

REVIEW ARTICLE

CURRENT CONCEPTS

Flavivirus Encephalitis

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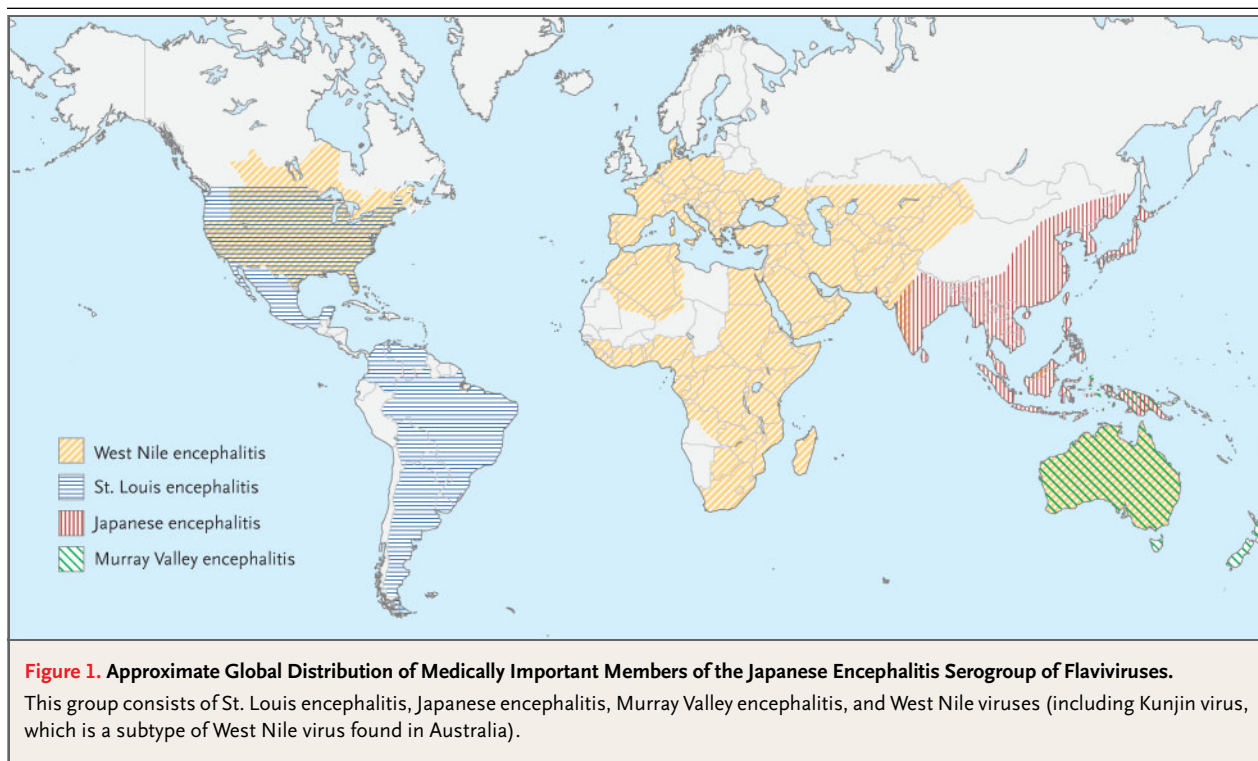
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DURING THE SUMMERS OF 2002 AND 2003, NORTH AMERICA WAS AFFECTED by its largest-ever outbreaks of arboviral encephalitis. West Nile virus caused 2942 cases of meningitis or encephalitis in 2002, with 276 deaths, and 2866 cases in 2003, with 246 deaths.^{1,2} West Nile virus, which in the United States was first detected in New York in 1999, is one of several mosquito-borne neurotropic members of the Japanese encephalitis (JE) serogroup of the genus flavivirus, family Flaviviridae, that cause similar disease patterns across the globe (Fig. 1 and Table 1). These include St. Louis encephalitis virus in the United States, Rocio virus, which has caused encephalitis outbreaks in Brazil, and Murray Valley encephalitis virus in Australia, New Guinea, and New Zealand. Kunjin virus, which also circulates in Australia, recently has been reclassified as a subtype of West Nile virus. In terms of numbers, the most important member of the group is Japanese encephalitis virus, which causes an estimated 30,000 to 50,000 cases of encephalitis and 10,000 deaths in Asia every year.³ In addition to viruses of the JE serogroup, the flavivirus genus includes mosquito-borne causes of hemorrhagic fever (e.g., yellow fever and dengue viruses, which also occasionally cause encephalitis) and tick-borne viruses,⁴ which are not discussed here.

Flaviviruses are small RNA viruses, with an envelope protein that is important for viral attachment and entry into host cells.⁴ The recent outbreaks of West Nile encephalitis have raised questions about the epidemiology, clinical features, and management of the disease^{5,6} — which, to some extent, have already been answered for other members of the serogroup. In this article I will review the similarities and differences between West Nile virus and other flaviviruses of the JE serogroup and consider what we might expect for West Nile virus in terms of epidemiology, pathogenesis, and clinical features, given current knowledge about the other viruses.

