



DISEASEDEX™ Emergency Medicine
Viral Encephalitis Sample Document

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VIRAL ENCEPHALITIS

0.1 CRITICAL FOCUS

A. GENERAL:

1. Initial diagnostic tests should focus on differentiating among acute bacterial infection, herpes simplex virus encephalitis, and other viral infection for patients presenting with suspected acute infectious encephalitis.
2. Careful history of possible exposure to mosquitoes or ticks, travel to areas of arboviral activity, or immunocompromise is valuable in determining potential cause of encephalitis. Clinical findings also are helpful in patients with suspected CNS bacterial or viral infection.
3. Prompt lumbar puncture and examination of cerebrospinal fluid is essential in identifying potentially treatable pathogens.

B. ANTIVIRAL DRUGS:

1. **ACYCLOVIR:** Drug of choice for treatment of laboratory-proven or strongly suspected herpes simplex encephalitis.
 - a. **ADULTS:** 10 mg/kg IV Q8H for 14 to 21 d.
 - b. **CHILDREN:** 20 mg/kg IV Q8H for 14 to 21 d.

C. SUPPORTIVE CARE:

1. **AIRWAY MANAGEMENT:** Endotracheal intubation and mechanical ventilation may be necessary in patients with severe-grade coma secondary to viral encephalitis.
2. **IV FLUIDS:** Indicated for resuscitation and appropriate maintenance of fluid status. Initial deficit replacement for dehydration is 1 to 2 L of NS for adults and 75 mL/kg/24 hours for children.
3. **ANTIPYRETICS:** For temperature >40 C to prevent febrile convulsions or increased intracranial pressure.
 - a. **ACETAMINOPHEN:**
 - (1) **ADULTS:** 650 to 1000 mg PO Q4H PRN; maximum, 4 g/day.
 - (2) **CHILDREN:** 10 to 15 mg/kg PO Q4-6H PRN; maximum, 650 mg/dose.
 - b. **IBUPROFEN:**
 - (1) **ADULTS:** 400 mg PO Q4-6H PRN; maximum 3.2 g/day.
 - (2) **CHILDREN:** 10 mg/kg PO Q6-8H PRN; maximum 40 mg/kg/day.
4. **COOLING MEASURES:** Tepid water sponging or cooling blanket used to reduce fever.
5. **SEDATION: DIAZEPAM:** CHILDREN: 0.1 to 0.3 mg/kg PO Q6-8H; may be given intravenously for patients with severe-grade coma.
6. **ANTICONVULSANTS:** Convulsions occur in over half of patients presenting with Japanese encephalitis (JE). Prophylactic and therapeutic anticonvulsants recommended for patients with JE.
 - a. **DIAZEPAM:**
 - (1) **ADULTS:** 5 to 10 mg IV at a rate not to exceed 5 mg/min, may be repeated every 10 to 15 min up to a maximum dose of 30 mg. May be repeated in 2 to 4 h if needed.
 - (2) **CHILDREN:** 0.2 to 0.5 mg/kg IV at a rate not to exceed 1 mg/min (maximum single dose 5 mg in infant, 10 mg in children).
 - b. **LORAZEPAM:**
 - (1) **ADULTS:** 0.05 to 0.15 mg/kg IV at a rate not to exceed 2 mg/min (maximum single dose, 8 mg).
 - (2) **CHILDREN:** 0.05 to 0.1 mg/kg IV at a rate of 1 to 2 mg/min (maximum single dose, 4 mg).
 - c. **FOSPHENYTOIN: ADULTS:**
 - (1) Loading dose: 15 to 20 mg of phenytoin equivalents (PE)/kg IV at a rate not to exceed 150 mg PE/min.
 - (2) Maintenance dose: 4 to 6 mg PE/kg/day given IV (at a rate not to exceed 150 mg PE/min) or IM as a single daily dose.
 - d. **PHENOBARBITAL:**
 - (1) **ADULTS:** Loading dose: 15 to 20 mg/kg IV at a rate not to exceed 100 mg/min. Maintenance dose: 2 to 3 mg/kg/day IV at a rate not to exceed 100 mg/min in a single daily dose.

- (2) **CHILDREN:** Loading dose: 10 to 20 mg/kg IV at a rate not to exceed 2 mg/kg/min.
Maintenance dose: 3 to 6 mg/kg/day IV at a rate not to exceed 2 mg/kg/min in 3 divided doses.

0.2 CLINICAL PRESENTATION

- A. **DEFINITION:** Acute viral infection of the brain that can range from relatively benign to devastating, fatal disease.
- B. **EPIDEMIOLOGY:**
1. Accounts for nearly 40% of all hospitalizations for encephalitis of known cause. Hospitalizations are highest among children <1 y and adults >65 y.
 2. Human West Nile virus (WNV) infections have occurred in US, Israel, Romania, Russia, and the Caribbean. Japanese encephalitis is the most common cause of viral encephalitis in children in China, Japan, Vietnam, and Australia.
- C. **PREDISPOSING FACTORS:** Travel, insect bites (esp mosquito, tick), outdoor recreational activities, immunodeficiency, organ transplantation, blood transfusions.
- D. **CLINICAL FINDINGS:**
1. **VITAL SIGNS:** Fever.
 2. **DERMATOLOGIC:** Rash.
 3. **HEENT:** Optic neuritis, photophobia.
 4. **NECK:** Nuchal rigidity.
 5. **RESPIRATORY:** Cough.
 6. **GASTROINTESTINAL:** Nausea and vomiting, diarrhea, abdominal pain.
 7. **MUSCULOSKELETAL:** Muscle weakness, muscle pain, joint pain, muscle rigidity, spasticity.
 8. **NEUROLOGIC:** Headache, altered mental status, confusion, absent or decreased tendon reflexes, paralysis, tremor, focal neurologic signs, including seizures, hemiparesis, aphasia.
 9. **PSYCHIATRIC:** Behavioral changes.
- E. **COMPLICATIONS:** Aspiration pneumonia, neurologic impairments (frequent).

0.3 DIAGNOSTICS

- A. **LABORATORY:**
1. **WBC COUNT:** Leukocytosis.
 2. **HEMOGLOBIN:** Anemia.
 3. **ELECTROLYTES:** Hyponatremia.
 4. **MICROBIOLOGY: POLYMERASE CHAIN REACTION ASSAY:** Enables rapid and specific diagnosis of viral encephalitis in children and adults.
 5. **SEROLOGY:** ELISA of cerebrospinal fluid is valuable in diagnosis of WNV encephalitis and Japanese encephalitis.
 6. **CSF EXAMINATION:** Demonstrates increased WBC, increased protein, and normal glucose.
- B. **RADIOLOGY:**
1. **HEAD MRI:** Most sensitive noninvasive test for early diagnosis of HSV encephalitis; superior to CT scan. Valuable in differentiating HSV encephalitis from JE.
 2. **HEAD CT:** May be more specific than MRI in diagnosing HSV encephalitis. Valuable in differentiating HSV encephalitis from JE.
- C. **DIAGNOSTIC AIDS:**
1. **LUMBAR PUNCTURE:** Recommended for all patients with suspected viral encephalitis unless contraindicated due to presence of increased intracranial pressure.
 2. **EEG:** May be useful in diagnosis of viral encephalitis.
 3. **EMG:** May demonstrate reduced motor response, preserved sensory responses, denervation without evidence of myopathy or polyneuropathy, and severely reduced recruitment.

0.4 DIFFERENTIAL DIAGNOSIS

- A. Includes numerous infections, including botulism, cerebral abscess, bacterial meningitis, neurocysticercosis, cerebral malaria, toxoplasmosis, Rocky Mountain spotted fever, ehrlichiosis.
- B. Other diagnoses include postinfectious encephalitis, hypercalcemia, hypomagnesemia, hypoglycemia, Reye's syndrome, CVA, Guillain-Barre syndrome.

1.0 CLINICAL PRESENTATION

1.1 INTRODUCTION

1.1.1 ETIOLOGY

A. **DEFINITION:** Acute viral infection of the brain that can range from relatively benign to devastating, fatal disease.

1.1.2 CLASSIFICATION

A. ENCEPHALITIS, WEST NILE VIRUS

1. INCIDENCE:

- a. Severe neurologic disease (eg, encephalitis or meningitis) reported in 1 in 100 to 150 West Nile virus (WNV) infections (Petersen, 2002a, 2002; Meek, 2002; Mostashari, 2001; Nash, 2001).
- b. A household-based seroepidemiological survey, conducted in New York City area, estimated that 8200 WNV infections occurred there in 1999, with 1700 of these resulting in febrile infections. Less than 1% resulted in serious neurological disease (Mostashari, 2001).
- c. In 2001, a total of 66 human cases of WNV infection were reported (64 cases of CNS infections and 2 cases of uncomplicated WNV fever). From January through November 22, 2002, a total of 3735 human cases of WNV infections have been documented with 215 deaths (CDC, 2002a, 2002b, 2002e).

2. ORGANISM (Petersen, 2002a, 2002, 2001; Meek, 2002):

- a. A single-stranded RNA virus of the family Flaviviridae, genus Flavivirus, first isolated in 1937 in Uganda. WNV is a member of the Japanese encephalitis virus serocomplex that includes other viruses associated with human encephalitis, including Japanese encephalitis, St Louis encephalitis, Murray Valley encephalitis, and Kunjin virus (a subtype of WNV). A close antigenic relationship exists among the flaviviruses and can result in cross reactions during laboratory testing.
- b. Two different lineages have been identified, but only lineage 1 causes human disease. The virus responsible for the New York City outbreak in 1999 was a lineage 1 virus and also caused the outbreak in Israel from 1997 to 2000 (Giladi, 2001).

3. TRANSMISSION: Infected mosquitoes transmit virus to humans; neither person-to-person nor bird-to-person transmission has been reported (Horga, 2001).

- a. **ARTHROPOD VECTOR:** West Nile virus is maintained in an enzootic cycle involving culicine mosquitoes and birds. The most important maintenance vectors of WNV in US are *Culex pipiens*, *Culex restuans*, *Culex salinarius*, and *Culex quinquefasciatus*, although it is unknown which species is most responsible for transmission to humans (Petersen, 2002a, 2002, 2001; Meek, 2002).
- b. **VERTEBRATE RESERVOIR HOSTS:** Wild birds are the principle hosts of WNV; virus has been isolated from terrestrial and wetland bird species. A secondary urban transmission cycle has been described, involving synanthropic or domestic birds and mosquitoes that feed on both birds and humans (Petersen, 2002a, 2002, 2001; Meek, 2002).

4. SEASON: Peak incidence is August; however, onset from July through December has been reported (Petersen, 2002a, 2002, 2001; Weiss, 2001). Data indicate year-round transmission of WNV is occurring in Florida and is possible in other southern states, especially Gulf Coast states (CDC, 2001, 2002d).

5. GEOGRAPHIC DISTRIBUTION: Outbreaks have been reported in Algeria, Morocco, Romania, Tunisia, the Czech Republic, Congo, Italy, Israel, Russia, United States, and France (Petersen, 2002; Meek, 2002).

- a. **ROMANIA:** Between July and October 1996, the first major European West Nile fever epidemic occurred in Romania. Outbreak involved nearly 400 cases and 17 deaths; approximately 90% of patients had acute CNS infections (Tsai, 1998).
- b. **RUSSIA:** An outbreak of WNV infection occurred in southern Russia between July and September 1999 involving approximately 1000 cases and 40 deaths (Platonov, 2001; Lvov, 2000). Mortality was nearly 50% in patients with meningoencephalitis (n=84) (Platonov, 2001).
- c. **ISRAEL:** Between summer and fall 2000, an outbreak of WNV infection occurred in central and northern Israel involving over 400 patients and 33 deaths (Hindiyeh, 2001; Chowders, 2001).
- d. **US:** Widespread WNV activity has occurred in the US since it was first detected in 1999 (Marfin, 2001):

- (1) In 1999, the first cases of WNV infection occurred in New York City. Data from the 1999 West Nile Outbreak Response Working Group identified 59 patients hospitalized with WNV infection between August and September 1999. Overall attack rate of clinical WNV infection was 6.5 cases/million population (Nash, 2001).
- (2) A household-based seroepidemiological survey, conducted in New York City area estimated that 8200 WNV infections occurred there in 1999, with 1700 of these resulting in febrile infections. Less than 1% resulted in serious neurological disease (Mostashari, 2001).
- (3) Since that time, the WNV has been isolated in birds, mosquitoes, horses, and other animals in over 40 states and the District of Columbia. Human cases of WNV infection have been identified in over 30 states and the District of Columbia (CDC, 2002d; Peterson, 2002a; McCarthy, 2002).
- e. **CANADA:** In 2001, WNV was isolated from birds in southwestern Ontario, Canada (CDC, 2002d).
- f. **CARIBBEAN:** Data suggest WNV has spread to the Caribbean region; a case of WNV encephalitis was reported in a resident of the Cayman Islands who had no recent travel history (CDC, 2002d).
6. **INCUBATION PERIOD:** Ranges from 3 to 15 days (Petersen, 2002a, 2002; Horga, 2001; Nash, 2001).
7. **AGE:** According to CDC data from 2002, median age of 52 y reported in patients with WNV infection (CDC, 2002a). Similar mean age (54 y) reported in patients with WNV infection in Israel in 2000 (Weinberger, 2001). In patients with WNV meningoencephalitis, median age was 65 y (CDC, 2002d; Weiss, 2001).
8. **GENDER:** 55% to 60% of patients with WNV infection are men (CDC, 2002a; Nash, 2001). Equal gender distribution reported in patients with WNV infection in Israel in 2000 (Weinberger, 2001).
9. **CLINICAL PRESENTATION:** Headache, fever, altered mental status, myalgias, fatigue, malaise, gastrointestinal symptoms (eg, anorexia, nausea, vomiting), arthralgia, eye pain, rash, and lymphadenopathy (Petersen, 2002a, 2002; Meek, 2002).
10. **OUTCOME:**
 - a. Mortality is 5% to 15%. Advanced age (over 50 y) is significant risk factor for death or significant neurologic disease (CDC, 2002d; Petersen, 2002; Hochberg, 2002; Meek, 2002; Hindiyeh, 2001; Nash, 2001; Weiss, 2001; Weinberger, 2001).
 - b. Substantial morbidity reported following WNV infection; frequent persistent deficits include fatigue, memory loss, difficulty walking, and muscle weakness (Petersen, 2002; Weiss, 2001).

