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Acute Encephalitis; A Short Review and Problems in Daily Practice for Clinicians

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Published Date: December 28, 2017

INTRODUCTION

Encephalitis is the presence of an inflammatory process caused by many possible infectious, post-infectious and non-infectious factors in the brain parenchyma associated with clinical evidence of brain dysfunction [1,1-7]. The term encephalitis generally refers to inflammation of the brain parenchyma. Infectious causes, including viruses, bacteria, fungus and parasites represent more than half of the known causes of encephalitis. Differentiation from encephalopathy due to other causes is difficult [2,3,8]. Although not a very common syndrome, encephalitis is of major importance to public health due to its morbidity and mortality. It is one of the most challenging syndromes for clinicians to manage. There are still many data to be clarified regarding to the epidemiology of encephalitis. In various studies, the incidence is estimated at 3.5 to 7.4 per 100,000 inhabitants per year [9-12]. In tropical regions the incidence of encephalitis is 6.3 per 100 000. In the western world, the incidence is between 0.7 to 13.8 per 100 000 [9-11,13]. Encephalitis can affect patients of all ages, but the incidence is higher in pediatric ages. Although both genders may be affected, some studies have found a slight predominance in males. Epidemiological data that can help establish an etiologic diagnosis include geographic position, seasonal distribution, travel history, occupation, contact with animals and insects, vaccination and immune status. Encephalitis can occur everywhere: some etiologic agents have a global distribution (herpes viruses) while others are geographically restricted (arboviruses) [3,14-17]. Epidemiology of

encephalitis is in continuous evolution. In countries where vaccines are widely used for measles, rubella, mumps and varicella infections the it incidence due to this virus has decreased [11-13]. Epidemiological data may indicate the emergence and/or spread of new causative agents, prompted by environmental, social and economic changes. Clinical presentation often includes a prodrome with fever, headache, myalgia, and mild respiratory infection. Changes in level of consciousness with focal neurologic deficits may follow. These may consist on abnormalities that can be categorized into four: cognitive dysfunction (acute memory, speech and disorientation disturbances, etc.), behavioral changes (disorientation, hallucinations, psychosis, personality changes, and agitation), focal neurological abnormalities, and seizures [3]. Seizures, both focal and generalized, are a common manifestation of the encephalitides. Prevention programs (vaccination, vector control) have helped reduce the incidence of certain infectious diseases linked to encephalitis (eg measles). The course of the disease depends on the causative agent, age, severity of the case, and immune status. Mortality rate vary substantly across studies and range from 3-15% [10,11,13,18-20].

CASE DEFINITIONS

The diagnosis of viral encephalitis is suspected in the context of a febrile disease accompanied by headache, altered level of consciousness and symptoms, and signs of cerebral dysfunction. After the diagnosis is suspected, the approach should consist of obtaining a meticulous history and a careful general and neurological examination. The international definition of encephalitis requires the presence of fever and the altered mental status lasting for at least one day [1,2,21,22]. Exclusion of encephalopathy caused by trauma, metabolic disturbance, tumors, alcohol abuse, sepsis and other noninfectious causes.

Table 1: Encephalitis case definition from the international encephalitis consortium.

Major Criteria:
Patients presenting to medical attention with altered mental status - defined as decreased or altered level of consciousness, lethargy or personality change - lasting ≥24h.
Minor Criteria (2 for possible encephalitis; ≥3 for probable or confirmed encephalitis):
1. Documented fever ≥38°C (100.4°F) within the 72 hour before or after presentation.
2. Generalized or partial seizures not fully attributable to a preexisting seizure disorder.
3. New onset of focal neurologic findings.
4. CSF WBC count ≥5/mm^3.
5. Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset.
6. Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.

The degree of altered consciousness is a measure of the severity of acute encephalitis and may range from drowsiness to coma. Seizures, both focal and generalized, are common. Anomia, hallucinations, psychosis, personality changes, and agitation are neuropsychiatric symptoms that often predominate in encephalitis.