ECOLOGY AND EPIDEMIOLOGY

The epidemiology of flavivirus encephalitis is governed by a complex interplay of climatic, entomologic, human behavioral, viral, and host factors that are not completely understood.⁶ Viruses are transmitted naturally among birds in enzootic cycles by bird-biting mosquitoes — especially the culex genus. Humans become infected inadvertently when they encroach on this cycle, but they are considered “dead-end” hosts because normally they do not have sufficiently high or prolonged viremia to transmit the virus further. However, during 2002 it became apparent that West Nile virus can be transmitted among humans through infected transplanted organs and blood products.⁷ In 2003 this finding prompted the screening of blood products, which appears to have been successful in limiting the spread of West Nile virus by this mechanism.⁸ Transplacental transmission occurs with Japanese encephalitis virus⁹ and recently has been described for West Nile virus as well.^{10,11} Ultrasonographic examination of the fetus is now recommended if maternal illness due to West Nile virus occurs during pregnancy.¹²



In Asia, pigs as well as birds are important natural hosts for Japanese encephalitis virus, and because these animals are often kept close to human dwellings, they serve as amplifying or bridging hosts that transmit the virus to humans. In the United States, the death of corvid birds (such as crows and blue jays) may serve as a warning that human disease is imminent.^{13,14}

Japanese encephalitis is mostly a disease of children, whereas in the United States, West Nile encephalitis and St. Louis encephalitis are more likely to affect adults (Fig. 2). This apparent paradox is probably explained, to some extent, by differences in the intensity of transmission and by acquired immunity. In rural Asia, where exposure to infected mosquitoes is unavoidable, serologic surveys show that almost everyone is exposed to Japanese encephalitis virus during childhood. However, fever develops in only a small proportion (about 1 in 300) of those exposed, and neurologic disease develops in even fewer persons.¹⁸ Thus, Japanese encephalitis does not often occur in adults because, in most cases, they are already immune to the virus. Recent work has examined the role of the virus's nonstructural proteins in eliciting this protective immunity.¹⁹ However, when previously unexposed adults be-

come infected — for example, when Japanese encephalitis virus spreads to new areas, or when travelers visit Asia — they, too, are at risk for the disease.³

The epidemiology of Murray Valley encephalitis in Australia and West Nile virus in Africa follows a pattern similar to that of Japanese encephalitis in Asia, despite the fact that far fewer cases of encephalitis occur in these areas. On both continents, disease tends to be seen more commonly in children or in visitors to areas of endemic disease than in resident adults, who have preexisting immunity.²⁰ Whereas the febrile syndrome caused by Murray Valley encephalitis virus is usually not diagnosed, West Nile virus can cause large outbreaks of a characteristic syndrome of fever, arthralgia, and rash known as West Nile fever²¹ — though in recent outbreaks, rash and arthralgia have been less common. However, when West Nile virus has spread to new areas (e.g., to North America or parts of Europe), the infection of large numbers of previously unexposed adults has resulted in large outbreaks of encephalitis (Fig. 2).

St. Louis encephalitis virus is already endemic in the southern United States, but most of the population does not have preexisting immunity because

Table 1. Epidemiologic Features of Flavivirus Encephalitis.*

Feature	Japanese Encephalitis	West Nile Encephalitis	St. Louis Encephalitis	Murray Valley Encephalitis
Geographic area	South Asia, Southeast Asia, China, Pacific Rim, North Australia	Africa, the Middle East, south Asia, Malaysia, Australia, southern Europe, North America	North America, Central America, and South America	Australia, New Guinea
Main vectors	<i>Culex tritaeniorhynchus</i> , <i>C. vishnui</i> , <i>C. gelidus</i> , <i>C. pipiens</i>	<i>C. pipiens</i> , <i>C. restuans</i> , <i>C. quinquefasciatus</i> , <i>C. tarsalis</i>	<i>C. pipiens</i> , <i>C. tarsalis</i> , <i>C. quinquefasciatus</i>	<i>C. annulirostris</i> , <i>C. quinquefasciatus</i> , <i>Aedes normanensis</i>
Main vertebrate hosts	Migrating birds, especially Asiatic cattle egret (<i>Bubulcus ibis coromandus</i>); domestic fowl, pigs	Birds of the family Corvidae (e.g., crows, blue jays) and other passerines (e.g., finches, blackbirds, warblers)	Pigeons, blue jays, sparrows	Birds, especially night heron (<i>Nycticorax caldonicus</i>); possibly feral pigs
Groups at risk	Children in areas of endemic disease and nonimmune adults	Elderly, immunosuppressed, and chronically ill persons	Elderly persons	Children and nonimmune adults
Approximate incidence	30,000–50,000 cases annually in Asia	Sporadic cases in Africa, larger outbreaks (300–3000) in the Middle East and North America	35 cases (median) annually with occasional outbreaks of up to 2800	40 cases in 25 years
Ratio of symptomatic to asymptomatic infections	1 in 25 (nonimmune adults) to 1 in 250–1000 (children)	1 in 5 (presenting with fever); 1 in 140–320 (presenting with central nervous system disease)	1 in 250	1 in 700 to 1 in 1200
Patients presenting with encephalitis (%)	60–75	58–62	58–85	50
Patients presenting with meningitis (%)	5–10	15–40	5–40	50
Case fatality rate (%)	20–30	4–16	3–30	15–30
Presence of neuropsychiatric sequelae at hospital discharge (%)	50–60	50–65	30–50	50

* Clinical data presented here for different viruses may not be directly comparable because of differences in study methods.

the rates of transmission of the virus to humans have been relatively low. When environmental conditions have favored substantial viral amplification in the bird–mosquito–bird cycle, however, large numbers of cases have occurred; for example, there were approximately 2000 cases of St. Louis encephalitis in 1975.²² It is unclear whether the epidemiology of West Nile encephalitis in North America will follow that of St. Louis encephalitis or will be more like that of Japanese encephalitis in Asia, with thousands of cases every year, though the large number of North American cases of West Nile disease two years in succession seems ominous.