B. ENCEPHALITIS, HERPES SIMPLEX

1. **INCIDENCE:** Most common cause of nonepidemic, acute focal encephalitis in the US; estimated annual frequency is 1/250,000 to 1/500,000 population (Whitley, 2002).
2. **SEASON:** Occurs throughout the year (Whitley, 2002).
3. **AGE:** 30% of patients are under 20 y; 50% are over 50 y (Whitley, 2002).
4. **CLINICAL PRESENTATION:** Headache, fever, altered level of consciousness, focal neurologic findings, including hemiparesis, seizures (Whitley, 2002).
5. **OUTCOME:** Factors influencing outcome include patient age, level of consciousness at presentation, and duration of encephalitis. Despite acyclovir treatment, substantial morbidity and mortality remain at long-term follow-up (Ito, 2000; McGrath, 1997). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: HERPES SIMPLEX)

C. ENCEPHALITIS, JAPANESE

1. **INCIDENCE:** One of the most common causes of acute encephalopathy affecting children and adolescents in the tropics. Approximately 50,000 cases occur annually worldwide (Tiroumourougane, 2002; Whitley, 2002; Solomon, 2000). Has an annual incidence of 10 to 100/100,000 population. Infection is often asymptomatic; symptomatic infection occurs in 1 of 25 to 1000 cases (Tiroumourougane, 2002; Solomon, 2000).
2. **ORGANISM:** Japanese encephalitis (JE) virus is a single positive stranded RNA genome of the family Flaviviridae (Tiroumourougane, 2002; Solomon, 2000).
3. **TRANSMISSION:** Infected mosquitoes transmit virus to humans.
 - a. **ARTHROPOD VECTOR:** JE virus is maintained in an enzootic cycle involving mosquitoes, wild and domestic birds, and pigs. The most important mosquito vector of JE in South East Asia is *Culex tritaeniorhynchus*; in India, *Culex vishnui* is implicated (Tiroumourougane, 2002; Solomon, 2000).

- b. **VERTEBRATE RESERVOIR HOSTS:** Primarily pigs and wading birds. Some data suggest cattle may be involved in natural transmission (Mackenzie, 2002). Humans are considered dead end hosts for JE (Tiroumourougane, 2002; Solomon, 2000).
- 4. **SEASON:** Occurs throughout year in warm southern areas; in northern regions, occurs during summer months (Whitley, 2002; Tiroumourougane, 2002; Solomon, 2000).
- 5. **GEOGRAPHIC DISTRIBUTION:** Has been identified in Cambodia, China, Indonesia, India, Japan, Malaysia, Myanmar, Nepal, Pakistan, Philippines, Republic of Korea, Sri Lanka, Thailand, Vietnam, southeastern Russian federation, and Australia (Mackenzie, 2002; Tiroumourougane, 2002; Solomon, 2000).
- 6. **INCUBATION:** Usually 1 to 6 days, although may occur up to 14 days after exposure (Tiroumourougane, 2002).
- 7. **CLINICAL PRESENTATION:** Manifested by febrile illness associated with altered sensorium, headache, seizures, and meningeal signs primarily affecting children and adolescents (Tiroumourougane, 2002; Whitley, 2002; Solomon, 2000):
 - a. **PRODROMAL STAGE** (1 to 3 days): Includes high grade fever, with or without rigor, headache, diarrhea, general malaise, nausea, and vomiting.
 - b. **ENCEPHALITIS STAGE** (3 to 6 days): Altered mental status, seizures, neck stiffness, muscular rigidity, mask-like facies, and abnormal movements.
 - c. **LATE STAGE:** Eventual recovery or persistent signs of CNS injury, including speech disturbance, motor deficits, intellectual involvement.
- 8. **OUTCOME:**
 - a. Reported mortality is 30%; nearly 50% of survivors have severe neurologic impairment (eg, seizures, motor weakness) (Tiroumourougane, 2002; Whitley, 2002; Solomon, 2000).
 - b. Factors associated with poor prognosis include age <10 y, low Glasgow Coma Scale score, hyponatremia, shock, presence of immune complexes in CSF, presence of antineurofilament protein antibodies, presence of antimyelin basic protein antibodies, coexisting evidence of neurocysticercosis (Tiroumourougane, 2002).
 - c. A retrospective 12-year study found the following factors significantly predictive of death or severe neurologic outcome: depressed level of consciousness, elevated concentration of CSF protein, low levels of serum JE IgM antibody, and serological response consistent with primary flavivirus infection. Patients able to generate an early and vigorous JE-antibody response had improved outcomes (Libraty, 2002).
 - d. Factors associated with good prognosis include high levels of neutralizing antibodies in CSF and high levels of Japanese encephalitis virus IgG in CSF (Tiroumourougane, 2002).

D. ENCEPHALITIS, ST LOUIS

- 1. **INCIDENCE:** From 0 to 2000 cases/yr (Douglas, 2000). Infection is often asymptomatic; symptomatic infection occurs in 1 of 85 to 800 cases and is more frequent in elderly (Douglas, 2000).
- 2. **ORGANISM:** St Louis encephalitis virus is a member of the family Flaviviridae.
- 3. **TRANSMISSION:** Infected mosquitoes transmit virus to humans.
- 4. **SEASON:** Usually July to September; however, may occur later in year in warm areas such as Florida (Douglas, 2000).
- 5. **GEOGRAPHIC DISTRIBUTION:** Central, western, southern US (Whitley, 2002).
- 6. **INCUBATION PERIOD:** 4 to 21 days (Douglas, 2000).
- 7. **AGE:** Frequently occurs among adults over 50 y (Whitley, 2002; Douglas, 2000).
- 8. **CLINICAL PRESENTATION:** Headache, nausea, vomiting, disorientation, stupor, irritability (Whitley, 2002; Douglas, 2000).
- 9. **OUTCOME:** Mortality of 10% to 20% reported; mortality higher in elderly patients (Whitley, 2002; Douglas, 2000).

E. ENCEPHALITIS, EASTERN EQUINE

- 1. **INCIDENCE:** 10 cases/year (Douglas, 2000). Poses threat as agent of bioterrorism; classified as a Category B (second highest priority agents which includes those that are moderately easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance) (CDC Strategic Planning Workgroup, 2000).
- 2. **ORGANISM:** Member of the family Togaviridae, genus alphavirus (Douglas, 2000).
- 3. **TRANSMISSION:** Infected mosquitoes transmit virus to humans (Douglas, 2000).

- a. **ARTHROPOD VECTOR:** Virus circulates between wild birds and *C. melanura* mosquitoes in freshwater swamp habitat. Transmission cycle extends to involve *Aedes* and *Coquillettidia* mosquitoes.
 - b. **VERTEBRATE RESERVOIR HOSTS:** Wild birds and horses.
4. **SEASON:** Late summer, early fall (Douglas, 2000).
 5. **GEOGRAPHIC DISTRIBUTION:** Eastern, Gulf Coast, southern US (Whitley, 2002), Caribbean, South America (Douglas, 2000).
 6. **CLINICAL PRESENTATION:** Abrupt onset and rapidly progressive illness with headache, vomiting, altered consciousness, seizures (Whitley, 2002; Douglas, 2000). In children, facial, periorbital, or generalized edema may be noted (Douglas, 2000).
 7. **OUTCOME:** Mortality of 50% to 70% reported (Douglas, 2000). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BIOTERRORISM)

F. ENCEPHALITIS, WESTERN EQUINE

1. **INCIDENCE:** 0 to 2 cases/year, primarily in infants and children. Symptomatic infection occurs in 1 of 58 to 1000 cases; however, in infants ratio is 1:1 (Douglas, 2000). Poses threat as agent of bioterrorism; classified as a Category B (second highest priority agents which includes those that are moderately easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance) (CDC Strategic Planning Workgroup, 2000).
2. **ORGANISM:** Member of the family *Togaviridae*, genus *alphavirus* (Douglas, 2000).
3. **TRANSMISSION:** Infected mosquitoes transmit virus to humans (Douglas, 2000).
 - a. **ARTHROPOD VECTOR:** Virus circulates between wild birds and *C. tarsalis* mosquitoes (Douglas, 2000).
 - b. **VERTEBRATE RESERVOIR HOSTS:** Wild birds and horses (Douglas, 2000).
4. **SEASON:** Early and midsummer (Douglas, 2000).
5. **GEOGRAPHIC DISTRIBUTION:** West, midwest US (Whitley, 2002), South America (Douglas, 2000).
6. **CLINICAL PRESENTATION:** Headache, altered consciousness, seizures (Whitley, 2002).
7. **OUTCOME:** Mortality of 3% to 5% in infants, lower in older patients (Whitley, 2002); residual damage reported in one third of infants (Douglas, 2000). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BIOTERRORISM)

G. ENCEPHALITIS, CALIFORNIA

1. **INCIDENCE:** Very rare (Eldridge, 2001; Douglas, 2000).
2. **ORGANISM:** California encephalitis virus is a member of the family *Bunyaviridae*, genus *Bunyavirus* (Douglas, 2000).
3. **TRANSMISSION:** Mosquito-borne illness (Douglas, 2000).
4. **SEASON:** July to September (Douglas, 2000).
5. **GEOGRAPHIC DISTRIBUTION:** Originally isolated in the Central Valley of California; also reported in Marin County, California (Eldridge, 2001).
6. **CLINICAL PRESENTATION:** Limited data suggest mild presenting symptoms, including blurred vision, dizziness (Eldridge, 2001).

H. ENCEPHALITIS, LA CROSSE

1. **INCIDENCE:**
 - a. Approximately 10 to 50 cases occur annually (Douglas, 2000). An important arboviral cause of pediatric encephalitis in the US (Roos, 1999).
 - b. A cohort study in eastern Tennessee identified 16 pediatric cases during 2000. Factors significantly associated with La Crosse infection include average number of hours spent outdoors, living within 100 meters of one or more tree holes, and total burden of *Aedes albopictus* mosquitoes around residence (Erwin, 2002).
2. **ORGANISM:** The La Crosse virus belongs to the California group of encephalitis viruses.
3. **TRANSMISSION:** Infected mosquitoes transmit virus to humans.
 - a. **ARTHROPOD VECTOR:** *Aedes triseriatus*, a forest-dwelling mosquito.
 - b. **VERTEBRATE RESERVOIR HOSTS:** Wild rodents (squirrels, chipmunks).
4. **SEASON:** Most cases occur in late summer and early fall (Roos, 1999).
5. **GEOGRAPHIC DISTRIBUTION:** Central, eastern US (Whitley, 2002); China, former USSR, southern Canada (Douglas, 2000).

6. **AGE:** Primarily occurs in children and adolescents (Roos, 1999).
7. **CLINICAL PRESENTATION** (Roos, 1999):
 - a. **PRODROMAL STAGE:** Characterized by fever, chills, headache, nausea, vomiting, and abdominal pain; lasts 1 to 4 days prior to onset of encephalitis symptoms.
 - b. **ENCEPHALITIS STAGE:** Characterized by fever, somnolence, and obtundation; seizures (50%), paralysis, focal neurologic signs (20%) reported (Whitley, 2002). A case of La Crosse viral encephalitis presenting with temporal lobe abnormalities similar to herpes simplex encephalitis has been reported (Sokol, 2001).
8. **OUTCOME:** Mortality of 10% to 15% reported (Whitley, 2002). Up to 15% of survivors experience complications of behavioral abnormalities or recurrent seizures (Roos, 1999).

I. ENCEPHALITIS, NIPAH VIRUS

1. **ORGANISM:** Member of the family Paramyxoviridae, genus Paramyxovirus.
2. **VERTEBRATE RESERVOIR HOSTS:** Appears to be pigs in Malaysia and Singapore (McCormack, 2002).
3. **GEOGRAPHIC DISTRIBUTION:** Malaysia and Singapore. Outbreak involving over 250 pig farmers in northern Malaysia in 1999; an outbreak in Singapore in 1999 involved 11 slaughterhouse workers (McCormack, 2002).
4. **CLINICAL PRESENTATION:** Fever, headache, dizziness, vomiting, altered consciousness, hypertension, tachycardia, absence of reflexes, and hypotonia (Whitley, 2002).
5. **OUTCOME:** Reported mortality is up to 50%; of survivors, 15% have persistent neurologic impairment (Whitley, 2002).

J. ENCEPHALITIS, POWASSAN

1. **INCIDENCE:** Rare, although prevalence may be greater than previously suspected. From 1958 to 1994, 27 cases were reported from US and Canada. During 1999 to 2001, 4 cases were reported in Maine and Vermont due to increased surveillance for West Nile virus infection (CDC, 2001b).
2. **ORGANISM:** Powassan virus, a North American tick-borne flavivirus related to Eastern Hemisphere's tick-borne encephalitis viruses (CDC, 2001b).
3. **TRANSMISSION:** A tick-borne disease.
 - a. **ARTHROPOD VECTOR:** *Ixodes cookei*, *Ixodes marxi*, *Ixodes spinipalpus*, and *Dermacentor andersoni* (CDC, 2001b).
 - b. **VERTEBRATE RESERVOIR HOSTS:** Primarily woodchucks, other small- and medium-sized mammals (eg, skunks, squirrels) (CDC, 2001b).
4. **SEASON:** May to December, peak occurs during June to September (CDC, 2001b).
5. **GEOGRAPHIC DISTRIBUTION:** Northeastern US and Canada (CDC, 2001b).
6. **CLINICAL PRESENTATION:** Febrile illness associated with altered mental status, generalized muscle weakness, diarrhea, anorexia, loss of balance, visual disturbances, dysarthria, headache, somnolence (CDC, 2001b).
7. **OUTCOME:** Powassan encephalitis is associated with significant long-term morbidity. Case-fatality rate is 10% to 15% (CDC, 2001b).