CLASSIFICATION

Infections of central nervous system (**CNS**) are notable for their diversity. They range from common to rare, acute to chronic and from benign to fatal. Acute encephalitis may be either diffuse or focal. Arboviruses are often associated with diffuse CNS dysfunction, whereas herpes simplex encephalitis typically results in focal manifestations. Causative agents of encephalitis are infective and non infective agents. Infectious causes, including viruses, bacteria, fungus and parasites [5,7,10,13,21,23-29]. Non infective etiologies of encephalitis are growing last years. Acute disseminated encephalomyelitis (**ADEM**) is a rare, immune-mediated disorder that is triggered by an environmental stimulus in genetically susceptible individuals [30-35]. Anti-N-methyl-D-aspartate receptor encephalitis has been shown to be one of the principal causes of encephalitis in recent large prospective studies. 'Limbic encephalitis' occurring in adults is often associated with malignancy [3,32,36,37]. The encephalitis may occur prior to the diagnosis, or during the course of cancer treatment.

1) Depending on the causative agents encephalitis is classified as:

- Infective encephalitis
- Non infective encephalitis or autoimmune encephalitis
- Posttraumatic encephalitis

2) Depending on the onset of symptoms, encephalitis is classified as:

- Acute encephalitis: Immediate symptoms eg herpetic encephalitis, encephalitis by enteroviruses
- Sub acute encephalitis: Development of symptoms within a few days to a few weeks eg measles
- Chronic encephalitis: Develops in long periods of time eg TB

3) Depending on the anatomic region involved:

- Focal encephalitis: Involving one or several brain lobes eg temporal lobe, parietal, limbic system
- Diffused (generalized) encephalitis: All the brain tissue is involved

4) According to the pathological process:

- Direct: When the infectious agent invades the brain and induces inflammation
- Indirectly: The infectious agent, after treatment, promotes inflammatory reactions mediated by the immune system due to antigen-antibody reactions eg acute disseminated encephalomyelitis

Etiology of Infective Encephalitis

Etiology of encephalitis varies with age, immune status, geography, climate and pathogen endemicity, and has changed over time due to changes in immunization, changing behaviors and discovery of novel etiologies [5,6,10,14,19,28,38,39]. Viruses are the most important causative agent of encephalitis. On the Table 2 are prescribed the most commune viral agents.

Table 2: Causes of acute viral encephalitis.

Herpes viruses (family Herpesviridae)	Herpes simplex virus type 1 Herpes simplex virus type 2 Varicella zoster virus Epstein-Barr virus Cytomegalovirus Human herpesviruses 6 and 7
Enteroviruses (family Picornaviridae)	Enterovirus Poliovirus Coxsackie viruses Echoviruses
Paramyxoviruses (family Paramyxoviridae)	Measles virus Mumps virus
Arthropod-borne and zoonotic viruses Flaviviruses (family Flaviviridae)	West Nile virus Japanese encephalitis virus Tick-borne encephalitis virus Dengue viruses
Alphaviruses (family Togaviridae)	Western, Eastern and Venezuelan equine encephalitis viruses Chikungunya virus
Bunyaviruses	La Crosse virus
Rhabdoviruses	Rabies, virus other lyssaviruses
Coltiviruses	Colorado tick fever virus
Henipaviruses	Nipah virus

a. Viruses are the mainly agents that cause acute encephalitis. See Table 2.

b. Bacterial causative. While many infectious encephalitis cases have viral etiology, bacterial causes are important agents to consider in the diagnosis of encephalitis. Mycobacterium tuberculosis; Leisteria monocitogenes; Haemophilus Influenzae; Borrelia species; Mycoplasma pneumoniae; Rickettsia spp.; Treponema pallidum, Leptospirosis etc.

c. Fungal agents. Usually do not cause encephalitis per se and often manifest as meningitis or assesses. Some patients present with encephalitis-like symptoms. These illnesses are more common in immunocompromised patients, but fungal neurologic infections can be seen in immonocompetent patients. Important fungal causes are: Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, and Blastomyces dermatitis.

d. Parasitic agents. A number of parasites can cause encephalitis. Helminthes including ascaries, hookworth, Angiostrongylus cantonensis, spirometra spp., Alaria spp., and other can cause larva migrans. Other neurotropic helmintes associated with eosinophilic encephalitis include Angiostrongylus species and Gnathostomiasis spinigerum. Malaria; Toxoplasma gondii and free-living ameba are ubiquitus in nature and a few have been associated with human diseases.

e. Unknown etiologies. About 1/3 of the cases do not have an identifiable causative agent.