PATHOGENESIS

The factors that govern which persons will become ill with neurologic disease, and how severely, are not completely understood. The host immune re-

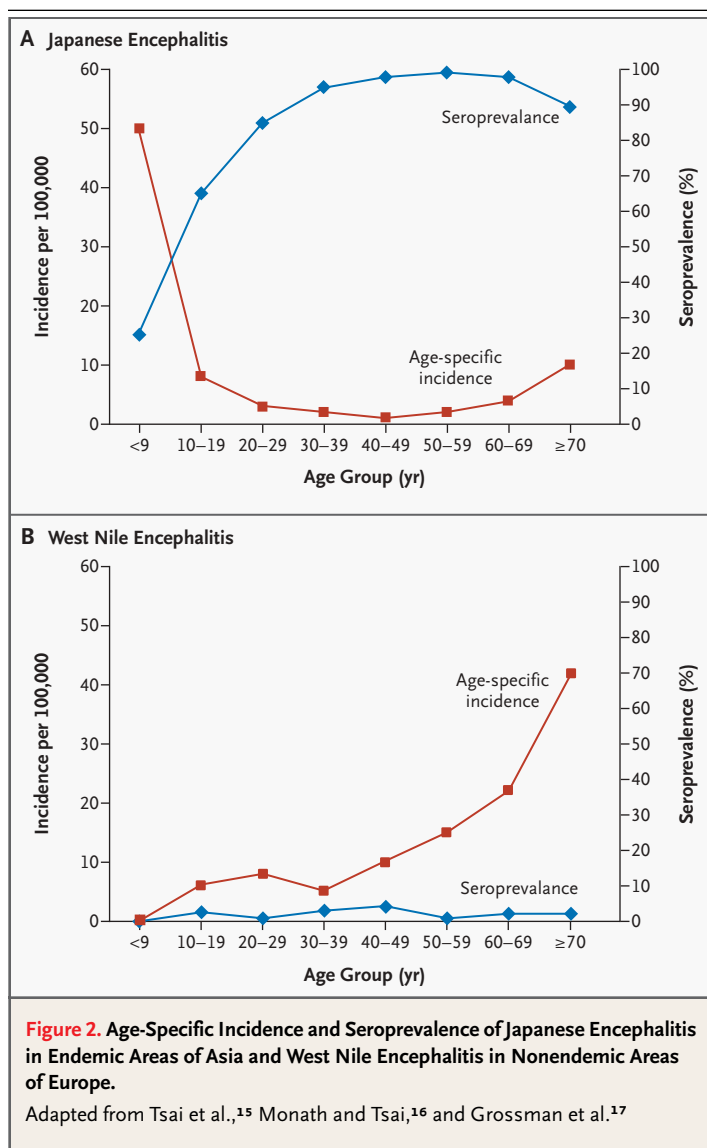
sponse is important to control replication of the virus in the skin, lymph nodes, and blood before the virus enters the brain. Thus, it has been shown that for Japanese encephalitis virus, the failure of the host to produce antibodies to the virus is associated with an increased likelihood that the virus will be isolated and with an increased risk of death.²³ For West Nile virus, chronic illness and immunosuppression also appear to be risk factors for severe disease and death^{7,14,24–27}; in an animal model, production of antibody is known to be important.^{28,29} In mice, the production of interferon is protective,³⁰ and a host gene for susceptibility to infection with flavivirus has recently been identified.^{31,32} Advanced age is associated with a greater severity of disease in West Nile encephalitis, St. Louis encephalitis, and Japanese encephalitis (for which there is a second peak of incidence in the elderly).^{24,33} The reason for the more severe illness in older persons

is not known, but impaired integrity of the blood–brain barrier due to cerebrovascular disease has been postulated. Disruption of the blood–brain barrier is also thought to explain why cysticercosis is a risk factor for Japanese encephalitis.³⁴

When a person has been exposed to one flavivirus, cross-reacting antibodies may affect the outcome of infection with a second flavivirus. Thus, for patients with Japanese encephalitis, prior infection with dengue virus, which circulates through much of Asia, appears to protect against severe disease.³⁵ Prior exposure to dengue may also explain why, during the 1962 epidemic of St. Louis encephalitis in Florida, longtime inhabitants of the area were mostly spared.³⁶ In contrast, serial infection with different serotypes of dengue virus appears to be associated with more severe disease (e.g., dengue hemorrhagic fever), possibly because of an antibody-dependent enhancement of infection,³⁷ though the strain of dengue virus may also be important.³⁸ These questions of reduced or increased severity in secondary flavivirus infections may be important in the parts of the United States and Central America where West Nile virus may circulate with St. Louis encephalitis or dengue virus. Determinants of the virulence of a virus may also be important. For both Japanese encephalitis and West Nile viruses, certain lineages or genotypes of virus appear to be associated with large encephalitis outbreaks, which suggests that these genotypes may have greater virulence.^{39,40} However, a recent detailed molecular analysis of the distribution of genotypes of Japanese encephalitis virus suggests that such interpretations may be overly simplistic.⁴¹ Nevertheless, in rodent models of infection with a flavivirus, the ability to enter the nervous system may be affected by a small number of changes in the amino acids in critical regions of the virus's envelope protein.^{42,43} Whether such subtle changes could be responsible for altered virulence in birds, and thus could explain the rapid spread of West Nile virus across North America, is under investigation.