K. ENCEPHALITIS, MURRAY VALLEY

1. **INCIDENCE:** Occurs in small epidemics, although data suggest incidence may be increasing (Brown, 2002; McCormack, 2002).
2. **ORGANISM:** Member of the family Flaviviridae, genus Flavivirus.
3. **TRANSMISSION:** A mosquito-borne disease.
 - a. **ARTHROPOD VECTOR:** *Culex annulirostris* (McCormack, 2002).
4. **SEASON:** February to July, at the end of the monsoon season.
5. **GEOGRAPHIC DISTRIBUTION:** Northern Australia, New Guinea (Beaman, 2002), central Australia (Brown, 2002).
6. **CLINICAL PRESENTATION:** Fever, diarrhea, rash, cough, seizures (especially in children), headache, dysphasia, memory impairment.
7. **OUTCOME:** Mortality of 20% reported; neurologic impairment noted in 50% of survivors (McCormack, 2002).

L. ENCEPHALITIS, INFLUENZA

1. **INCIDENCE:** Rare, although may be a more frequent cause of encephalitis than previously suspected (Straumanis, 2002; McCullers, 1999).

2. **CLINICAL PRESENTATION:** Abrupt onset of fever, sore throat, malaise, myalgia, and nonproductive cough. Neurologic manifestations include lethargy, coma, delirium, psychosis, behavioral disturbances, profound weakness, and oculogyric crisis (Straumanis, 2002; McCullers, 1999).
3. **OUTCOME:** Reported morbidity and mortality are high, although this may reflect the virulence of pandemic strains (McCullers, 1999). (FOR FURTHER INFORMATION: SEE CLINICAL REVIEW, INFLUENZA)

M. ENCEPHALITIS, RABIES

1. **INCIDENCE:** In US, about 35 cases reported from 1980 to 1999, 2/3 of which occurred during the 1990s. Prior to 1990, majority of US cases were imported; however, since then, majority are indigenous cases (most caused by infected bats) (CDC, 1999; Noah, 1998).
2. **CLINICAL PRESENTATION:** Consider rabies in any patient presenting with encephalitis of unknown origin (particularly sign of autonomic disturbance in absence of coma), regardless of whether or not patient reports history of animal bite. Two forms: (1) "furious" rabies (80% to 85% of cases), characterized by hydrophobia, pharyngeal spasms, and hyperactivity leading to paralysis, coma, and death; and (2) less common "paralytic" (dominant symptom) form.
3. **OUTCOME:** Because rabies is so rarely seen, it often is not diagnosed before death (Sang, 1996). Death nearly always follows once a person has become clinically ill with rabies. (FOR FURTHER INFORMATION: SEE CLINICAL REVIEW, RABIES)

1.1.3 EPIDEMIOLOGY

- A. **INCIDENCE:** Accounts for nearly 40% of all hospitalizations for encephalitis of known cause. Based upon data from a 10-year national US study, the most common causes of viral encephalitis are herpesvirus, accounting for 21,000 hospitalizations; varicella, accounting for over 4700 hospitalizations; and arboviruses, accounting for 3200 hospitalizations (Khetsuriani, 2002).
- B. **AGE:** Based upon data from a 10-year national US study, encephalitis-associated hospitalizations are highest in children <1 y and adults >65 y (Khetsuriani, 2002).

1.1.4 PATHOPHYSIOLOGY

A. ARBOVIRUSES:

1. Are transmitted by the bite of arthropod vectors, including mosquitoes and ticks. Includes West Nile virus, La Crosse virus, St Louis encephalitis virus (Redington, 2002).
2. Data from the ArboNET Cooperative Surveillance Group suggest WNV avian data may be a sensitive indicator of the level of activity associated with subsequent human cases. In 2000, all 21 patients had illness onset at least 15 d after WNV-infected birds were first collected in the county of residence (Marfin, 2001).

B. JAPANESE ENCEPHALITIS VIRUS:

1. In human infection, JE virus appears to multiply locally at site of mosquito bite and in regional lymph nodes. Transient viremia develops and subsequent invasion of CNS occurs. Brain invasion is thought to occur via vascular endothelial cells by endocytosis (Tiroumourogane, 2002; Solomon, 2000).
2. Brain appears edematous with involvement primarily of gray matter. Areas most commonly affected include thalamus, substantia nigra, anterior horns of the spinal cord, cerebral cortex, and cerebellum (Tiroumourogane, 2002; Solomon, 2000).

- C. **HERPESVIRUSES:** Herpes simplex virus (HSV) type 1 is the cause in adults and in children beyond the neonatal period; temporal lobe localization is characteristic. HSV type 2 is generally the cause in neonates, and widespread involvement of the brain is present (Schlesinger, 1995).

1.1.5 PREDISPOSING FACTORS

A. TRAVEL

1. Travel to areas where outbreaks of arboviral activity have occurred may provide valuable clues to diagnosis (Whitley, 2002).

B. BITE, INSECT

1. BITE, MOSQUITO

- a. History of mosquito bite may provide valuable clue to diagnosis of arthropod-borne virus encephalitis (Whitley, 2002).

2. BITE, TICK

- a. History of tick bite may provide valuable clue to diagnosis of arthropod-borne virus encephalitis (CDC, 2001b).

C. EXPOSURE, ANIMAL

1. BITE, ANIMAL

- a. History of animal bite may provide valuable clue to diagnosis (Whitley, 2002).

D. RECREATIONAL ACTIVITIES

1. Outdoor activities at dawn and/or dusk increase risk of arthropod-borne virus transmission from mosquitoes. Caving or hiking may be valuable clue to diagnosis (Whitley, 2002). In the 1999 NYC WNV infection outbreak, all patients reported engaging in outdoor activities (eg, gardening) in the evening (Nash, 2001).

E. IMMUNODEFICIENCY

1. **GENERAL:** Reported in 15% of patients in the 1999 NYC WNV infection outbreak. Immunosuppression was due to cancer, HIV infection, alcoholism, and use of prednisone for asthma (Nash, 2001).
2. **HIV INFECTION:** WNV encephalitis has been reported in patients with HIV infection. Whether patients with HIV infection will be more likely to develop clinical encephalitis in association with arbovirus infection is not known. Arbovirus infection should be included in the differential diagnosis of HIV patients presenting with CNS infections (Szilak, 2000).

F. TRANSPLANTATION, ORGAN

1. West Nile virus (WNV) encephalitis has been reported in all 4 recipients of organ transplant from a common donor. Testing of donor serum was positive for WNV. Origin of WNV infection in donor is unclear; may have been due to mosquito bite or blood transfusions since donor received numerous blood transfusions prior to death (CDC, 2002, 2002f).

G. TRANSFUSION, BLOOD

1. Preliminary data suggest West Nile virus (WNV) infection may be transmitted via blood transfusions. Additional investigations are underway (Stephenson, 2002). Several cases of patients who developed WNV meningoencephalitis or meningitis within one month after blood transfusion are highly suggestive of infection via WNV-containing blood (CDC, 2002f, 2002h, 2002j, 2002k).
2. WNV encephalitis has been reported in all 4 recipients of organ transplant from a common donor. Testing of donor serum was positive for WNV. Origin of WNV infection in donor is unclear; may have been due to mosquito bite or blood transfusions since donor received numerous blood transfusions prior to death (CDC, 2002, 2002f).
3. There is apparently some risk of acquiring WNV infection by blood transfusion or organ transplantation; the risk is currently believed to be low. Clinicians and patients should consider the immediate benefits of transfusion or transplantation (CDC, 2002f):
 - a. In emergency situations and other settings where blood transfusion and organ transplants may be lifesaving, the benefits of blood transfusion and organ transplantation outweigh the risk of WNV infection.
 - b. In elective situations, medical decisions about transfusion should take into account the personal preferences and concerns of individual patients and their health care providers. Options may include deferral of elective procedure or, in some instances, use of autologous (self) blood transfusions.

H. BREAST FEEDING

1. Evidence of WNV genetic material in breast milk has been reported in a woman who received blood transfusion and subsequently developed WNV infection. The infant has remained healthy; however, a blood sample from the infant demonstrated IgM antibodies to the WNV, indicating that the infant had been infected with the WNV (CDC, 2002g, 2002i).
2. Because the health benefits of breast feeding are well established and the risk for WNV transmission through breast-feeding is unknown, the CDC does not suggest a change in breast feeding recommendations. Women who are ill or experiencing difficulties, as always, may wish to consult with their physician about breast feeding (CDC, 2002g).

I. INFLUENZA

1. Both acute and postinfectious encephalitis have been described in association with influenza A and B infections. Mechanism not clear, but may be caused by a toxin or result from an immunologic reaction due to a shared antigen (McCullers, 1999).

J. MEASLES

1. Approximately 1 to 2 in 1000 patients with measles develop encephalitis (CDC, 2000a, 1998; Gold, 1996); results in death or permanent neurologic damage in >50% of cases (Gold, 1996).

2. Appears to occur more frequently in immunocompromised patients with measles. In one series, encephalitis developed in 20% of cancer patients and in 1 of 24 HIV-infected patients (Kaplan, 1992).

1.1.6 DIAGNOSTIC CRITERIA

A. ENCEPHALITIS, WEST NILE VIRUS

1. **CONFIRMED CASE:** Febrile illness with neurologic manifestations plus at least one of the following (Petersen, 2002; Meek, 2002):
 - a. Isolation of West Nile virus from tissue, blood, CSF, or other body fluid.
 - b. Demonstration of West Nile viral antigen or genomic sequences in tissue, blood, CSF, or other body fluids.
 - c. Demonstration of West Nile virus IgM antibody in an acute CSF sample using IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA).
 - d. Demonstration of four-fold change in plaque reduction neutralization test (PRNT) antibody titer to West Nile virus in paired, appropriately timed acute (collected 0 to 7 days after onset of illness) and convalescent (collected 14 to 21 days after onset of illness) serum samples.
 - e. Demonstration of both West Nile virus-specific IgM (by MAC-ELISA) and IgG (by IgG ELISA or HI antibody titer; confirm by PRNT) in a single serum sample.
2. **PROBABLE CASE:** Febrile illness with neurologic syndrome plus at least one of the following (Petersen, 2002):
 - a. Demonstration of West Nile virus IgM antibody in acute serum sample using MAC-ELISA.
 - b. Demonstration of elevated titer of West Nile virus-specific IgG (by ELISA) or hemagglutination inhibition (HI) antibody in a convalescent serum sample relative to titer in an acute serum sample (confirm by PRNT).
3. **POSSIBLE CASE:** Febrile illness with neurologic syndrome (ranging from headache to serious neurologic illness, eg, aseptic meningitis, myelitis, encephalitis). Suggested specimens (if indicated) for West Nile virus diagnostic studies are the following (Petersen, 2002):
 - a. Acute serum sample (collected within 7 d of illness onset).
 - b. Acute CSF sample (collected within 7 d of illness onset).
 - c. Convalescent serum sample (collected 14 to 21 d after illness onset)
4. **NON-CASE OF WEST NILE VIRUS ENCEPHALITIS:** A febrile illness with neurologic manifestations ranging from headache to aseptic meningitis or encephalitis that does not meet any of the above laboratory criteria. There should be a negative test result for at least one of the following:
 - a. IgM antibody to West Nile virus by MAC-ELISA in serum or CSF collected 8 to 21 d after onset of illness.
 - b. IgG antibody to West Nile virus by enzyme immunoassay (EIA), HI antibody titer, or PRNT in serum collected 22 days after onset of illness.

B. ENCEPHALITIS, ARBOVIRAL

1. **LABORATORY CRITERIA FOR DIAGNOSIS: NOTE:** It may be epidemiologically important to attempt to pinpoint the infecting virus by conducting cross-neutralization tests using an appropriate battery of closely related virus in areas when 2 or more closely related arboviruses occur or in imported arboviral disease cases (CDC, 2001a):
 - a. Fourfold or greater change in virus-specific serum antibody titer, or
 - b. Isolation of virus from or demonstration of spiral viral antigen or genomic sequences in tissue, blood, CSF, or other body fluid, or
 - c. Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF by antibody-capture enzyme immunoassay (EIA), or
 - d. Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same or a later specimen by another serologic assay (eg, neutralization or hemagglutination).
2. **CONFIRMED CASE:** An encephalitis case that is laboratory confirmed (CDC, 2001a).
3. **PROBABLE CASE:** An encephalitis case occurring during a period when arboviral transmission is likely, and with the following supportive serology (CDC, 2001a):
 - a. A single or stable (less than or equal to twofold change) but elevated titer of virus-specific serum antibodies; or
 - b. Serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen.

1.1.7 TRANSMISSION

- A. **MOSQUITO-BORNE ENCEPHALITIDES:** West Nile, Japanese, St Louis, Eastern Equine, Western Equine, California, La Crosse, Murray Valley.
- B. **TICK-BORNE ENCEPHALITIS:** Powassan.

1.2 ASSOCIATED CONDITIONS

A. MYELITIS

- 1. A case of West Nile virus encephalomyelitis has been reported; patient developed an incomplete flaccid areflexic tetraparesis. Despite multidisciplinary rehabilitation, patient had residual incomplete flaccid upper limb paresis at the time of discharge (Ohry, 2001).

B. HEMORRHAGE, GASTROINTESTINAL

- 1. GI hemorrhage, in the absence of bleeding diathesis, has been reported as an extraneuronal involvement in patients with JE (Tiroumourougane, 2002).

C. PULMONARY EDEMA, NONCARDIOGENIC

- 1. Has been reported as an extraneuronal involvement in patients with JE (Tiroumourougane, 2002).

1.3 VITAL SIGNS

A. TEMPERATURE

1. TEMPERATURE, INCREASED

- a. The triad of fever, altered mental status, and headache is clinical hallmark of viral encephalitis (Whitley, 2002). Fever reported in over 90% of patients presenting with West Nile virus infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001). Reported in 95% to 100% of patients with Japanese encephalitis (Tiroumourougane, 2002).