Pathogenesis of Encephalitis

Encephalitis represents an inflammatory process of the brain parenchyma. It is clinically associated with manifestations of cerebral dysfunction due to infectious (usually viral) and non-infectious (usually autoimmune) factors [2,8,11,12,14,15,20,26,31,35,36]. The features of these processes involving the brain tissue depend on the specific pathogens, immune status of the host, as well as environmental factors. In viral encephalitis, the virus first enters the body and then replicates in local or regional tissues, such as gastrointestinal tract, skin, urogenital, or respiratory system. Subsequent dissemination in the central nervous system occurs through hematogenic routes (enterovirus, arbovirus, HSV, HIV, mumps) or through retrograde transportation via axons, such as in the case of herpes virus, rabies virus, or prion protein [2,3,22,34,39-42]. Infection and inflammation of the cerebral parenchyma depends on the interactions between the neurotropic properties of the virus and the immune response of the host (mediated by humoral antibodies, cytotoxic T cells, cytokines, the innate immunity) [39,42-45]. Autoimmune processes, with antibodies directed against normal brain components (eg, myelin), play a role in acute disseminated encephalomyelitis (**ADEM**) and paraneoplastic syndromes [30,33,34,36,37,46]. The neurotropic virus must first enter the host. The entry takes place through a variety of pathways, depending on the virus, including the respiratory tract (eg, measles, VZV), the gastrointestinal tract (enteroviruses), the genitourinary tract (HIV) cutaneous/subcutaneous tissue (arbovirus), conjunctiva (enterovirus 70), and direct inoculation in the blood (HIV or CMV associated with transfusions). After entering the organism, the precise pathogenetic pathways leading to systemic invasion are still not well known, but we have summarized in the following paragraph [5,6,10,14,19,28,38,39]:

- Adherence to M cells (specialized epithelial cells of the mucosa-associated lymphoid tissues in the intestine), and
- Transport through M cells in lymphoid tissue, from which it spreads via the hematogenous way (through the blood) and through the nerves.

Hematogenous and neurogenesis spread are the primary mechanisms by which neurotropic viruses enter the central nervous system [2,3,22,47-50].

a. The virus may invade CNS in sites where endothelial capillary cells are not joined in tight junctions and the basal membrane is thin - e.g. choroid plexus. Infection of the epithelial cells

of the choroid plexus leads to the entry of the virus into the ventricular CSF and later on into the ependymal cells covering the ventricles and sub-ependymal tissue.

b. The virus can directly infect the endothelial cells of the cerebral capillaries and then spread to the surrounding cerebral tissue

c. The virus can infect and get transported from circulating cells (including monocytes, macrophages, neutrophils, lymphocytes) which then enter the CNS through diapedesis bringing the virus with them.

d. Dissemination through the nerves is another important mechanism by which the virus enters the CNS.

Many neurons within the CNS (including motor spinal cord neurons and olfactory neurons) extend beyond the blood-brain barrier, this way axonal transport within these neurons can bring viruses directly to the CNS [2,47,51,52]. Spreading within the neurons is the primary way of infecting the CNS for the rabies virus and HSV. Rabies virus enters the axon of motoneurons in the neuromuscular junction (where it replicates in the muscle after inoculation) and then is transported in a retrograde way in the CNS [53,54]. Meanwhile, in the case of herpes viruses (**HSV**), there is a latency stage in the dorsal root ganglions [7,12,17,18,39]. Once reactivated, the virus can be transported anterograde to the skin where it manifests clinically with vesicular lesions on the skin, or can be transported retrograde to the CNS and cause encephalitis. Neurotropic viruses entering the host through the gastrointestinal tract (eg poliovirus) may infect the neurons in the myenteric plexus and transport them to the CNS through the vague nerve.

Neurovirulence: Upon reaching the CNS, many neurotropic viruses infect neurons and the result of the infection may be latency (the cell has little or no change in morphology or its function), radical changes in cellular functions, or cell death via apoptosis or necrosis. Cell death through necrosis involves early cessation of the integrity of the cytoplasmic membrane with the subsequent release of intracellular protein and an inflammatory response. Clinical manifestations of neuronal death or dysfunction depend partially on the anatomic localization (cortical infection leading to alteration of the neuro-cognitive functions, coma, and respiratory insufficiency). Rarely, oligodendroglial cells can be infected, as in the JC virus infection, which, when reactivated in immunocompromised individuals, leads to demyelination and Multifocal Progressive Leukoencephalopathy syndrome [2,41,43,51,55].