CLINICAL FEATURES

Neurologic disease typically develops in patients after an incubation period of 5 to 15 days (though this period can be as brief as 2 to 3 days) and a short, nonspecific febrile prodrome. The neurologic manifestations depend on which part of the nervous system is infected — the meninges (to



cause meningitis), the parenchyma of the brain (encephalitis), or the spinal cord (myelitis).⁴⁴ Aseptic meningitis is less common than encephalitis (Table 1). The more important presentations (which often overlap) include a reduced level of consciousness, which may be associated with seizures, a flaccid paralysis resembling that of poliomyelitis, and parkinsonian movement disorders.

SEIZURES

Seizures are common in children with flavivirus encephalitis — they occur in approximately 85 percent of children with Japanese encephalitis or Murray Valley encephalitis⁴⁵⁻⁴⁷ — and in up to 10 percent

of adults with West Nile encephalitis. An association between seizures — especially multiple seizures and status epilepticus — and poor outcome has been shown for Japanese encephalitis and for St. Louis encephalitis.^{46,48} In addition to clinically obvious status epilepticus, subtle convulsive status, of which the only manifestation is the twitching of a digit, an eyebrow, or the mouth, has been described in Japanese encephalitis and St. Louis encephalitis^{46,49} and is associated with a grave prognosis. The importance of subtle convulsive status in West Nile encephalitis has yet to be established, although in one study it was not seen.⁵⁰ Electroencephalograms may also reveal periodic lateralized epileptiform discharges,^{46,49} which are often encountered in herpes simplex encephalitis. Multiple uncontrolled seizures may be associated with raised intracranial pressure and with clinical signs of brain-stem herniation syndromes.⁴⁶

Approximately 50 percent of patients with Japanese encephalitis and 30 percent of patients with St. Louis encephalitis have elevated cerebrospinal fluid opening pressures. Brain swelling is seen at autopsy, although herniation is not often reported.^{7,33,51} Distinguishing the clinical signs of brain-stem herniation from those of direct viral damage in the brain stem may be difficult, but the possibility of this reversible complication should not be overlooked. Severe brain-stem encephalitis may result in the locked-in syndrome.²⁷

POLIOMYELITIS-LIKE PARALYSIS

Motor weakness is common in patients with flavivirus encephalitis. In addition to weakness of the upper motor neurons, which is reported in 30 to 50 percent of patients, flaccid weakness of the limbs, with reduced or absent reflexes, is also common. This weakness is associated with respiratory or bulbar paralysis and is reported in approximately 20 to 60 percent of patients.^{24,27,45,52} In addition to causing flaccid weakness in comatose patients who have encephalitis, flaviviruses can also cause an acute flaccid paralysis similar to that of poliomyelitis in fully conscious patients. The earliest outbreaks of Murray Valley encephalitis were thought to be an aberrant form of poliomyelitis,⁵³ and illness that resembles poliomyelitis has been described in patients infected with Japanese encephalitis virus⁵⁴ and those with West Nile viruses.⁵⁵⁻⁵⁸

Nerve-conduction studies typically show reduced or absent compound muscle action potentials, with preserved sensory-nerve action potentials and nor-

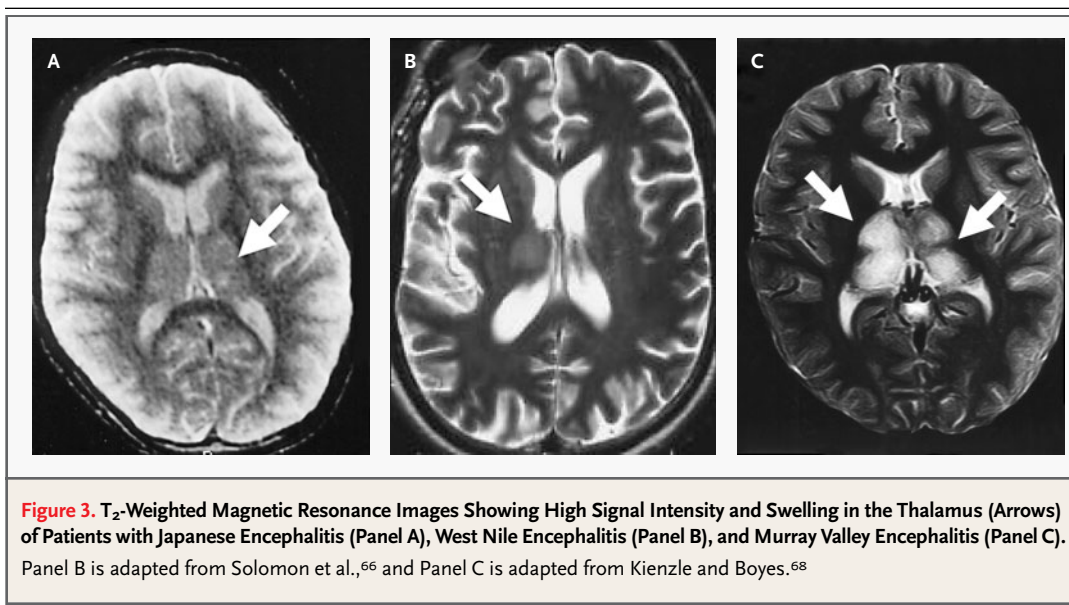
mal conduction velocities.^{54,57,58} Although initially ascribed by some to the Guillain-Barré syndrome, in most cases these responses probably indicate damage to the lower motor neurons in the anterior horns of the spinal cord (i.e., anterior myelitis), as seen at autopsy^{53,58-62} and on imaging of the spinal cord.^{52,57} However, demyelination, involvement of the sensory nerves, and radiculitis also occur occasionally.^{27,63,64} Electromyography typically shows positive sharp waves and spontaneous fibrillations, which are consistent with denervation. Acute retention of urine owing to an atonic bladder may be an early clue that paralysis is the result of a flavivirus.^{44,54} In some patients, damage to both upper and lower motor neurons can lead to bizarre mixtures of clinical signs, which may change hourly during the acute stages of infection.