1.4 PRESENTATION BY BODY SYSTEM

1.4.2 DERMATOLOGIC PRESENTATION

A. RASH

- 1. An erythematous macular, papular, or morbilliform eruption involving neck, trunk, or extremities has been reported in 20% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Chowders, 2001).

1.4.3 HEENT PRESENTATION

A. NEURITIS, OPTIC

- 1. Has been reported in patients presenting with WNV infection (Petersen, 2002; Vaispapur, 2002).

B. PHOTOPHOBIA

- 1. Reported in 30% patients presenting with WNV infection (Weiss, 2001).

1.4.4 NECK PRESENTATION

A. NUCHAL RIGIDITY

- 1. Often present in patients with viral encephalitis. Less severe than in meningitis; may be noted only at extreme neck flexion. Reported in 20% to 55% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001). Neck stiffness reported in 15% to 80% of patients with Japanese encephalitis (Tiroumourougane, 2002).

1.4.5 RESPIRATORY PRESENTATION

A. COUGH

- 1. Reported in 20% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001).

1.4.7 GASTROINTESTINAL PRESENTATION

A. NAUSEA

- 1. Often present in patients with viral encephalitis. Reported in 50% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001).

B. VOMITING

- 1. Often present in patients with viral encephalitis. Reported in 30% to 50% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001).

C. DIARRHEA

- 1. Reported in 25% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001).

D. PAIN, ABDOMINAL

1. Reported in 20% of patients presenting with WNV infection (Weiss, 2001).

1.4.9 MUSCULOSKELETAL PRESENTATION

A. WEAKNESS, MUSCLE

1. Often present in patients with viral encephalitis. Reported in 25% to 50% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001).

B. PAIN, MUSCLE

1. Reported in 15% to 30% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001).

C. PAIN, JOINT

1. Reported in 15% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001).

D. RIGIDITY, MUSCLE

1. Reported in patients with JE during encephalitis stage (Tiroumourougane, 2002).

E. SPASTICITY

1. Hypertonia is commonly reported in patients with JE (Solomon, 2000).

1.4.10 NEUROLOGIC PRESENTATION

A. HEADACHE

1. The triad of headache, altered mental status, and fever is clinical hallmark of viral encephalitis (Whitley, 2002). Reported in 50% to 75% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001). Headache reported in 25% to 100% of patients with Japanese encephalitis (Tiroumourougane, 2002).

B. ALTERED MENTAL STATUS

1. The triad of altered mental status, headache, and fever is clinical hallmark of viral encephalitis. Helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002).
2. Reported in 35% to 50% of patients presenting with WNV infection (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001). Altered sensorium reported in 75% to 100% of patients with Japanese encephalitis (Tiroumourougane, 2002).

C. CONFUSION

1. A common clinical finding helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002). Reported in 35% of patients presenting with West Nile virus infection (Petersen, 2002; Chowders, 2001).

D. NEUROLOGIC SIGNS, FOCAL

1. OVERVIEW

- a. Critical to differentiate between generalized and focal neurologic findings. In nonepidemic setting, most common cause of focal neurologic findings is herpes simplex encephalitis. However, other viruses that normally present with generalized findings may occasionally present with focal findings (Whitley, 2002).

2. HEMIPARESIS

- a. A common clinical finding helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002).
- b. Flaccid paralysis reported in 10% of patients presenting with WNV infection (Petersen, 2002).

3. PARALYSIS

- a. Constellation of findings suggestive of poliomyelitis-like syndrome have been reported in patients with WNV infection, including flaccid paralysis, areflexia, and normal sensation (CDC, 2002c; Leis, 2002; Glass, 2002). Acute flaccid paralysis reported in 10% of patients in NYC in 1999 (Nash, 2001).
- b. Acute, asymmetric, flaccid paralysis also reported in patients with JE (Solomon, 2000).
- c. A case of West Nile virus encephalomyelitis has been reported; patient developed an incomplete flaccid areflexic tetraparesis. Despite multidisciplinary rehabilitation, patient had residual incomplete flaccid upper limb paresis at the time of discharge (Ohry, 2001).

4. DYSARTHRIA

- a. Speech disturbances are a common clinical finding helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002).

E. REFLEXES, TENDON

1. REFLEXES, TENDON, ABSENT

- a. Constellation of findings suggestive of poliomyelitis-like syndrome have been reported in patients with WNV infection, including areflexia and flaccid paralysis with normal sensation (CDC, 2002c; Leis, 2002; Glass, 2002).

2. REFLEXES, TENDON, DECREASED

- a. Reported in 30% of patients with WNV infection (Weiss, 2001).

F. SEIZURES

1. A common clinical finding helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002). Reported in over 85% of children and 10% of adults with JE (Tiroumourougane, 2002; Solomon, 2000). Reported in 15% of patients with WNV infection (Weiss, 2001).

G. TREMOR

1. Commonly reported in patients with JE (Solomon, 2000). Reported in over 10% of patients with WNV infection (Nash, 2001).

H. GLASGOW COMA SCALE

1. OVERVIEW

a. GENERAL:

- (1) Permits descriptive and reproducible assessment of patient's state of consciousness; best scale for predicting outcome and is simplest and least time-consuming system.
- (2) Use of GCS score should replace terms such as lethargy or stupor, which are nonspecific and vary in meaning from one observer to another.

b. INJURY SEVERITY: Rate of change of GCS may be as important as the absolute value.

- (1) **MILD:** GCS between 13 and 15.
- (2) **MODERATE:** GCS between 9 and 12.
- (3) **SEVERE:** GCS between 3 and 8.

c. LIMITATIONS:

- (1) **INTOXICATION:** May not be accurate in presence of alcohol or drugs.
- (2) **MENTAL STATUS EXAMINATION:** GCS score does not provide information regarding mental status. Mental status examination should be performed on all patients with normal GCS scores and should include determination of orientation to time, person, and place and evaluation of short-term memory. Less significant in patients with abnormal GCS scores because they already are in higher risk group for intracranial injury.

2. GLASGOW COMA SCALE, ADULTS

a. BEST MOTOR RESPONSE:

- (1) Obeys = 6
- (2) Localizes pain = 5
- (3) Withdraws = 4
- (4) Flexion to pain = 3
- (5) Extension to pain = 2
- (6) None = 1

b. BEST VERBAL RESPONSE:

- (1) Oriented = 5
- (2) Confused conversation = 4
- (3) Inappropriate words = 3
- (4) Incomprehensible = 2
- (5) None = 1

c. EYE OPENING:

- (1) Spontaneously = 4
- (2) To speech = 3
- (3) To pain = 2
- (4) None = 1

3. GLASGOW COMA SCALE, CHILDREN

a. CHILDREN >1 YEAR:

(1) BEST MOTOR RESPONSE:

- (a) Obey commands = 6
- (b) Localizes pain = 5
- (c) Withdraws to pain = 4
- (d) Abnormal flexion to pain = 3
- (e) Abnormal extension to pain = 2
- (f) None = 1

(2) BEST VERBAL RESPONSE: CHILDREN 2 to 5 YEARS:

- (a) Appropriate words and phrases = 5
- (b) Inappropriate words = 4
- (c) Persistent crying or screaming to pain = 3
- (d) Grunts or moans to pain = 2
- (e) None = 1

(3) BEST VERBAL RESPONSE: CHILDREN OVER 5 YEARS:

- (a) Oriented and converses = 5
- (b) Confused conversation = 4
- (c) Inappropriate words = 3
- (d) Incomprehensible words = 2
- (e) None = 1

(4) EYE OPENING:

- (a) Spontaneous = 4
- (b) To verbal commands = 3
- (c) To pain = 2
- (d) None = 1

b. CHILDREN <1 YEAR:

(1) BEST MOTOR RESPONSE:

- (a) Spontaneous = 6
- (b) Localizes pain = 5
- (c) Withdraws to pain = 4
- (d) Abnormal flexion to pain = 3
- (e) Abnormal extension to pain = 2
- (f) None = 1

(2) BEST VERBAL RESPONSE:

- (a) Babbles, coos appropriately = 5
- (b) Cries but is consolable = 4
- (c) Persistent crying or screaming to pain = 3
- (d) Grunts or moans to pain = 2
- (e) None = 1

(3) EYE OPENING:

- (a) Spontaneous = 4
- (b) To shout = 3
- (c) To pain = 2
- (d) None = 1

1.4.12 INFECTIOUS PRESENTATION

A. LYMPHADENOPATHY

1. Reported in 10% of patients presenting with WNV infection (Petersen, 2002).

1.4.14 PSYCHIATRIC PRESENTATION

A. BEHAVIOR CHANGES

1. A common clinical finding helpful in distinguishing viral encephalitis from viral meningitis (Whitley, 2002). May be the only presenting feature, especially in older children and adults with JE (Solomon, 2000).

1.4.15 MISCELLANEOUS SYMPTOMS

A. FATIGUE

1. Reported in over 60% of patients with WNV infection (Weiss, 2001).

1.5 COMPLICATIONS

A. PNEUMONIA, ASPIRATION

1. Common complication in patients with JE and reduced gag reflex (Solomon, 2000).

B. NEUROLOGIC SEQUELA

1. **WEST NILE VIRUS ENCEPHALITIS:** Frequent neurologic impairments noted following WNV encephalitis, including fatigue, memory loss, difficulty walking, and muscle weakness.
2. **JAPANESE ENCEPHALITIS:** Nearly 50% of survivors of JE have severe neurologic impairment, including seizures and motor weakness.
3. **LA CROSSE ENCEPHALITIS:** Up to 15% of patients experience complications, including behavioral abnormalities or recurrent seizures.

2.0 LABORATORY DATA

2.2 HEMATOLOGIC

A. WHITE BLOOD CELLS

1. WHITE BLOOD CELLS, INCREASED

- a. The majority of patients with JE have a WBC count of greater than 10,000 to 34,000/mm³ (Tiroumourougane, 2002).

2. WHITE BLOOD CELLS, DIFFERENTIAL

- a. Reveals neutrophilia of 50% to 90% in patients with JE (Tiroumourougane, 2002).

B. HEMOGLOBIN

1. HEMOGLOBIN, DECREASED

- a. Reported in 40% of patients with WNV infection. Presence of anemia on admission was an independent predictor of mortality in one study (Chowers, 2001).

2.3 ELECTROLYTES

A. SODIUM

1. SODIUM, DECREASED

- a. Reported in 30% to 40% of patients with WNV infection, especially those with encephalitis (Petersen, 2002; Weiss, 2001; Chowers, 2001).

2.4 CHEMICAL SURVEY

A. LIVER FUNCTION TESTS

1. ASPARTATE AMINOTRANSFERASE

a. ASPARTATE AMINOTRANSFERASE, INCREASED

- (1) Levels over twice upper limit reported in 20% to 25% of patients with WNV infection (Weiss, 2001; Chowers, 2001).

2.7 MICROBIOLOGY

A. POLYMERASE CHAIN REACTION ASSAY

1. **GENERAL:** Enables rapid and specific diagnosis of viral encephalitis in children and adults (Whitley, 2002).
2. **HERPES SIMPLEX ENCEPHALITIS:** Can detect HSV DNA in CSF with accuracy, usually within 24 h to 48 h (Anderson, 1993).
 - a. European Consensus identified CSF PCR as having a 95% sensitivity and 100% specificity (Cinque, 1996). Positive and negative predictive values of 100% and 98%, respectively, have been reported (Troendle-Atkins, 1993). Also appears to be of comparable sensitivity and specificity (100% and 99.6%, respectively) in HIV-coinfected patients and of value for follow-up of antiviral treatment (Cinque, 1998).

- b. There have been some cases of neonatal HSV encephalitis where the PCR is initially negative in setting of abnormal CSF indices and abnormal EEG; these cases uniformly became PCR-positive at a later date, suggesting progression of disease (Kimberlin, 1996).
 - c. An initial negative HSV-1 PCR result early in the course of infection does not rule out the presence of HSV encephalitis. Diagnosis should be based upon clinical findings in combination with neuroimaging and diagnostic testing. A second lumbar puncture and subsequent PCR testing should be considered in patients for whom HSV-1 encephalitis is still suspected (ie, temporal lobe involvement without alternative diagnosis) (Weil, 2002; Dominques, 1998).
3. **WEST NILE VIRUS ENCEPHALITIS:** Reported sensitivity of PCR test of CSF was only 57%; therefore, use is considered experimental and should not replace tests for the detection of virus-specific antibody in CSF and serum, tests which are far more sensitive (CDC, 2001).
 4. **JAPANESE ENCEPHALITIS:** A reverse transcriptase PCR has been used to detect JE virus RNA, but its reliability as a routine diagnostic test has not been demonstrated (Solomon, 2000).
 5. **LA CROSSE VIRUS ENCEPHALITIS:** A La Crosse RNA PCR test for CSF enables rapid diagnosis; helps differentiate between La Crosse virus and HSV encephalitis, especially in patients presenting with temporal lobe abnormalities (Sokol, 2001).
- B. CULTURE, CEREBROSPINAL FLUID**
1. Of limited value in patients with viral encephalitis (Whitley, 2002; Tiroumourougane, 2002; Solomon, 2000).
- C. CULTURE, BLOOD**
1. May demonstrate presence of Japanese encephalitis virus in blood samples during first 6 days of illness (Tiroumourougane, 2002).

2.8 SEROLOGY

A. ENZYME-LINKED IMMUNOSORBENT ASSAY, WEST NILE VIRUS

1. ANTIBODY, WEST NILE VIRUS, IGM

- a. Valuable in diagnosis of patients with West Nile virus infection. May be detected in serum or CSF samples by IgM antibody capture ELISA. Used to confirm case of WNV infection (Petersen, 2002).
- b. Presence of IgM in CSF is useful in detecting central nervous system infection, since IgM antibody does not cross the blood-brain barrier; 95% of patients in New York City outbreaks from 1999 to 2000 had demonstrable IgM antibody (Petersen, 2002).
- c. Because of potential cross-reaction with other flaviviruses, positive IgM antibody tests for West Nile virus may occur in patients who have recently received yellow fever or Japanese encephalitis vaccines or have recently been infected with a related flavivirus (eg, St Louis encephalitis) (Petersen, 2002).
- d. Paired acute-phase (collected 0 to 7 days after onset of illness) and convalescent-phase (collected 14 to 21 days after the acute specimen) serum specimens are useful for demonstration of seroconversion to West Nile and other arboviruses by ELISA or neutralization tests. A fourfold change helps confirm diagnosis of WNV infection (CDC, 2001).
- e. Although tests of a single acute-phase serum specimen can provide evidence of a recent WNV infection, a negative acute-phase specimen is inadequate for ruling out such an infection (CDC, 2001).