Immunopathology: As with many viral infections, a significant role in the pathology is played by the host immune response to viral infection. In severe cases of encephalitis, inflammatory reaction is usually apparent in meninges and in a perivascular distribution within the brain. So far we have discussed encephalitis caused from the direct viral invasion of the cerebral parenchyma. However, the brain (as well as the spinal cord and peripheral nerves) may also be affected by post-infectious demyelinating processes that do not necessarily involve direct brain

involvement with the etiologic agent. Acute Disseminated Encephalomyelitis (**ADEM**) is a CNS disease in which demyelination occurs after infection with a virus, and it manifests clinically several days -weeks after systemic signs. Clinical manifestations may be difficult to distinguish from encephalitis caused by direct virus invasion. The pathogenesis of this syndrome is thought to be associated with the induction of an immune response to CNS myelin. Meanwhile, systemic infections associated with measles, varicella and influenza A, have been associated with post-viral Encephalomyelitis [21,30-33,46].

Complications of Encephalitis

The majority of patients who have encephalitis go on to have at least one complication, especially elderly patients, those who had symptoms of coma, and individuals who did not receive treatment at an early stage. Despite use of antiviral drugs, squeals remain high and relapses may occur [62]. Mortality rates in non-herpes viral encephalitis may range from very low (eg, EBV encephalitis) to very high (eg, Eastern equine encephalitis). Established rabies encephalitis is invariably fatal. Mortality rates in untreated HSE are around 70% and fewer than 3% would return to normal function. In a retrospective analysis of patients with a diagnosis of HSE, only 16% of untreated patients had survived [6,11,19,20]. A number of secondary complications may also arise in the course of acute viral encephalitis. These are: raised intracranial pressure; cerebral infarction; cerebral venous thrombosis; syndrome of inappropriate secretion of antidiuretic hormone; aspiration pneumonia; upper gastrointestinal bleeding; urinary tract infections; and disseminated intravascular coagulopathy [64-67]. The late squeals of viral encephalitis largely depend on the age of the patient, etiology of the encephalitis, and the severity of the clinical episode. Epilepsy, persistent anomie, aphasia, motor deficit, and a chronic amnestic state similar to Korsakoff's psychosis have been known among the survivors of severe HSE [11,34,68-70]. Extrapyramidal syndrome (Parkinsonism) as a late sequel of viral encephalitis was first recognized after the epidemic of influenza virus encephalitis that was characterized by a somnolent-ophthalmoplegic syndrome and fatigue (encephalitis lethargica or von Economo's disease). Occasional cases of postencephalitic parkinsonism have been reported after sporadic viral encephalitis, especially after Japanese encephalitis. Nearly a third of all children with Japanese encephalitis will die and up to 75% of the surviving children may be left with major neurological sequelae, including mental retardation, epilepsy, behavioural abnormalities (obsessive-compulsive personality), speech and extrapyramidal (parkinsonian) movement disorders [71,72]. The syndrome of prolonged and persistent fatigue, myalgia, nervousness, concentration impairment, and postexertional malaise is well recognised after viral encephalitis (postviral chronic fatigue syndrome).

Diagnosis of Encephalitis

Preliminary diagnosis is often based on the patient's clinical features, places and dates of travel, activities, and epidemiologic history of the location where infection occurred while diagnosis has been defined on the basis of selected clinical, laboratory, electroencephalographic,