PARKINSONIAN MOVEMENT DISORDERS

In Japanese encephalitis, movement disorders are common, both in the acute stages of infection and as part of the sequelae. In one recent series of cases, one quarter of patients had acute manifestations.⁴⁶ A characteristic “parkinsonian syndrome” includes mask-like facies, tremors, and cogwheel rigidity. Other movement disorders include generalized rigidity, jaw dystonia, opisthotonos, choreoathetosis, orofacial dyskinesias (e.g., involuntary tongue protrusions), myoclonic jerks, and opsoclonus myoclonus.^{46,65} Similar movement disorders have been reported for Murray Valley encephalitis, St. Louis encephalitis, and, more recently, West Nile encephalitis^{27,66,67} and are thought to be the clinical correlate of the inflammation often seen in the basal ganglia — particularly the thalamus and substantia nigra — on magnetic resonance imaging and at autopsy (Fig. 3).^{33,44,46,59,65,66,68-72} In some patients, intention tremors and ataxia may suggest cerebellar involvement.²⁷

DIAGNOSIS AND TREATMENT

Attempts to isolate virus from the blood of patients with flavivirus encephalitis are usually unsuccessful because viremia is transient and titers are low. Virus is occasionally isolated from the cerebrospinal fluid of patients who do not yet have antibody, particularly those who subsequently die,^{23,26} and from postmortem brain tissue.^{7,23,73} Viral ribonucleic acid occasionally may be detected in the cerebrospinal fluid by the reverse transcriptase polymerase chain reaction (PCR)^{74,75}; for West Nile virus,



real-time PCR has proved more useful.⁷⁶ However, the accepted standard for diagnosing flavivirus encephalitis is the IgM capture enzyme-linked immunosorbent assay (ELISA). This assay will often detect antibody on a single cerebrospinal fluid or serum sample.^{1,3} Not all patients have antibody on admission to the hospital, and the test should be repeated if it is initially negative. False positive results can occur in patients who live in areas where more than one flavivirus circulates or in patients who have received a flavivirus vaccine, but this problem can be minimized by parallel testing for antibody against various flaviviruses.⁷⁷⁻⁷⁹ Assays for neutralizing antibodies are more specific than ELISAs but can be performed only in specialized laboratories that can grow dangerous viruses. Antibody may persist in the serum for many months after infection.^{80,81}

There is no established antiviral treatment for any flavivirus infection. The most promising compound was interferon alfa. This is produced naturally in patients with flavivirus infections, and recombinant interferon alfa has efficacy in some animal models. Interferon alfa was reported to have shown promise in open clinical trials against Japanese encephalitis⁸² and St. Louis encephalitis⁸³ and, on that basis, was given empirically to patients with West Nile encephalitis during 2002. However, a randomized, double-blind, placebo-controlled trial of interferon alfa in Vietnamese children with Japanese encephalitis showed that it had no effect on the

outcome.⁸⁴ Ribavirin and intravenous immune globulin also have been given empirically to patients with West Nile encephalitis.^{85,86} There are supportive data from animal models for the use of immune globulin,⁸⁷ and a clinical trial has been set up by the National Institute of Allergy and Infectious Diseases. Treatment of flavivirus encephalitis currently consists of managing the complications of infection and, with good nursing care and physical therapy, avoiding bedsores and contractures. Even with intensive therapy, severe neuropsychiatric sequelae are common in survivors (Table 1).

FUTURE PROSPECTS

Formalin-inactivated and live attenuated vaccines against Japanese encephalitis exist, but because of costs and logistics, they are not available to much of the population of rural Asia that needs them.⁸⁸ The inactivated vaccine is licensed in the United States, but there is some controversy about which travelers to Asia should receive it.⁸⁹ A three-dose regimen (administered on days 0, 7, and 30) is recommended for travelers who spend prolonged periods (i.e., more than one month) in the rural parts of Asia where Japanese encephalitis is endemic or epidemic.⁹⁰ However, because Japanese encephalitis has appeared in short-term travelers, some physicians recommend more liberal use of the vaccine.⁹¹ Approximately 20 percent of vaccine recipients have local cutaneous or mild systemic reac-

tions. More serious allergic reactions occur in about 0.6 percent of recipients. Vaccines against St. Louis encephalitis have never been fully developed because the disease burden has not been considered great enough. A crude formalin-inactivated vaccine against West Nile virus is being used to protect horses (in which encephalitis can also develop). Newer vaccines that are being developed for flavivirus encephalitis include DNA vaccines and chi-

meric vaccines.^{88,92} Further research is needed to understand the pathogenesis of flavivirus encephalitis and thus to provide a rational approach to new treatments.