2. ANTIBODY, WEST NILE VIRUS, IGG

- a. Demonstration of both West Nile virus-specific IgM (by MAC-ELISA) and IgG (by IgG ELISA or HI antibody titer; confirm by PRNT) in a single serum sample helps confirm diagnosis of WNV infection (Petersen, 2002).

B. ANTIGEN, WEST NILE VIRUS

1. Demonstration of West Nile viral antigen or genomic sequences in tissue, blood, CSF, or other body fluids helps confirm diagnosis of WNV infection (Petersen, 2002).

C. ENZYME-LINKED IMMUNOSORBENT ASSAY, JAPANESE ENCEPHALITIS VIRUS

1. ANTIBODY, JAPANESE ENCEPHALITIS VIRUS, IGM

- a. An ELISA assay that identifies IgM antibodies in CSF from patients with suspected Japanese encephalitis is sensitive and specific; majority of patients have antibodies present at the time of admission; almost all patients have antibodies by 3rd day of illness (Whitley, 2002; Solomon, 2000).

- b. IgM antibody capture ELISA (Mac-ELISA) is test of choice for demonstrating virus-specific antibody in blood or CSF of patients with JE. When serum IgM is used for confirming JE, demonstration of IgG antibodies should be done by another serologic assay (Tiroumourougane, 2002).

D. ANTIGEN, JAPANESE ENCEPHALITIS VIRUS

1. Detection of antigen in CSF using reverse passive hemagglutination, immunofluorescence, and staphylococcal coagglutination tests using polyclonal or monoclonal antibodies is a rapid, effective technique in diagnosing JE (Tiroumourougane, 2002).

2.9 MISCELLANEOUS

A. EXAMINATION, CEREBROSPINAL FLUID

1. WHITE BLOOD CELLS, CEREBROSPINAL FLUID

a. WHITE BLOOD CELLS, CEREBROSPINAL FLUID, INCREASED

- (1) Pleocytosis, predominantly mononuclear cells, is generally found in patients with viral encephalitis (Whitley, 2002). A predominance of lymphocytes is usually seen in patients with West Nile virus infection, (Petersen, 2002; Nash, 2001; Weiss, 2001; Chowders, 2001) and Japanese encephalitis (Solomon, 2000).

2. PROTEIN, CEREBROSPINAL FLUID

a. PROTEIN, CEREBROSPINAL FLUID, INCREASED

- (1) A common finding in patients with viral encephalitis (Petersen, 2002; Whitley, 2002; Tiroumourougane, 2002; Nash, 2001; CDC, 2001b; Weiss, 2001; Chowders, 2001; Solomon, 2000).

3. GLUCOSE, CEREBROSPINAL FLUID

- a. The CSF glucose level is usually normal in patients with viral encephalitis (Petersen, 2002; Weiss, 2001; Chowders, 2001; Solomon, 2000).

3.0 RADIOLOGIC DATA

3.5 CT SCANS

A. COMPUTED TOMOGRAPHY, HEAD

1. HERPES SIMPLEX ENCEPHALITIS:

a. INDICATIONS:

- (1) CT is less sensitive, but more specific, than EEG (Domingues, 1997).
- (2) Diffuse or multifocal abnormalities are more efficiently detected by magnetic resonance imaging (Schlesinger, 1995).

b. FINDINGS:

(1) ADULTS AND OLDER CHILDREN:

- (a) May be abnormal in adults and older children with HSV encephalitis. Temporal lobe findings are common (Cameron, 1992).
- (b) In one study, 80% of CT scans were abnormal, with areas of low density and irregular contrast enhancement in the temporal lobe region, as well as showing intracranial hemorrhage and edema. While 20% of the patients had no CT findings, all of these scans were obtained within the first week of illness. A normal CT in the first 2 weeks of illness does not rule out HSV encephalitis (Marton, 1996).

(2) INFANTS AND YOUNG CHILDREN: CT findings in infants and young children with HSV encephalitis are different from those of older children and adults (Sugimoto, 1985). Diffuse multifocal abnormalities with temporal lobe involvement are characteristic in children beyond the neonatal period (Schlesinger, 1995).

- (a) CT scans are generally an inadequate means of establishing an early diagnosis in infants and young children, but they are potentially effective in anticipating the pathologic change of multicystic degeneration of the brain.
- (b) The appearance of gyriform calcification and multicystic encephalomalacia indicates a severe, wide-spread necrotizing encephalitis, while these CT findings in older children and adults have not been reported.

(3) NEONATES: Early findings of HSV encephalitis include low attenuation in both cerebral hemispheres (Benator, 1985).

2. **WEST NILE VIRUS:** CT of brain shows no evidence of acute disease (Petersen, 2002; Nash, 2001).

3. JAPANESE ENCEPHALITIS:

- a. Valuable in differentiating JE from HSV encephalitis. In JE, the diencephalon and basal ganglion regions are mainly affected, while in HSV encephalitis, the frontotemporal regions are primarily involved (Tiroumourougane, 2002).
- b. May show nonenhancing low density areas in the thalamus, basal ganglia, midbrain, pons, and medulla; however, MRI is more sensitive in demonstrating neural lesions (Tiroumourougane, 2002; Solomon, 2000).

3.7 MAGNETIC RESONANCE IMAGING

A. IMAGING, MAGNETIC RESONANCE, HEAD

1. HERPES SIMPLEX ENCEPHALITIS:

a. INDICATIONS:

- (1) Because of its high sensitivity to inflammatory increased brain water content, MRI is the most sensitive noninvasive test for the early diagnosis of HSV encephalitis.
- (2) Superior to CT in localizing the pathognomonic lesions of the limbic system (Neils, 1987; Bale, 1987; Schroth, 1987) and in detecting diffuse multifocal abnormalities seen with HSV encephalitis (Schlesinger, 1995).
- (3) Valuable in establishing alternative diagnosis in PCR-negative patients (Domingues, 1998).

b. FINDINGS:

- (1) An abnormality on both sides of the sylvian fissure is a useful imaging finding that suggests HSV encephalitis, especially if the abnormality is bilateral (Neils, 1987).
- (2) Detects temporal lobe lesions in almost 90% of HSV PCR-positive patients (Domingues, 1997). Typically, neuroimaging is normal in early hours of the disease process (Cinque, 1996).

2. **WEST NILE VIRUS:** Brain MRI demonstrates enhancement of leptomeninges, periventricular areas, or both, in approximately 30% of cases (Petersen, 2002; Nash, 2001).

3. JAPANESE ENCEPHALITIS:

- a. Valuable in differentiating JE from HSV encephalitis. In JE, the diencephalon and basal ganglion regions are mainly affected, while in HSV encephalitis, the frontotemporal regions are primarily involved (Tiroumourougane, 2002).
- b. Is more sensitive than CT in demonstrating neural lesions. On T2 weighted images, extensive hyperintense lesions of the thalamus, cerebrum, and cerebellum are found (Tiroumourougane, 2002; Solomon, 2000).

4. **NIPAH VIRUS ENCEPHALITIS:** During acute illness, multiple small foci of high-signal intensity are seen within the white matter on T2-weighted images; occasionally, cortical and brain stem lesions or diffusion-weighted images depicting hyperintensities also are detected. At 1-month follow-up, widespread tiny foci of high-signal intensity of T1-weighted images are noted in cerebral cortex. Diffusion-weighted images show decreased prominence or disappearance of lesions over time. At 6-month follow-up, no evidence of progression or relapse noted (Lim, 2002).

5. **POWASSAN ENCEPHALITIS:** Parietal or temporal lobe abnormalities consistent with microvascular ischemia or demyelinating disease (CDC, 2001b).

4.0 DIAGNOSTIC AIDS

4.2 MISCELLANEOUS

A. LUMBAR PUNCTURE

1. **INDICATIONS:** Recommended for all patients with suspected viral encephalitis unless contraindicated due to presence of increased intracranial pressure (Whitley, 2002).
2. **FINDINGS:** Raised opening pressure seen in 50% of patients with JE (Tiroumourougane, 2002; Solomon, 2000).

B. ELECTROENCEPHALOGRAPHY

1. **GENERAL:** May be useful in the diagnosis of viral encephalitis.
2. **HERPES SIMPLEX ENCEPHALITIS:** EEG is extremely sensitive but is not as specific as CT (Cinque, 1996).
 - a. In one study of patients with HSV encephalitis, EEG was normal in only 1/30 patients with 2/3 demonstrating focal changes; none had both a normal EEG and a normal CT (Marton, 1996).
 - b. Abnormal early EEG may be diagnostic of herpes encephalitis (Gasecki, 1991); may help confirm the presence of HSV encephalitis and locate the disease process (Cameron, 1992; Gasecki, 1991).

- c. Characteristic findings in patients with HSV encephalitis include periodic high-voltage spike wave activity emulating from temporal regions and slow-wave complexes at 2- to 3-second intervals (Whitley, 2002).
3. **JAPANESE ENCEPHALITIS:** Nonspecific findings include diffuse theta and delta coma, burst suppression, epileptiform activity, and alpha coma. These generalized findings may be helpful in differentiating JE from HSV encephalitis (Tiroumourougane, 2002; Solomon, 2000).
4. **POWASSAN ENCEPHALITIS:** Diffuse background slowing consistent with encephalitis (CDC, 2001b).

C. ELECTROMYOGRAPHY

1. Constellation of findings suggestive of poliomyelitis-like syndrome have been reported in patients with WNV infection. Findings from electrodiagnostic studies include reduced motor responses, preserved sensory responses, denervation without evidence of myopathy or polyneuropathy, severely reduced recruitment (CDC, 2002c; Glass, 2002; Leis, 2002). Similar abnormalities have been reported in patients with Japanese encephalitis (JE) (Solomon, 2000). This is not a study normally ordered from the emergency department.
2. EMG findings confirm anterior horn cell damage in patients with acute flaccid paralysis associated with WNV infection and JE (Glass, 2002; Solomon, 2000).

D. TOMOGRAPHY, POSITRON EMISSION

1. **JAPANESE ENCEPHALITIS:** In some cases, photon emission tomography demonstrates hyperperfusion of the thalamus and putamen (Tiroumourougane, 2002; Solomon, 2000).

5.0 DIFFERENTIAL DIAGNOSIS

5.3 INFECTIOUS

A. BOTULISM

1. Patients with West Nile virus infection may present with profound muscle weakness progressing to flaccid paralysis suggestive of botulism (CDC, 2001).
2. Patients with botulism present with acute, afebrile symmetric, descending flaccid paralysis that always begins in bulbar musculature; extent and pace of paralysis may vary considerably among patients. Precipitous respiratory failure is most immediate threat to life. Symptoms usually begin 12 to 36 hours after ingestion of toxin; the shorter the interval, the more serious the disease. Patients typically present with difficulty seeing, speaking, and/or swallowing.
3. Presence of pleocytosis, electromyographic and nerve-conduction study demonstrating axonal and demyelinating lesions with axonal changes most prominent are suggestive of West Nile virus infection (Petersen, 2002). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BOTULISM)

B. ABSCESS, CEREBRAL

1. Parameningeal infections present with varying findings, including fever, headache, meningeal signs, papilledema, and focal neurologic deficits, depending upon which entity is involved. Presence of papilledema should arouse the suspicion of an associated pathologic process (brain abscess, subdural empyema, or venous sinus thrombosis).
2. If a brain abscess is suspected, a lumbar puncture should NOT be done unless a mass lesion is ruled out by a CT scan.
3. Diseases in this category have CSF findings characterized by <1000 WBC/mm³ (usually mononuclear cells), a normal glucose level, and a slightly elevated protein level. Unless there is extension into the subarachnoid space or the ventricles, Gram stains and cultures are negative. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BRAIN ABSCESS)

C. MENINGITIS, BACTERIAL

1. Bacterial meningitis tends to have acute, or less commonly, subacute presentation with headache and meningeal signs. Altered consciousness, focal neurologic signs, and seizures are commonly associated with meningitis due to a bacterial agent.
2. The results of the CSF analysis and other tests should provide enough data to separate these entities. Laboratory findings in bacterial meningitis include CSF cell count >1000/mm³ with polys predominating; CSF protein >50 mg/dL but usually >100 mg/dL; CSF glucose usually <40 mg/dL; and positive Gram stain, cultures, CIE, and limulus assays. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: BACTERIAL MENINGITIS)

D. NEUROCYSTICERCOSIS

1. **GENERAL:** Active parenchymal neurocysticercosis (NCC) is most common form (>60% of cases). Most, if not all, patients with symptomatic parenchymal NCC are infected with parasites that have lost their ability to suppress host response and are in process of dying (White, 1997).

2. PRESENTATION:

- a. Vast majority of patients present with seizures; other symptoms include headache and confusion; neurologic examination usually nonfocal.
- b. Cysticercal encephalitis is particularly severe form of parenchymal disease in which there are multiple cysts associated with intense inflammatory reaction. Patients (primarily young girls) present with elevated ICP secondary to diffuse cerebral edema.