and neuroimaging features (see Table 1) [2,27,34,37,56,57]. Clinicians who identify the classic symptoms in adults: fever, headache, confusion, and occasionally seizures, may order further diagnostic tests. Encephalitis is a neurological emergency. A number of case definitions have been developed, which generally require encephalopathy, as characterized by alteration in consciousness or personality change lasting for a sustained period of time (typically greater than 24 hours) [2,6,7,20,26,37,38,56,58]. Investigations for the diagnosis of encephalitis included blood test (biochemical and hematological), chest radiography, cerebrospinal fluid: cells, biochemistry, and molecular diagnostic tests (polymerase chain reaction), ectroencephalography, computed tomography, magnetic resonance imaging of head (with contrast), single photon emission computed tomography (SPECT, optional, depending on availability), and brain biopsy (in a very few selected cases) [2,20,30,37,58-60]. Relative lymphocytosis in the peripheral blood is common in viral encephalitis. Leukopenia and thrombocytopenia are characteristic of rickettsial infections and viral haemorrhagic fevers. The most sensitive and specific test for cerebral malaria is the peripheral blood film and both thick and thin peripheral smears are necessary. Peripheral blood monocytes may reveal the characteristic cytoplasmic inclusions in patients with human monocytic ehrlichiosis, 10% of whom are known to develop a meningoencephalitic syndrome. Chest x-Ray is also advisable in all patients with acute encephalitis. Characteristic changes on chest radiography may point to the possibility of mycoplasma, legionella, or tuberculous infections. But the most important and usefull examination for the detection of CNS infections is lumbar puncture (**LP**). A LP should be performed if there is no contraindication or following appropriate imaging and/or clinical observation. Central spinal fluid (**CSF**) examination is the easy and the best away to distinguish between viral, bacterial and fungal causes of encephalitis or meningitis. CSF investigations should include: opening pressure; total and differential white cell count, red cell count, microscopy and culture; protein; lactate and glucose, which should be compared with a plasma value; virological investigations; and antibody detection. Laboratory diagnosis of arboviral infections is generally accomplished by testing of serum or CSF to detect virus-specific IgM and neutralizing antibodies. In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry and virus culture of autopsy tissues can also be useful. Cerebrospinal fluid pleocytosis (>5 lymphocytes/mm^3) is present in >95% of cases of acute viral encephalitis. However, encephalitis can occur without significant CSF pleocytosis or demonstrable neuroimaging abnormalities. A high cerebrospinal fluid lymphocytosis might indicate mumps encephalitis, Eastern equine encephalitis, California encephalitis, lymphocytic choriomeningitis virus while atypical lymphocytes in cerebrospinal fluid are occasionally seen in EBV, cytomegalovirus, and rarely in HSV encephalitis. Cerebrospinal fluid polymorphnuclear leucocytosis may be present in primary amoebic encephalitis due to *Naegleria fowlerii*. Diagnosis is helped even in specialized laboratory tests of blood or spinal fluid and occasionally in enterovirus, echovirus 9 and Eastern equine virus encephalitis [1,2,4,6,9,11,12,17,18,20,25,27,33,37,44,45,53-56,58]. Any significant reduction in cerebrospinal fluid glucose (as a ratio of the corresponding plasma glucose) is unusual in viral encephalitis. Low cerebrospinal fluid glucose is also seen in other bacterial,

fungal, parasitic encephalitis, occasionally in mumps and lymphocytic choriomeningitis virus encephalitis, and very rarely in the late stages of HSE [61]. CSF polymerase chain reaction (**PCR**) testing has revolutionised the diagnosis of viral CNS infections. It can be performed for many viruses including herpes viruses, enterovirus, JC virus, mumps etc. Serum antibodies may also be useful in the setting of suspected cases. Sensitivity of cerebrospinal fluid polymerase chain reaction for the detection of cytomegalovirus encephalitis is around 79% with a specificity of 95% (27,44). The tests typically detect antibodies that the immune system makes against the viral infection. Direct and sensitive virological diagnosis in Herpes simplex encephalitis is available, but may be difficult at early stages of the disease. Detection of CSF antibodies to VZV may be a more sensitive approach to diagnosing VZV encephalitis.

A CT scan may be useful in detecting changes in brain structure. CNS imaging (Figure 1) should be performed in all patients. However, an MRI is the best imaging option for encephalitis; it can identify the classic brain changes that suggest encephalitis. MRI should be performed as soon as possible on all patients with suspected encephalitis in whom the diagnosis is uncertain; ideally this should be within 24 hours of hospital admission, but certainly within 48 hours. The role of MR spectroscopy is uncertain; SPECT and PET are not indicated in the acute viral encephalitis.

Electroencephalography (**EEG**) is generally regarded as a nonspecific investigation, although it is still sometimes a useful tool in certain situations. An EEG that monitors the electrical activity of the brain may show sharp waves in one or both of the temporal lobes in patients with encephalitis [2,20,30,31,37,54,58,61]. EEG isn't recommended in every suspected case of acute encephalitis because anly in rare instances does the EEG show specific features that may give clues as to the diagnosis. it may help in distinguishing focal encephalitis from generalized encephalopathy. Often In the latter, EEG shows diffuse, bihemispheric slow wave forms, for example, triphasic slow waves in hepatic encephalopathy. It is almost always abnormal in herpes simplex encephalitis [2,8,34,54].