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REFERENCES

- Petersen LR, Roehrig JT, Hughes JM. West Nile virus encephalitis. *N Engl J Med* 2002;347:1225-6.
- Centers for Disease Control and Prevention. West Nile Virus update — current case count. (Accessed June 25, 2004, at <http://www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm>.)
- Solomon T, Dung NM, Kneen R, Gainsborough M, Vaughn DW, Khanh VT. Japanese encephalitis. *J Neurol Neurosurg Psychiatry* 2000;68:405-15.
- Burke DS, Monath TP. Flaviviruses. In: Knipe DM, Howley PM, eds. *Fields' virology*. 4th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2001:1043-126.
- Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002;359:507-13.
- Solomon T, Ooi MH, Beasley DW, Mallewa M. West Nile encephalitis. *BMJ* 2003;326:865-9.
- Iwamoto M, Jernigan DB, Guasch A, et al. Transmission of West Nile virus from an organ donor to four transplant recipients. *N Engl J Med* 2003;348:2196-203.
- Detection of West Nile virus in blood donations — United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:769-72.
- Chaturvedi UC, Mathur A, Chandra A, Das SK, Tandon HO, Singh UK. Transplacental infection with Japanese encephalitis virus. *J Infect Dis* 1980;141:712-5.
- Intrauterine West Nile virus infection — New York, 2002. *MMWR Morb Mortal Wkly Rep* 2002;51:1135-6.
- Alpert SG, Ferguson J, Noel LP. Intrauterine West Nile virus: ocular and systemic findings. *Am J Ophthalmol* 2003;136:733-5.
- Interim guidelines for the evaluation of infants born to mothers infected with West Nile virus during pregnancy. *MMWR Morb Mortal Wkly Rep* 2004;53:154-7.
- Mostashari F, Kulldorff M, Hartman JJ, Miller JR, Kulasekera V. Dead bird clusters as an early warning system for West Nile virus activity. *Emerg Infect Dis* 2003;9:641-6.
- O'Leary DR, Marfin AA, Montgomery SP, et al. The epidemic of West Nile virus in the United States, 2002. *Vector Borne Zoonotic Dis* 2004;4:61-70.
- Tsai TF, Popovici F, Cernescu C, Campbell GL, Nedelcu NI. West Nile encephalitis epidemic in southeastern Romania. *Lancet* 1998;352:767-71.
- Monath TP, Tsai TF. Flaviviruses. In: Richman DD, Whitley RJ, Hayden FG, eds. *Clinical virology*. 2nd ed. Washington, D.C.: ASM Press, 2002:1097-151.
- Grossman RA, Edelman R, Willhight M, Pantuwatana S, Udomsakdi S. Study of Japanese encephalitis virus in Chiangmai Valley, Thailand. III. Human seroepidemiology and inapparent infections. *Am J Epidemiol* 1973;98:133-49.
- Vaughn DW, Hoke CH Jr. The epidemiology of Japanese encephalitis: prospects for prevention. *Epidemiol Rev* 1992;14:197-221.
- Kumar P, Sulochana P, Nirmala G, Chandrashekar R, Haridattatreya M, Satchidanandam V. Impaired T helper 1 function of nonstructural protein 3-specific T cells in Japanese patients with encephalitis with neurological sequelae. *J Infect Dis* 2004;189:880-91.
- Hawkes RA. Murray Valley encephalitis and related infections. In: Porterfield JS, ed. *Exotic viral infections*. London: Chapman & Hall, 1995:175-81.
- Johnson RT. West Nile virus in the US and abroad. *Curr Clin Top Infect Dis* 2002;22:52-60.
- Monath TP. Epidemiology. In: Monath TP, ed. *St Louis encephalitis*. Washington, D.C.: American Public Health, 1980:239-312.
- Burke DS, Lersomrudee W, Leake CJ, et al. Fatal outcome in Japanese encephalitis. *Am J Trop Med Hyg* 1985;34:1203-10.
- Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001;344:1807-14.
- Chowers MY, Lang R, Nassar F, et al. Clinical characteristics of the West Nile fever outbreak, Israel, 2000. *Emerg Infect Dis* 2001;7:675-8.
- Huang C, Slater B, Rudd R, et al. First isolation of West Nile virus from a patient with encephalitis in the United States. *Emerg Infect Dis* 2002;8:1367-71.
- Pepperell C, Rau N, Krajden S, et al. West Nile virus infection in 2002: morbidity and mortality among patients admitted to hospital in southcentral Ontario. *CMAJ* 2003;168:1399-405.
- Diamond MS, Shrestha B, Marri A, Mahan D, Engle M. B cells and antibody play critical roles in the immediate defense of disseminated infection by West Nile encephalitis virus. *J Virol* 2003;77:2578-86.
- Diamond MS, Sitati EM, Friend LD, Higgs S, Shrestha B, Engle M. A critical role for induced IgM in the protection against West Nile virus infection. *J Exp Med* 2003;198:1853-62.
- Wang T, Scully E, Yin Z, et al. IFN-gamma-producing gamma delta T cells help control murine West Nile virus infection. *J Immunol* 2003;171:2524-31.
- Mashimo T, Lucas M, Simon-Chazottes D, et al. A nonsense mutation in the gene encoding 2'-5'-oligoadenylate synthetase/L1 isoform is associated with West Nile virus susceptibility in laboratory mice. *Proc Natl Acad Sci U S A* 2002;99:11311-6.
- Pereygin AA, Scherbik SV, Zhulin IB, Stockman BM, Li Y, Brinton MA. Positional cloning of the murine flavivirus resistance gene. *Proc Natl Acad Sci U S A* 2002;99:9322-7.
- Brinker KR, Monath TP. The acute disease. In: Monath TP, ed. *St Louis encephalitis*. Washington, D.C.: American Public Health, 1980:503-34.
- Desai A, Shankar SK, Jayakumar PN, et al. Co-existence of cerebral cysticercosis with Japanese encephalitis: a prognostic modulator. *Epidemiol Infect* 1997;118:165-71.
- Libraty DH, Nisalak A, Endy TP, Suntayakorn S, Vaughn DW, Innis BL. Clinical and immunological risk factors for severe disease in Japanese encephalitis. *Trans R Soc Trop Med Hyg* 2002;96:173-8.
- Bond JO, Hammon WM. Epidemiologic studies of possible cross protection between dengue and St. Louis encephalitis arboviruses in Florida. *Am J Epidemiol* 1970;92:321-9.
- Halstead SB. Pathogenesis of dengue: challenges to molecular biology. *Science* 1988;239:476-81.
- Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. *Lancet* 1998;352:971-7.
- Lanciotti RS, Ebel GD, Deubel V, et al. Complete genome sequences and phylogenetic analysis of West Nile virus strains isolated from the United States, Europe, and the Middle East. *Virology* 2002;298:96-105.
- Chen WR, Tesh RB, Rico-Hesse R. Ge-