3. NEUROIMAGING STUDIES:

- a. Evidence of inflammation (edema, enhancement of either cyst wall or surrounding brain parenchyma, or calcifications from prior acute infection) found in all patients with symptomatic parenchymal NCC. Cysts reach sizes of 1 to 2 cm in diameter.
- b. Edema or enhancement present in 50% to 80% of cases. Cases of symptomatic parenchymal NCC in absence of inflammatory response extremely rare (<1%). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: NEUROCYSTICERCOSIS)

E. MALARIA, CEREBRAL

1. Children with malaria often demonstrate nausea, vomiting, anorexia, headache, malaise, lethargy, and other symptoms, coupled with periodic fevers (without the other features of malarial paroxysms). These symptoms may suggest meningitis or encephalitis.
2. The diagnosis of malaria should be based on history of travel to endemic areas and clinical suspicion, prompting blood studies. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: MALARIA)

F. TOXOPLASMOSIS

1. CNS toxoplasmosis should be considered in HIV-infected persons presenting with neurologic dysfunction, with or without risk factors for AIDS. May present as diffuse encephalopathy, meningoencephalitis, or focal mass lesions; may be initial presentation of AIDS.
2. Most patients present with headache and confusion, and almost 50% have fever; seizures are a presenting symptom in almost one third of patients but rarely are sole symptom.
3. About 70% of patients present with focal neurologic signs, most commonly hemiparesis, ataxia, and cranial nerve palsies
4. Guidelines for presumptive diagnosis CNS toxoplasmosis as indicative of AIDS include the presence of all of the following:
 - a. Recent onset of a focal neurologic abnormality consistent with intracranial disease or a reduced level of consciousness.
 - b. Brain imaging evidence of a lesion having a mass effect (on CT or MRI) or the radiographic appearance of which is enhanced by injection of contrast medium.
 - c. Serum antibody to toxoplasmosis or successful response to therapy for toxoplasmosis; however, absence of antitoxoplasma antibodies on immunofluorescence does not exclude the diagnosis. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: AIDS)

G. ROCKY MOUNTAIN SPOTTED FEVER

1. May present with fever, headache, and progressive maculopapular or petechial rash.
2. History of tick exposure in endemic area suggests the diagnosis; in some cases, lumbar puncture may be necessary to rule out viral encephalitis. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: ROCKY MOUNTAIN SPOTTED FEVER)

H. EHRLICHIOSIS

1. Tick-borne bacterial disease with two distinct forms: human monocytic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*, which infects mononuclear phagocytes in blood and tissues; and human granulocytic ehrlichiosis (HGE), caused by an agent closely related to *E. equi* and *E. phagocytophila*, which infects granulocytes.
2. Characterized by abrupt onset of nonspecific flu-like illness (fever, rigors, headache, myalgia, nausea, and vomiting), often accompanied by nausea, chills, arthralgias, malaise, and rash.
3. Characteristic findings of thrombocytopenia and leukopenia, usually accompanied by elevated hepatic transaminases, suggest diagnosis in febrile patients with history of possible recent tick exposure. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: EHRLICHIOSIS)

I. RABIES

1. Defined as an acute encephalomyelitis that almost always progresses to coma or death within 10 days after the first symptom. Many of the encephalitides (herpes simplex, West Nile, St Louis, and La Crosse viruses) may have symptoms in common with rabies, but hydrophobia will be absent.

2. A history of animal exposure (when present at all) and a rapid progression suggest rabies as a likely etiology. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: RABIES)

J. TUBERCULOSIS, CEREBRAL

1. In adults, the most prominent clinical features of tuberculosis meningitis (TBM) include fever, headache, and vomiting, with a variable degree of mental status abnormalities and meningismus and evidence of hydrocephalus on neuroimaging. Malaise, anorexia, or tiredness also is present in approximately half of patients. Cranial-nerve palsies occur in approximately one fourth of patients. Hemiparesis, papilledema, and seizures occur in 10% to 15% of the patients.
2. In children, fever, meningismus, vomiting, and altered sensorium or behavioral changes are usually present. In contrast with adults, fewer children complain of headache, and hydrocephalus is more frequently present. Occasionally, children present with abdominal pain and constipation.
3. There is convincing evidence that PCR is more sensitive than microscopic examination and cultures of CSF for M tuberculosis. Diagnostic sensitivity of the PCR in CSF has been variable; however, its full use for the diagnosis of TBM is limited by the lack of standardization.
4. Enhancement of the basal cisterns either on contrast CT scan or on postgadolinium MRI is often striking, corresponding to the thick exudate that is observed pathologically; the interpeduncular fossa, the ambient cistern, and the chiasmatic region are particularly involved. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: TUBERCULOSIS)

5.4 INFLAMMATORY

A. ENCEPHALITIS, POSTINFECTIOUS

1. Usually a complication of a viral infection that appears to have an immune mechanism. Demyelination is the predominant pathologic finding. Clinically presents like viral encephalitis, but is distinguished by imaging features and by the fact that a virus cannot be identified in CSF or serum.

B. CEREBRITIS, LUPUS ERYTHEMATOSUS

1. The cerebritis of SLE may be the only manifestation of the disease or may be part of multisystem involvement.
 - a. Patients may present with mild cognitive dysfunction, headaches, depression, anxiety, seizures.
 - b. Less frequently, patients may present with psychosis, acute confusional states, demyelinating disorders, cerebrovascular disease, movement disorders, myelopathy, mononeuropathy or polyneuropathy of cranial or peripheral nerves, acute demyelinating polyneuropathy, optic neuritis.
2. Appropriate laboratory studies, particularly a positive test for ANA, should help make the diagnosis.
3. CSF usually shows <50 WBC/mm³ (predominantly mononuclear), a normal glucose level, and a normal or slightly elevated protein level. Gram stain, cultures, and PCR are negative. MRI with contrast is most sensitive imaging technique for identifying acute and chronic lesions, although changes are often nonspecific.

5.5 METABOLIC

A. HYPERCALCEMIA

1. Nausea, vomiting, and anorexia are common symptoms. Constipation and abdominal pain also may be present. Bone pain and muscle weakness are common. Alterations in mental status ranging from confusion to obtundation and coma common.
2. Serum calcium level is diagnostic. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: HYPERCALCEMIA)

B. HYPOMAGNESEMIA

1. Anorexia, nausea, vomiting, paralytic ileus, esophageal spasm with dysphagia reported. Painful muscle cramps, carpopedal spasm, tetany, athetoid movements, myoclonic jerks, positive Chvostek's or Trousseau's sign may be noted. Seizures, tremor, hyperactive deep tendon reflexes, dysarthria, ataxia, vertigo, nystagmus, focal cerebral deficits also reported.
2. Serum magnesium level is diagnostic. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: HYPOMAGNESEMIA)

C. HYPOGLYCEMIA

1. Mental status abnormalities may range from confusion to coma; tremor, syncope, and seizures also may be observed. Focal (lateralizing) neurologic signs that mimic a stroke may be seen. Anxiety and emotional/behavioral changes may be noted.

2. Diagnosis based on presence of hypoglycemic symptoms, low plasma glucose level, and response to glucose ingestion. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: HYPOGLYCEMIA)

D. REYE'S SYNDROME

1. Onset marked by protracted vomiting and varying degrees of neurologic impairment, including fluctuating personality changes and deterioration in consciousness; extreme irritability, agitation, confusion, delirium, coma may develop as encephalopathy becomes more severe.
2. Acute, noninflammatory encephalopathy documented clinically by alteration in consciousness and, if available, a record of the CSF containing less than or equal to 8 leukocytes/mm³ or a histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation.
3. Hepatopathy documented by either a liver biopsy or a 3-fold or greater increase in the levels of AST or ALT coupled with suggestive prodrome is sensitive indicator of stage I disease. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: REYE'S SYNDROME)

5.6 VASCULAR

A. CEREBROVASCULAR ACCIDENT

1. History should aid in distinguishing a CVA from viral encephalitis, particularly if TIAs have been present. Often present with "hard" neurologic findings which are not considered a part of the spectrum of viral encephalitis. Meningeal signs are not seen unless there is blood in the CSF due to intraventricular rupture of a hematoma.
2. CT scan should identify hemorrhage and infarction. CSF analysis is differentiating. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEWS: THROMBOEMBOLIC STROKE, INTRACEREBRAL HEMORRHAGE)

5.7 NEOPLASTIC

A. PARANEOPLASTIC SYNDROME

1. Most commonly seen with testicular cancer and small cell lung cancer. Defined as neurologic dysfunction caused by cancer but not ascribable to such well-defined secondary effects of cancer as infection, coagulation abnormalities, nutritional and metabolic disorders, or side effects of therapy.
2. Diagnosis of paraneoplastic syndrome should be made only after a thorough evaluation has excluded metastatic or other nonmetastatic causes of neurologic dysfunction.
3. Appropriate imaging studies, CSF examination, and other laboratory tests are valuable in differentiating diagnosis. Detection of serum antibodies against Ma2 may prove valuable in identifying patients with limbic or brain stem encephalitis with underlying testicular cancer.

5.10 MISCELLANEOUS

A. GUILLAIN-BARRE SYNDROME

1. Patients with WNV infection may present with profound muscle weakness or acute flaccid paralysis suggestive of Guillain-Barre syndrome (CDC, 2002c; Glass, 2002; Petersen, 2002; Horga, 2001).
2. Generally, patients with GBS have symmetrical flaccid paralysis with sensory changes or paresthesias vs asymmetric paralysis and normal sensation reported in patients with WNV infection (CDC, 2002c).
3. Patients with GBS have increased protein without pleocytosis in CSF versus presence of pleocytosis in patients with WNV infection.
4. Additional features of typical GBS include an onset several days following signs of acute infection and a generally favorable outcome with rapid improvement in strength (CDC, 2002c).
5. Electromyographic and nerve-conduction studies typically demonstrate a predominantly demyelinating picture or a combined axonal and demyelinating process in patients with GBS (CDC, 2002c; Glass, 2002; Petersen, 2002). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: GUILLAIN-BARRE SYNDROME)

6.0 TREATMENT

6.1 TREATMENT SUMMARY

A. GENERAL:

1. Initial diagnostic tests should focus on differentiating among acute bacterial infection, herpes simplex virus encephalitis, and other viral infection for patients presenting with suspected acute infectious encephalitis.

2. Careful history of possible exposure to mosquitoes or ticks, travel to areas of arboviral activity, or immunocompromise is valuable in determining potential cause of encephalitis. Clinical findings also are helpful in patients with suspected CNS bacterial or viral infection.
3. Prompt lumbar puncture and examination of cerebrospinal fluid is essential in identifying potentially treatable pathogens.

B. ANTIVIRAL DRUGS:

1. **ACYCLOVIR:** Drug of choice for treatment of laboratory-proven or strongly suspected herpes simplex encephalitis.
 - a. **ADULTS:** 10 mg/kg IV Q8H for 14 to 21 d.
 - b. **CHILDREN:** 20 mg/kg IV Q8H for 14 to 21 d.

C. SUPPORTIVE CARE:

1. **AIRWAY MANAGEMENT:** Endotracheal intubation and mechanical ventilation may be necessary in patients with severe-grade coma secondary to viral encephalitis.
2. **IV FLUIDS:** Indicated for resuscitation and appropriate maintenance of fluid status. Initial deficit replacement for dehydration is 1 to 2 L of NS for adults and 75 mL/kg/24 hours for children.
3. **ANTIPYRETICS:** For temperature >40 C to prevent febrile convulsions or increased intracranial pressure.
 - a. **ACETAMINOPHEN:**
 - (1) **ADULTS:** 650 to 1000 mg PO Q4H PRN; maximum, 4 g/day.
 - (2) **CHILDREN:** 10 to 15 mg/kg PO Q4-6H PRN; maximum, 650 mg/dose.
 - b. **IBUPROFEN:**
 - (1) **ADULTS:** 400 mg PO Q4-6H PRN; maximum 3.2 g/day.
 - (2) **CHILDREN:** 10 mg/kg PO Q6-8H PRN; maximum 40 mg/kg/day.
4. **COOLING MEASURES:** Tepid water sponging or cooling blanket used to reduce fever.
5. **SEDATION: DIAZEPAM:** CHILDREN: 0.1 to 0.3 mg/kg PO Q6-8H; may be given intravenously for patients with severe-grade coma.
6. **ANTICONSULSANTS:** Convulsions occur in over half of patients presenting with Japanese encephalitis (JE). Prophylactic and therapeutic anticonvulsants recommended for patients with JE.
 - a. **DIAZEPAM:**
 - (1) **ADULTS:** 5 to 10 mg IV at a rate not to exceed 5 mg/min, may be repeated every 10 to 15 min up to a maximum dose of 30 mg. May be repeated in 2 to 4 h if needed.
 - (2) **CHILDREN:** 0.2 to 0.5 mg/kg IV at a rate not to exceed 1 mg/min (maximum single dose 5 mg in infant, 10 mg in children).
 - b. **LORAZEPAM:**
 - (1) **ADULTS:** 0.05 to 0.15 mg/kg IV at a rate not to exceed 2 mg/min (maximum single dose, 8 mg).
 - (2) **CHILDREN:** 0.05 to 0.1 mg/kg IV at a rate of 1 to 2 mg/min (maximum single dose, 4 mg).
 - c. **FOSPHENYTOIN: ADULTS:**
 - (1) Loading dose: 15 to 20 mg of phenytoin equivalents (PE)/kg IV at a rate not to exceed 150 mg PE/min.
 - (2) Maintenance dose: 4 to 6 mg PE/kg/day given IV (at a rate not to exceed 150 mg PE/min) or IM as a single daily dose.
 - d. **PHENOBARBITAL:**
 - (1) **ADULTS:** Loading dose: 15 to 20 mg/kg IV at a rate not to exceed 100 mg/min. Maintenance dose: 2 to 3 mg/kg/day IV at a rate not to exceed 100 mg/min in a single daily dose.
 - (2) **CHILDREN:** Loading dose: 10 to 20 mg/kg IV at a rate not to exceed 2 mg/kg/min. Maintenance dose: 3 to 6 mg/kg/day IV at a rate not to exceed 2 mg/kg/min in 3 divided doses.

6.2 NON-PHARMACOLOGIC TREATMENT

A. AIRWAY MANAGEMENT

1. INTUBATION, RAPID SEQUENCE

- a. **DEFINITION:** Definitive airway management technique in which a potent sedative or induction agent is administered virtually simultaneously with a paralyzing dose of a neuromuscular blocking agent to facilitate rapid tracheal intubation.