A brain biopsy is indicated only when CSF serology is negative or equivocal in a suspected case to assess the presence of inclusion bodies, measles virus antigens, or viral RNA. Although pathologic examination and testing of brain tissue is considered to be the "gold standard" diagnostic test for this syndrome, this is rarely done premortem due to potential morbidity associated with an invasive neurosurgical procedure [37].

Management of Encephalitis

Patients with encephalitis are acutely ill and require supportive medical management [56]. In that patient initial assessment must address the basics-airway protection, adequate respiration, and circulation. Supportive treatment consists in the administration of acetaminophen or ibuprofen to control the temperature and headache, fluid administration, corticosteroids to reduce edema and intracranial pressure, and the use of anticonvulsants. Seizures are common in HSV and autoimmune encephalitis so appropriate treatment is necessary. Although increased

intracranial pressure is always a concern in patients with an inflammatory intracranial process, this seems to be a relatively infrequent issue in patients with encephalitis, a fortunate circumstance given the conflicting evidence on use of corticosteroids. For HSV and VZV encephalitis, guidelines regarding acyclovir duration and corticosteroids vary, as does advice regarding antivirals for CMV or HHV-6 encephalitis [3,56-58]. Complications from encephalitis can be serious, that`s why hospitalization is always required. Treatment depends on the age, patient`s condition as well as the cause. Antiviral treatment should be started right away. In the initial stages of the disease, the patient can be hospitalized in the intensive care unit. Vital signs such as respiratory rate and blood pressure should be monitored on a continuous basis. Basic management should include a careful ICP control, avoidance of hypotonic fluids and temperature control. Convulsions should be treated with standard anticonvulsant regimens. In patients with altered mental status and immobilized complications may occur, such as aspiration pneumonia, decubitus, contractures, deep vein thrombosis, intravenous catheter infections. Antibiotics for possible meningitis or sepsis should be administered promptly as per local and national guidelines (ACEM advise within 20 min of presentation) and should not be delayed if LP is contraindicated or neuroimaging delayed [4,17,25,59-64]. Corticosteroid therapy administration is not routinely recommended; however, more prospective, randomized studies are required to confirm benefits [66].

Treatment of Encephalitis

The two most common human herpesviruses identified in the setting of encephalitis are HSV-1 and VZV [2]. With the exception of the herpesviruses, most viral causes have no specific treatment. Patients with 'suspected meningo-encephalitis' should be commenced on acyclovir [1]. Acyclovir has beneficial outcome on HSV treatment and should be empirically started immediately when viral encephalitis is suspected, while awaiting the results of serology. The treatment should be discontinued if encephalitis from HSV is not confirmed but can be continued if the possible cause is VZV or EBV. Acyclovir dose is 10 mg/kg body weight, every 8 hours for 14 days. Consider repeat LP for PCR HSV at planned completion of treatment in immunocompromised patients and children. Neonatal encephalitis from HSV is less sensitive compared to adults, therefore, the dose used should be 20mg / kg per day every 8 hours for 21 days. It is recommended that acyclovir is diluted in 100 ml of physiologic saline administered at a slow rate for 1 hour (not quickly or in a bolus) to minimize the risk of kidney damage [1,3,4,11,12,27,32,40,52,58,66,67]. It should not be administered im or sc.

Table 3: Directed management of viral and immune-mediated encephalitis.

HSV: Minimum 14 days intravenous acyclovir for immunocompetent patients and 21 days for immunocompromised patients (adults and children > 12 years: 10 mg/kg 8 hourly; children: <3 mo 20 mg/kg 8 hourly; 3 mo-12 yo 500 mg/m^2 8 hourly).
VZV: Consider 7-14 days intravenous acyclovir (adults and children > 12 years: 10 to 12.5 mg/kg 8 hourly; children: 500 mg/m^2 8-hourly (approximately 20 mg/kg for child 5 years or less, 15 mg/kg for child 5-12 years)) with or without corticosteroids in consultation with an infectious diseases specialist.
Enterovirus: Intravenous immunoglobulin if hypogammaglobulinaemic. Intravenous Immunoglobulin is used widely in Asia for enterovirus 71.
CMV/HHV6: Reduce immunosuppression and consider ganciclovir and/or foscarnet in consultation with infectious diseases specialist.
Rabies or ABLV: Consider Milwaukee protocol.