- netic variation of Japanese encephalitis virus in nature. *J Gen Virol* 1990;71:2915-22.
41. Solomon T, Ni H, Beasley DW, Ekkelenkamp M, Cardosa MJ, Barrett AD. Origin and evolution of Japanese encephalitis virus in Southeast Asia. *J Virol* 2003;77:3091-8.
 42. Ni H, Barrett ADT. Molecular differences between wild-type Japanese encephalitis virus strains of high and low mouse neuroinvasiveness. *J Gen Virol* 1996;77:1449-55.
 43. Beasley DW, Li L, Suderman MT, Barrett AD. Mouse neuroinvasive phenotype of West Nile virus strains varies depending upon virus genotype. *Virology* 2002;296:17-23.
 44. Solomon T, Vaughn DW. Pathogenesis and clinical features of Japanese encephalitis and West Nile virus infections. *Curr Top Microbiol Immunol* 2002;267:171-94.
 45. Burrow JN, Whelan PI, Kilburn CJ, Fisher DA, Currie BJ, Smith DW. Australian encephalitis in the Northern Territory: clinical and epidemiological features, 1987-1996. *Aust N Z J Med* 1998;28:590-6.
 46. Solomon T, Dung NM, Kneen R, et al. Seizures and raised intracranial pressure in Vietnamese patients with Japanese encephalitis. *Brain* 2002;125:1084-93.
 47. Kumar R, Mathur A, Kumar A, Sharma S, Chakraborty S, Chaturvedi UC. Clinical features & prognostic indicators of Japanese encephalitis in children in Lucknow (India). *Indian J Med Res* 1990;91:321-7.
 48. Southern PM Jr, Smith JW, Luby JP, Barnett JA, Sanford JP. Clinical and laboratory features of epidemic St. Louis encephalitis. *Ann Intern Med* 1969;71:681-9.
 49. Wasay M, Diaz-Arrostia R, Suss RA, et al. St. Louis encephalitis: a review of 11 cases in a 1995 Dallas, Tex., epidemic. *Arch Neurol* 2000;57:114-8.
 50. Gandelman-Marton R, Kimiagar I, Itzhaki A, Klein C, Theitler J, Rabey JM. Electroencephalography findings in adult patients with West Nile virus-associated meningitis and meningoencephalitis. *Clin Infect Dis* 2003;37:1573-8.
 51. Johnson RT, Burke DS, Elwell M, et al. Japanese encephalitis: immunocytochemical studies of viral antigen and inflammatory cells in fatal cases. *Ann Neurol* 1985;18:567-73.
 52. Misra UK, Kalita J. Anterior horn cells are also involved in Japanese encephalitis. *Acta Neurol Scand* 1997;96:114-7.
 53. Breinl A. Clinical, pathological and experimental observations on the "mysterious disease," a clinically aberrant form of poliomyelitis. *Med J Aust* 1918;1:209-13, 229-34.
 54. Solomon T, Kneen R, Dung NM, et al. Poliomyelitis-like illness due to Japanese encephalitis virus. *Lancet* 1998;351:1094-7.
 55. Gadoth N, Weitzman S, Lehmann EE. Acute anterior myelitis complicating West Nile fever. *Arch Neurol* 1979;36:172-3.
 56. Leis AA, Stokic DS, Polk JL, Dostrow V, Winkelmann M. A poliomyelitis-like syndrome from West Nile virus infection. *N Engl J Med* 2002;347:1279-80.
 57. Li J, Loeb JA, Shy ME, et al. Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection. *Ann Neurol* 2003;53:703-10.
 58. Sejvar JJ, Leis AA, Stokic DS, et al. Acute flaccid paralysis and West Nile virus infection. *Emerg Infect Dis* 2003;9:788-93.
 59. Zimmerman HM. The pathology of Japanese B encephalitis. *Am J Pathol* 1946;22:965-91.
 60. McCordock HA, Collier W, Gray SH. The pathologic changes of the St. Louis type of acute encephalitis. *JAMA* 1934;103:822-5.
 61. Newman W, Southam CM. Virus treatment in advanced cancer: a pathological study of fifty-seven cases. *Cancer* 1954;7:106-18.
 62. Kelley TW, Prayson RA, Isada CM. Spinal cord disease in West Nile virus infection. *N Engl J Med* 2003;348:564-5.
 63. Park M, Hui JS, Bartt RE. Acute anterior radiculitis associated with West Nile virus infection. *J Neurol Neurosurg Psychiatry* 2003;74:823-5.
 64. Jeha LE, Sila CA, Lederman RJ, Prayson RA, Isada CM, Gordon SM. West Nile virus infection: a new acute paralytic illness. *Neurology* 2003;61:55-9.
 65. Misra UK, Kalita J. Movement disorders in Japanese encephalitis. *J Neurol* 1997;244:299-303.
