain of the JE virus, which elicits broad immunity against heterologous JE viruses. Reversion to neurovirulence is considered highly unlikely. The price per dose of the vaccine is comparable to the EPI measles vaccine. 0.5 mL dose is to be administered subcutaneously to children at eight months of age and a second opportunity again at two years. In some areas, a booster dose is given at seven years. It should not be used as an "outbreak response vaccine". It can also be offered to all susceptible children up to 15 yrs, and should be administered as a catch-up vaccination [59]. The vaccine should be stored and shipped at 8ºC, protected from sunlight. After a single dose, antibody responses are produced in 85 to 100% of non-immune 1- to 12-year-old children [61].

In India, one dose of SA-14-14-2 imported from China is being used in many states since 2006 [63], and the number of districts covered under the vaccine have been increased recently. Children between the age group of 1 to 15 years were vaccinated with a single dose of SA14-14-2 vaccine, with a coverage >80% [63]. The efficacy of a single dose of this vaccine was reported to be 94.5% (95% CI, 81.5 to 98.9) [64]. Preliminary results of recent case control study carried out by ICMR on impact of JE vaccine shows an unadjusted protective effect of 62.5% in those with any report of vaccination [65].

CONCLUSIONS

Consensus guidelines on evaluation and management of acute viral encephalitis in Indian children are provided. Early stabilization and institution of non-specific supportive measures is the cornerstone of management. Investigations are aimed at recognition of etiological agent for specific therapeutic and control measures. Reporting and appropriate workup of all cases would strengthen the AES surveillance and go a long way in reducing the morbidity and mortality due to this disorder.

***Annexure* I**

LIST OF PARTICIPANTS (in alphabetical order)

Chairperson: Prof T Jacob John, Vellore; *Co-Chair:* Dr Rohit Agarwal,Mumbai, *President IAP 2012*
Prof S. Aneja, LH Medical College, Delhi (Convener);Dr Milind M Gore, NIV (Gorakhpur unit); Dr S. Gulati, AIIMS, Delhi; Prof Amita Jain, CSSMU, Lucknow; Prof V Kalra, Indraprastha Apollo Hospital, Delhi; Prof R Kumar, CSSMU, Lucknow; Prof KP Kushwaha, BRD Medical College, Gorakhpur; Prof S Mahadevan, JIPMER, Puducherry; Dr D. Mishra, MA Medical College, Delhi (Co-Convener); Dr Veena Mittal, NCDC, Delhi; Dr S. Sharma, LH Medical College, Delhi; Prof P Singhi, PGIMER, Chandigarh; Dr Vipin M Vashistha (Convener, IAPCOI), Bijnor, UP. Prof V Ravi (NIMHANS, Bangalore) and Dr Rakesh Lodha (AIIMS, Delhi) were invited but could not attend.

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Disclaimer: These clinical guidelines have been developed by expert members of the IAP and are intended to provide an overview of currently recommended treatment strategies for suspected viral encephalitis. The usage and application of these clinical guidelines will take place at the sole discretion of treating clinicians, who retain professional responsibility for their actions and treatment decisions.
Contributors: The list of participants in the Expert group meeting is provided in ***Annexure* 1**. All the members of the writing group made equal contribution to the literature search and manuscript preparation. Prof. S. Aneja would be the guarantor for the manuscript.
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