- b. **CAUTION:** Physicians performing rapid sequence intubation must possess training, knowledge, and experience in the techniques and pharmacologic agents used to perform RSI. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: RAPID SEQUENCE INTUBATION)

2. VENTILATION, MECHANICAL

- a. **GENERAL:** Used as a temporizing measure to provide ventilatory support. May be administered invasively (eg, endotracheal tube, tracheostomy) or noninvasively (eg, face or nasal mask). Modalities used may include assist/control, intermittent mandatory, synchronized intermittent mandatory, and pressure support ventilation. Adjuncts include continuous positive airway pressure, positive end expiratory pressure, permissive hypercapnia, and tracheal gas insufflation.
- b. **CAUTION:** Physicians managing mechanically ventilated patients must be experienced and knowledgeable in the monitoring and therapeutic modalities used. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: MECHANICAL VENTILATION)

B. NOTIFICATION, HEALTH DEPARTMENT

- 1. The following arboviral encephalitides are nationally notifiable diseases in the US (CDC, 2001a):
 - a. St Louis encephalitis
 - b. West Nile virus encephalitis
 - c. Powassan encephalitis
 - d. Eastern equine encephalitis
 - e. Western equine encephalitis
 - f. California serogroup viral encephalitis, including infections with the following viruses: La Crosse, Jamestown Canyon, Snowshoe Hare, Trivittatus, Keystone, and California encephalitis viruses.

C. COOLING MEASURES

- 1. Tepid water sponging or cooling blanket should be used to reduce temperature, but must be combined with antipyretic drugs, eg, acetaminophen, to prevent shivering and subsequent increased intracranial pressure (Tiroumourougane, 2002).

D. MONITORING, CENTRAL VENOUS PRESSURE

- 1. Should be used to guide fluid management in children with severe-grade coma (eg, Glasgow Coma Scale score of 8 or less) (Tiroumourougane, 2002).

E. PREVENTION

- 1. **GENERAL:** Risk of acquiring arboviral encephalitides (eg, West Nile virus encephalitis, St Louis encephalitis, Powassan encephalitis, La Crosse, Eastern equine encephalitis, Western equine encephalitis, California viral encephalitis) and Japanese encephalitis can be decreased by avoiding mosquito and tick habitats, wearing light-colored clothing with long sleeves and long pants, using mosquito and tick repellents, and netting.
- 2. **MOSQUITO/TICK REPELLENTS:**
 - a. Formulations containing DEET (N,N-diethyl-3-methylbenzamide) are the most effective and widely used; DEET concentrations range from 10% to 50% (Petersen, 2002; Fradin, 2002). Products should be used according to manufacturer's instructions. Repellents containing no more than 10% DEET are recommended for children; DEET should not be used in infants under 2 months of age (Petersen, 2002).
 - b. DEET repellents provide substantially longer protection compared with non-DEET repellents; repellents containing 23.8% DEET provided complete protection for 300 minutes; other botanical repellents provided protection for <20 minutes (Fradin, 2002).

6.3 PHARMACOLOGIC TREATMENT

A. ANTIVIRALS

1. ACYCLOVIR

- a. **INDICATIONS:** Drug of choice for treatment of laboratory-proven or strongly suspected herpes simplex encephalitis. Should be given as early in course as possible, prior to deterioration in consciousness (Med Lett, 2002).
- b. **RECOMMENDATION:**
 - (1) **ADULTS:** 10 milligrams/kilogram intravenously every eight hours for 14 to 21 days.
 - (2) **CHILDREN:** 20 milligrams/kilogram intravenously every eight hours for 14 to 21 days.
- c. **AVAILABLE FORMS:** Zovirax(R), generics (injection).

- d. **SOLUTION PREPARATION:** Each 10-mL vial contains 500 mg acyclovir; dissolve vial in 10 mL sterile water (final concentration of vial is 50 mg/mL of acyclovir) and shake well; remove calculated dose and add to any appropriate solution at volume selected for each one-hour infusion; infusion concentrations of 7 mg/mL or lower are recommended; may add to dextrose in water and normal saline; use vial (50 mg/mL dilution) within 12 hours; after dilution for administration, each dose should be used within 24 hours.
- e. **DOSING IN SPECIAL SITUATIONS:** Reduce dose in renal impairment. Give standard dose and increase dosage interval to 12 hours if creatinine clearance is between 25 and 50 mL/min and to 24 hours if clearance is between 10 and 25 mL/min; when clearance is less than 10 mL/min, give 50% of standard dose every 24 hours.
- f. **MAJOR ADVERSE REACTIONS:** Phlebitis and inflammation at injection site; nausea/vomiting; diarrhea; nephrotoxicity; itching, hives, or rash; hypotension; hematuria; encephalopathic changes (lethargy, obtundation, confusion, agitation, tremors, hallucinations, seizures, coma). Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, which has resulted in death, has occurred in immunocompromised patients.
- g. **PRECAUTIONS:** For IV infusion only (avoid IM, SC, or IV bolus injections); renal insufficiency (reduce dose); nephrotoxicity is reduced by adequate hydration during treatment, slow IV infusion (at least over 1 hour), and avoidance of nephrotoxic drugs. Use with caution in patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities, or significant hypoxia.
- h. **MONITORING PARAMETERS:** Renal function tests during treatment.

B. ANTIPYRETICS

1. ACETAMINOPHEN

- a. **INDICATIONS:** Temperature >40 C to prevent intracranial hypertension or febrile convulsions. Safer choice in those cases when an antipyretic is needed in children.
- b. **RECOMMENDATION:**
 - (1) **ADULTS:** 650 to 1000 milligrams orally every four hours as needed; maximum 4 grams/day.
 - (2) **CHILDREN:** 10 to 15 milligrams/kilogram orally every four to six hours as needed; maximum, 650 milligrams/dose.
- c. **AVAILABLE FORMS:** Tylenol(R) (tablets, elixir).
- d. **DOSING IN SPECIAL SITUATIONS:** Dose reduction not required in renal failure or geriatric patients.
- e. **MAJOR ADVERSE REACTIONS:** Hepatotoxicity in overdose (adults); thrombocytopenia; hemolytic anemia (rare); adverse reactions during prolonged use.
- f. **PRECAUTIONS:** Use with caution in patients with G-6-PD deficiency.

2. ASPIRIN

- a. **INDICATIONS:** In adults, temperature >40 C to prevent febrile convulsions or cardiac compromise.
- b. **RECOMMENDATION:** ADULTS: 650 to 1000 milligrams orally every four to six hours.
- c. **AVAILABLE FORMS:** Ecotrin(R); Bufferin(R); many generic preparations.
- d. **DOSING IN SPECIAL SITUATIONS:** Dose reductions not required in impaired renal function but may exacerbate uremic symptoms; avoid in severe hepatic insufficiency.
- e. **MAJOR ADVERSE REACTIONS:** Increased bleeding time and potential bleeding episodes; hypersensitivity reaction (urticaria or anaphylaxis); hepatotoxicity with high doses; overdose toxicity (tinnitus); adverse reactions with prolonged use.
- f. **PRECAUTIONS:** Contraindicated in bleeding disorders, in last month of pregnancy, hypersensitivity to aspirin; caution in asthma, nasal polyps, ulcers, and in patients receiving anticoagulants; many drug interactions.

3. IBUPROFEN

- a. **INDICATIONS:** Temperature >40 C to prevent febrile convulsions or cardiac compromise. Safer choice in those cases when an antipyretic is needed in children.
- b. **RECOMMENDATION:**
 - (1) **ADULTS:** 400 milligrams orally every four to six hours as needed; maximum, 3.2 grams/day.
 - (2) **CHILDREN:** 10 milligrams/kilogram orally every six to eight hours as needed; maximum, 40 milligrams/kilogram/day.

- c. **AVAILABLE FORMS:** Motrin(R) (tablets, oral suspension); Nuprin(R) (tablets, caplets); Advil(R) (tablets, oral suspension); Medipren(R) (tablets); generic preparations.
- d. **DOSING IN SPECIAL SITUATIONS:** Increase dosage interval in renal failure.
- e. **MAJOR ADVERSE REACTIONS:** Tinnitus; hearing loss; GI bleeding; cholestatic jaundice; anaphylaxis.
- f. **PRECAUTIONS:** Contraindicated in patients hypersensitive to aspirin or other NSAIDS; caution in active peptic ulcer disease, renal insufficiency, hepatic dysfunction, and patients with compromised cardiac function (edema); potentiates effects of warfarin; concomitant antacid administration may reduce absorption.

C. INTRAVENOUS FLUID

1. **GENERAL:** Intravenous hydration provides a reliable source of fluid intake and should be used in all hospitalized patients for at least 24 to 48 hours to supplement oral fluids and maintain good urine output.
2. **INDICATIONS:**
 - a. **CHILDREN:** Rate of rehydration and type of fluid and electrolytes utilized depend on amount and type of dehydration present (isotonic in most instances). Deficits of water and electrolytes must be calculated and then added to maintenance needs to properly replenish the dehydrated patient.
 - b. **ADULTS:** Fluid resuscitation is directed at restoring depleted extracellular fluid volume and deficits in body electrolytes (eg, sodium, potassium, and chloride). Continuing fluid and electrolyte losses must be replaced and the pathologic states creating the losses corrected. Mild deficits may be corrected orally, but more severe depletion, especially in the presence of an altered mental status, must be corrected with intravenous fluids.
 - c. **CALCULATE DEFICITS:** During initial resuscitation, determine whether dehydration is isotonic (Na = 130-145 mEq), hypotonic (Na <130 mEq), or hypertonic (Na >145 mEq) based on serum sodium content. Calculate deficits of water, sodium, and potassium based upon clinical (orthostatic vital signs, skin turgor, urine output, etc) and laboratory data.
3. **RECOMMENDATION:**
 - a. After stabilization of vital signs and other parameters of severe dehydration, maintenance and deficit fluids can be replaced by a combination of 0.5NS, 0.25NS, and D5W at a rate to maintain normal vital signs and urine output. This assumes that most patients will have isotonic dehydration.
 - b. Maintenance fluids and electrolyte guidelines are as follows:
 - (1) **WATER:**
 - (a) **CHILDREN:** 75 milliliters/kilogram/24 hours with allowances for temperature, hyperventilation, and excess urine output. Central venous pressure monitoring should be used to guide fluid management in children with severe-grade coma (ie, Glasgow coma score less than or equal to 8) (Tiroumourougane, 2002).
 - (b) **ADULTS:** 1 to 2 L NS initially.
 - (2) **ELECTROLYTES: CHILDREN:**
 - (a) Sodium = 3 milliequivalents/kilogram/24 hours.
 - (b) Potassium = 2 milliequivalents/kilogram/24 hours.

D. SEDATIVES/HYPNOTICS

1. DIAZEPAM

- a. **INDICATIONS:** Treatment of patients with Japanese encephalitis and intracranial hypertension; prevents further increases in ICP secondary to pain or arousal (Tiroumourougane, 2002).
- b. **RECOMMENDATION:** CHILDREN: 0.1 to 0.3 milligram/kilogram orally every six to eight hours as needed. May be given intravenously for patients with severe-grade coma (ie, Glasgow coma score less than or equal to 8) (Tiroumourougane, 2002).
- c. **AVAILABLE FORMS:** Valium(R) (syrup, injection).
- d. **DOSING IN SPECIAL SITUATIONS:** Reduce dose in elderly patients and patients with hepatic insufficiency; dose reduction not required in renal failure.
- e. **MAJOR ADVERSE REACTIONS:** Apnea with rapid IV injection (greater than 5 mg/min) especially in patients receiving barbiturates; venous thrombosis and phlebitis at injection site; physical dependence and other adverse reactions with prolonged use.

- f. **PRECAUTIONS:** Contraindicated in acute narrow-angle glaucoma; caution in patients with shock, coma, or alcoholic intoxication with depressed respiratory rate; diazepam potentiates effects of other CNS depressants.
- g. **MONITORING PARAMETERS:** Blood pressure and respirations with IV administration.

E. ANTICEREBRAL EDEMA AGENTS

- 1. **GENERAL:** Aggressive management of secondary complications, including increased intracranial pressure, substantially decreases morbidity and mortality in patients with viral encephalitis. Early identification and management essential (Tiroumourougane, 2002).
- 2. **MODALITIES:** Cerebral edema treatment modalities may include head elevation, osmotic therapy, diuretics, rapid sequence intubation, barbiturates, hyperventilation, mechanical decompression.
- 3. **CAUTION:** Physicians managing cerebral edema must be experienced and knowledgeable in the monitoring techniques and therapeutic modalities used to treat cerebral edema. (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: INCREASED INTRACRANIAL PRESSURE)

F. ANTICONVULSANTS

1. OVERVIEW

- a. **GENERAL:** Seizures are a common clinical finding in patients with viral encephalitis (Whitley, 2002). Reported in over 50% to 90% of patients with Japanese encephalitis (Tiroumourougane, 2002).
- b. **INDICATIONS:** Anticonvulsants should be administered prophylactically and therapeutically in patients with Japanese encephalitis (Tiroumourougane, 2002).
- c. **DRUGS OF CHOICE:** The choice of anticonvulsant is dependent on the type of seizures, the underlying cause, the age of the patient, and previous seizure activity. The general recommendation is use of a benzodiazepine (eg, diazepam or lorazepam) in combination with a long-acting anticonvulsant (eg, phenytoin/fosphenytoin or phenobarbital). (FOR FURTHER INFORMATION, SEE CLINICAL REVIEW: STATUS EPILEPTICUS)

2. DIAZEPAM

- a. **INDICATIONS:** Prophylactic and therapeutic anticonvulsant therapy recommended for patients with Japanese encephalitis (Tiroumourougane, 2002).
 - (1) Both lorazepam and diazepam are effective in terminating status epilepticus; choice depends on physician preference. However, lorazepam may be preferable because it has a longer duration of action on CNS, resulting in more sustained seizure control and possibly a lower incidence of serious adverse effects.
 - (2) Administration of a long-acting anticonvulsant should be initiated with diazepam because of its short duration of anticonvulsant effect.
- b. **RECOMMENDATION:**
 - (1) **ADULTS:** 5 to 10 milligrams intravenously at a rate not to exceed 5 milligrams/minute. Dose may be repeated every 10 to 15 minutes up to a maximum dose of 30 milligrams. Therapy may be repeated in 2 to 4 hours if needed.
 - (2) **CHILDREN:** 0.2 to 0.5 milligram/kilogram intravenously at a rate not to exceed 1 milligram/minute (maximum single dose, 5 milligrams in infants, 10 milligrams in children). Although IV administration is preferred, undiluted diazepam IV solution given per rectum is an alternative when venous access is not possible.
- c. **AVAILABLE FORMS:** Valium(R) (injection).
- d. **DOSING IN SPECIAL SITUATIONS:** Reduce dose in elderly patients and patients with hepatic insufficiency; dose reduction not required in renal failure.
- e. **MAJOR ADVERSE REACTIONS:** Apnea with rapid IV injection (greater than 5 mg/min) especially in patients receiving barbiturates; venous thrombosis and phlebitis at injection site; physical dependence and other adverse reactions with prolonged use.
- f. **PRECAUTIONS:** Contraindicated in acute narrow-angle glaucoma; caution in patients with shock, coma, or alcoholic intoxication with depressed respiratory rate; diazepam potentiates effects of other CNS depressants.
- g. **MONITORING PARAMETERS:** Blood pressure and respirations with IV administration.
- h. **EFFICACY:** Various studies have shown effective termination of seizure activity in 70% to 75% of cases.