Acyclovir alkaline ph can cause phlebitis (9%) and local inflammation. Dosage adjustment should be made in patients with impaired glomerular filtration. CSF penetration is very good. Complications include increased BUN and creatinine (5%), thrombopenia (6%), nausea and vomiting (7%), and neurotoxicity (lethargy, disorientation, confusion, agitation, tremor, and convulsions) (11%). Until now resistance to acyclovir has not been important in immunocompetent patients but some resistant HSV strains have been isolated in immunocompromised patients such as HIV / AIDS.

Oral valacyclovir, the prodrug L-valyl ester of acyclovir, possesses excellent bioavailability and at doses of 1000 mg every 8 hours has demonstrated sustained CSF concentrations above target over a 20-day treatment period [66,68,69]. Ganciclovir and foscarnet have been shown to be effective in treating encephalitis from CMV. Recommended ganciclovir dosing is 5 mg/kg intravenous every 12 hours. The oral prodrug of ganciclovir, valganciclovir, is rapidly converted to ganciclovir and is approximately 60% bioavailable. Foscarnet is a pyrophosphate analogue that acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases as well as HIV reverse transcriptase. They can also be combined together. Cidofovir is another alternative in treatment failure with ganciclovir and foscarnet, although the data for its use in CMV infections are scarce. Ganciclovir triphosphate acts as an inhibitor of CMV DNA (polymerase and incorporation into native viral DNA). With intravenous treatment, the CSF concentrations of ganciclovir reach 25-70% of the plasma concentration. The therapeutic dose is 5 mg/kg every 12 hours for 1 hour with a maintenance dose of 5 mg / every day for an indefinite period until the CMV-DNA in the liquid is decreased. The dose should be adjusted in patients with renal impairment. Thrombopenia and granulocytopenia (20-25%) may require dose reduction or discontinuation of therapy. Gastrointestinal side effects include nausea, vomiting, diarrhea and abdominal pain (20%). Some patients who have been treated with ganciclovir for CMV retinitis have had retinal detachment, but this relationship remains unclear. The usual dose of foscarnet for CMV-related neurological

diseases is 60 mg/kg every 8 hours given iv for 1 hour. Therapy that lasts 14 to 21 days is followed by a 60-120 mg/kg maintenance dose. Therapy may be continued longer in patients who don't have a decrease in CMV DNA in CSF quantitative PRC tests (if available). Approximately one-third of patients have renal impairment during therapy, which may lead to its discontinuation. This manifests with increased creatinine levels and rarely with albuminuria. Some patients have fatigue and nausea. A decrease in calcium, magnesium and phosphorus levels may occur in 15% of patients and may manifest with tetanus, cardiac rhythm disorders or convulsions. Cidofovir is a nucleotide analog that is effective in treating CMV retinitis and more effective than ganciclovir in treating encephalitis from CMV, but its data are limited. Cidofovir acts through inhibition of viral DNA synthesis by incorporation of cidofovir into replicating viral DNA. The dose is 5 mg/kg intravenously 1 time a week for 2 weeks. Then 2 times a week with 2 or more doses depending on the response, the patient should be pre-hydrated (1-2 hours) with physiological saline. Nephrotoxicity is common, the dose should be reduced if it occurs. Ribavirin intravenous 15-25 mg/kg in 2 doses every 8 hours is highly effective in severe California encephalitis (Lacrosse virus). There is no specific antiviral therapy for WNV encephalitis. Brincidofovir (CMX001) is a orally administered lipid conjugate of cidofovir, administered twice weekly for 12 weeks, being developed for the treatment of adenovirus infection in immunocompromised patients. Brincidofovir can be used to treat infants with neonatal HSV involving the CNS and treatment for CMV, adenovirus, and smallpox [66,70]. Contravir is developing FV-100, a once-daily (400 mg) oral therapy for the treatment of VZV. The duration of therapy is 7 days [71]. Globavir is a GBV006 for the treatment of Ebola. It has also shown *in vivo* activity against Dengue virus. Treatment of ZIKV-infected mice with BCX4430 significantly improved outcome even when treatment was initiated during the peak of viremia [72]. Although there are a number of agents available for the acute treatment of CNS viral infections, there are still significant needs for antiviral therapy specifically related to arboviruses for which there is no currently available active antiviral agent.

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