3. LORAZEPAM

- a. **INDICATIONS:** Prophylactic and therapeutic anticonvulsant therapy recommended for patients with Japanese encephalitis (Tiroumourougane, 2002).

- (1) Both lorazepam and diazepam are effective in terminating status epilepticus; choice depends on physician preference. However, lorazepam may be preferable because it has a longer duration of action on CNS, resulting in more sustained seizure control and possibly a lower incidence of serious adverse effects.
- (2) Administration of a long-acting anticonvulsant should be initiated with lorazepam because of its short duration of anticonvulsant effect.

b. RECOMMENDATION:

- (1) **ADULTS:** 0.05 to 0.15 milligram/kilogram intravenously at a rate not to exceed 2 milligrams/minute (maximum single dose, 8 milligrams).
- (2) **CHILDREN:** 0.05 to 0.1 milligram/kilogram intravenously at a rate of 1 to 2 milligrams/minute (maximum single dose, 4 milligrams). Rectal administration available when venous access is not possible.

c. AVAILABLE FORMS: Ativan(R) (injection).

d. DOSING IN SPECIAL SITUATIONS: Dose reductions not required in liver or renal disease; reduce dose in elderly patients.

e. MAJOR ADVERSE REACTIONS: Apnea with rapid IV injection (greater than 5 mg/minute), especially in patients receiving barbiturates; venous thrombosis and phlebitis at injection site; physical dependence and other adverse reactions with prolonged use. Because lorazepam has an anti-epileptic duration of action of 4 to 14 hours, late respiratory depression may occur.

f. PRECAUTIONS: Contraindicated in acute narrow-angle glaucoma; caution in patients with shock, coma, or alcoholic intoxication with depressed respiratory rate; lorazepam potentiates effects of other CNS depressants.

g. MONITORING PARAMETERS: Blood pressure and respirations with IV administration.

h. EFFICACY: Various studies have shown effective termination of seizure activity in 75% to 90% of cases.

4. FOSPHENYTOIN

a. INDICATIONS: Prophylactic and therapeutic anticonvulsant therapy recommended for patients with Japanese encephalitis (Tiroumourougane, 2002).

b. RECOMMENDATION: ADULTS: Loading dose: 15 to 20 milligrams of phenytoin equivalents (PE)/kilogram intravenously at a rate not to exceed 150 milligrams PE/minute. Maintenance dose: 4 to 6 milligrams PE/kilogram/day intravenously (at a rate not to exceed 150 milligrams PE/minute) or intramuscularly as a single daily dose.

c. AVAILABLE FORMS: Cerebyx(R) (injection).

d. DOSING IN SPECIAL SITUATIONS: Reduce dose in patients with hepatic or renal impairment, the elderly or those with hypoalbuminemia. The safety of fosphenytoin in pediatric patients has not been established.

e. MAJOR ADVERSE REACTIONS: Hypotension; dizziness; nystagmus; ataxia; drowsiness; vasodilatation; tachycardia; hepatotoxicity; blood dyscrasias; pruritus.

f. PRECAUTIONS: Contraindicated in patients with hypersensitivity to phenytoin, sinus bradycardia, sino-atrial block, second and third degree heart block, and Adams-Stokes syndrome. Caution in patients with hypotension, severe myocardial insufficiency, liver or renal disease, diabetes mellitus, porphyria, hypothyroidism, leukopenia, thrombocytopenia, anemia, or febrile illness.

g. MONITORING PARAMETERS: Cardiac, respiratory, and blood pressure monitoring required during IV administration. Serum concentrations (therapeutic levels 10 to 20 mcg/mL, toxic levels > 20 mcg/mL) should not be drawn until 2 hours following IV administration or 4 hours following IM administration.

h. EFFICACY: Clinical studies evaluating the efficacy of intravenous or intramuscular fosphenytoin for either treatment or prevention of seizures have not been completed. However, fosphenytoin by either route of administration produces reliable and predictable serum levels of phenytoin, which render the agent useful for control of generalized seizures.

5. PHENOBARBITAL

a. INDICATIONS:

- (1) Usually second-line agent for managing or preventing seizures. Has a slow onset of action, with a peak serum concentration 20 to 60 minutes after administration.

Prophylactic and therapeutic anticonvulsant therapy recommended for patients with Japanese encephalitis (Tiroumourouane, 2002).

- (2) Can be used as a first-line medication in children in whom it may become the maintenance drug.
- (3) Also used as a first-line medication in patients allergic to phenytoin/fosphenytoin, with cardiac conduction or automaticity problems, or with history of unresponsiveness to phenytoin/fosphenytoin.

b. RECOMMENDATION:

- (1) **ADULTS:** Loading dose: 15 to 20 milligrams/kilogram intravenously at a rate not to exceed 100 milligrams/minute. Maintenance dose: 2 to 3 milligrams/kilogram/day intravenously at a rate not to exceed 100 milligrams/minute as a single daily dose.
- (2) **CHILDREN:** Loading dose: 10 to 20 milligrams/kilogram intravenously at a rate not to exceed 2 milligrams/kilogram/minute. Maintenance dose: 3 to 6 milligrams/kilogram/day intravenously at a rate not to exceed 2 milligrams/kilogram/minute in three divided doses.

c. AVAILABLE FORMS: Luminal(R) (injection); Eskabarb(R) (injection).

d. DOSING IN SPECIAL SITUATIONS: Increase dosing interval in renal failure; dose reductions required in patients with severe liver disease.

e. MAJOR ADVERSE REACTIONS: Sedation; hypotension and respiratory depression with IV use; severe skin rash; hepatotoxicity; paradoxical restlessness and excitement.

f. PRECAUTIONS: Contraindicated in acute intermittent porphyria; caution in pulmonary insufficiency, hepatic disease, and pregnancy; withdrawal seizures may occur following abrupt termination of high doses; may reduce efficacy of quinidine and warfarin.

g. MONITORING PARAMETERS: Cardiac, respiratory, and blood pressure monitoring required during IV administration. Serum concentrations (therapeutic, 10 to 40 mcg/mL; toxic, above 40 mcg/mL).

h. EFFICACY: Phenobarbital has demonstrated effectiveness in the treatment of status epilepticus; however, it is slower acting than diazepam and lorazepam and causes more sedation than phenytoin/fosphenytoin.

6. PHENYTOIN

a. INDICATIONS: Second-line agent used for maintaining prolonged antiseizure effect after rapid termination of generalized convulsive status seizures with a benzodiazepine or when benzodiazepines fail (Lowenstein, 1998).

b. PHENYTOIN VS FOSPHENYTOIN: Unlike fosphenytoin, phenytoin cannot be combined with glucose-containing IV fluids, requires longer infusion time, and is associated with more infusion site reactions. No differences between the two drugs in frequency or scope of adverse reactions have been demonstrated (Lowenstein, 1998).

c. RECOMMENDATION: ADULTS & CHILDREN: 20 milligrams/kilogram intravenously at rate not to exceed 50 milligrams/minute (1 milligram/kilogram/minute in children); if seizures continue, give additional 5 to 10 milligrams/kilogram (Haafiz, 1999; Lowenstein, 1998).

d. ONSET & DURATION OF ACTION: Onset, 20 min at 40 to 50 mg/min; duration, 1 to 2 d.

e. AVAILABLE FORMS: Dilantin(R) (injection); generic preparations.

f. DOSING IN SPECIAL SITUATIONS: Reduce dose in patients with hepatic impairment, the elderly or those with hypoalbuminemia.

g. MAJOR ADVERSE REACTIONS: Hypotension, ECG abnormalities; dizziness; nystagmus; ataxia; drowsiness; vasodilatation; tachycardia; hepatotoxicity; blood dyscrasias; pruritus.

h. PRECAUTIONS: Contraindicated in patients with hypersensitivity to phenytoin, sinus bradycardia, sino-atrial block, second and third degree heart block, and Adams-Stokes syndrome. Caution in patients with hypotension, liver disease, diabetes mellitus, hypothyroidism, leukopenia, thrombocytopenia, porphyria, or febrile illness.

i. MONITORING PARAMETERS: Cardiac, respiratory, and blood pressure monitoring required during IV administration. Serum concentrations (therapeutic levels 10 to 20 mcg/mL, toxic levels over 20 mcg/mL) should not be drawn until 2 hours following IV administration.

G. STEROIDS

1. A randomized, double-masked study of 65 patients with acute JE found no statistically significant benefit from use of high-dose dexamethasone (Hoke, 1992).

H. IMMUNE GLOBULIN

1. A case report from Israel suggest dramatic improvement of a patient with serious WNV infection following treatment with intravenous immunoglobulin. Further investigation demonstrated high titers (1:1600) of WNV antibodies in pooled immunoglobulin preparations from donors in Israel; in contrast, preparations from US had no detectable WNV antibodies (Shimoni, 2001).

I. INTERFERON ALFA

1. A placebo-controlled, double-blind study is currently underway to investigate effectiveness of recombinant interferon alfa in treatment of persons with JE (Solomon, 2000).
2. A randomized, controlled trial is currently underway to determine whether interferon alfa can lessen symptoms and duration of illness in patients with WNV infections.

J. VACCINES

1. VACCINE, JAPANESE ENCEPHALITIS

- a. **INDICATIONS:** Immunity against Japanese encephalitis virus in the following groups (Tiroumourouane, 2002; CDC, 1993):
 - (1) People living in endemic areas.
 - (2) Travelers spending 30 days or more in an endemic area.
 - (3) Travelers spending less than 30 days during epidemics or extensive outdoor activity in rural areas is expected.
 - (4) Laboratory workers with potential risk of exposure to JE.
- b. **RECOMMENDATION:**
 - (1) **ADULTS AND CHILDREN 4 YEARS AND OLDER:** 1 milliliter subcutaneously; repeat dose on days 7 and 30 (WHO, 1998; CDC, 1993).
 - (2) **CHILDREN 1 to 3 YEARS:** 0.5 milliliter subcutaneously; repeat dose on days 7 and 30 (WHO, 1998; CDC, 1993).
- c. **AVAILABLE FORMS:** JE-VAX(R) (powder for injection).
- d. **MAJOR ADVERSE REACTIONS:** Fever; headache; malaise; rash; injection site pain, redness, or swelling; hypersensitivity reactions, including generalized urticaria and angioedema.
- e. **PRECAUTIONS:** Contraindicated in patients with hypersensitivity Japanese encephalitis virus vaccine product, murine-derived products, or thimerosal.
- f. **EFFICACY:**
 - (1) Immunization with inactivated Japanese encephalitis vaccine failed to induce development of cross-neutralizing antibodies against West Nile virus (Kanasa-Thanan, 2002).
 - (2) A single dose of SA 14-14-2 Japanese encephalitis vaccine was 99% effective, even when administered within days or weeks of exposure, based upon data from a case-control trial in Nepal. Further investigations are being conducted to determine duration of protection from single-dose vaccine (Bista, 2001).

2. VACCINE, WEST NILE VIRUS

- a. An experimental West Nile virus vaccine appears to be effective in protecting animals exposed to the virus. Preliminary animal testing, including mice, hamsters, monkeys, and horses, found all animals developed antibodies following inoculation; when animals were subsequently exposed to the virus, none developed signs of illness or died. Human studies are planned (Monath, 2002).

7.0 DISPOSITION

7.1 ADMISSION CRITERIA

- A. All patients in whom the diagnosis of viral encephalitis is suspected should be admitted for further evaluation and treatment.

7.2 HOME CRITERIA

- A. All U.S. emergency department patients must be screened, stabilized, and discharged in accordance with the EMTALA (COBRA) law.

7.3 CONSULT CRITERIA

A. NEUROLOGY/NEUROSURGERY:

1. May be helpful in cases in which the emergency department physician is concerned about the presence of a mass lesion but is reluctant to do a lumbar puncture on his/her own.

2. Also helpful in those cases in which the emergency department physician is concerned about the appearance of neurologic findings (eg, seizures, cranial nerve palsies), or in cases in which the patient is not responding to treatment as anticipated.

B. **INFECTIOUS DISEASE:** Cases in which the ED physician is uncomfortable about interpreting the results of CSF analysis or Gram stain.

C. **CDC:** Can be consulted for advice on presence of any epidemics of viral encephalitis caused by arboviruses.

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9.0 AUTHOR INFORMATION

A. Written by: DISEASEDEX(TM) Emergency Medicine Editorial Staff, Greenwood Village, CO, 12/2002 (CR2373)