 66. Solomon T, Fisher AF, Beasley DW, et al. Natural and nosocomial infection in a patient with West Nile encephalitis and extrapyramidal movement disorders. *Clin Infect Dis* 2003;36:e140-e145 (Web only). (Available at <http://www.journals.uchicago.edu/CID/journal/>.)
 67. Sejvar JJ, Haddad MB, Tierney BC, et al. Neurologic manifestations and outcome of West Nile virus infection. *JAMA* 2003;290:511-5. [Erratum, *JAMA* 2003;290:1318.]
 68. Kienzle N, Boyes L. Murray Valley encephalitis: case report and review of neuro-radiological features. *Australas Radiol* 2003;47:61-3.
 69. Bennett NM. Murray Valley encephalitis, 1974: clinical features. *Med J Aust* 1976;2:446-50.
 70. Cerna F, Mehrad B, Luby JP, Burns D, Fleckenstein JL. St. Louis encephalitis and the substantia nigra: MR imaging evaluation. *AJNR Am J Neuroradiol* 1999;20:1281-3.
 71. Weiss D, Carr D, Kellachan J, et al. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. *Emerg Infect Dis* 2001;7:654-8.
 72. Bosanko CM, Gilroy J, Wang AM, et al. West Nile virus encephalitis involving the substantia nigra: neuroimaging and pathologic findings with literature review. *Arch Neurol* 2003;60:1448-52.
 73. George S, Prasad SR, Rao JA, Yergolkar PN, Setty CV. Isolation of Japanese encephalitis and West Nile viruses from fatal cases of encephalitis in Kolar district of Karnataka. *Indian J Med Res* 1987;86:131-4.
 74. Petersen LR, Marfin AA. West Nile virus: a primer for the clinician. *Ann Intern Med* 2002;137:173-9.
 75. Igarashi A, Tanaka M, Morita K, et al. Detection of West Nile and Japanese encephalitis viral genome sequences in cerebrospinal fluid from acute encephalitis cases in Karachi, Pakistan. *Microbiol Immunol* 1994;38:827-30.
 76. Lanciotti RS, Kerst AJ, Nasci RS, et al. Rapid detection of West Nile virus from human clinical specimens, field-collected mosquitoes, and avian samples by a TaqMan reverse transcriptase-PCR assay. *J Clin Microbiol* 2000;38:4066-71.
 77. Innis BL, Nisalak A, Nimmanitya S, et al. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. *Am J Trop Med Hyg* 1989;40:418-27.
 78. Solomon T, Thao LTT, Dung NM, et al. Rapid diagnosis of Japanese encephalitis by using an immunoglobulin M dot enzyme immunoassay. *J Clin Microbiol* 1998;36:2030-4.
 79. Martin DA, Biggerstaff BJ, Allen B, Johnson AJ, Lanciotti RS, Roehrig JT. Use of immunoglobulin M cross-reactions in differential diagnosis of human flaviviral encephalitis infections in the United States. *Clin Diagn Lab Immunol* 2002;9:544-9.
 80. Burke DS, Nisalak A, Ussery MA, Laorakpongse T, Chantavilul S. Kinetics of IgM and IgG responses to Japanese encephalitis virus in human serum and cerebrospinal fluid. *J Infect Dis* 1985;151:1093-9.
 81. Roehrig JT, Nash D, Maldin B, et al. Persistence of virus-reactive serum immunoglobulin M antibody in confirmed West Nile virus encephalitis cases. *Emerg Infect Dis* 2003;9:376-9.
 82. Harinasuta C, Nimmanitya S, Titsyakorn U. The effect of interferon-alpha A on two cases of Japanese encephalitis in Thailand. *Southeast Asian J Trop Med Public Health* 1985;16:332-6.
 83. Rahal J, Anderson J, Rosenberg C, Reagan T, Thompson L. Effect of interferon alpha-2b on St. Louis (SL) virus meningoencephalitis: clinical and laboratory results. In: Program and abstracts of the 40th Meeting of the Infectious Diseases Society of America, Chicago, October 24-27, 2002: 823. abstract.
 84. Solomon T, Dung NM, Wills B, et al. Interferon alfa-2a in Japanese encephalitis: a randomised double-blind placebo-controlled trial. *Lancet* 2003;361:821-6.
 85. Shimoni Z, Niven MJ, Pitlick S, Bulvik S. Treatment of West Nile virus encephalitis with intravenous immunoglobulin. *Emerg Infect Dis* 2001;7:759.
 86. Haley M, Retter AS, Fowler D, Gea-Banacloche J, O'Grady NP. The role for intravenous immunoglobulin in the treatment of West Nile virus encephalitis. *Clin Infect Dis* 2003;37:e88-e90 (Web only). (Available at <http://www.journals.uchicago.edu/CID/journal/>.)

- 87.** Agrawal AG, Petersen LR. Human immunoglobulin as a treatment for West Nile virus infection. *J Infect Dis* 2003;188:1-4.
- 88.** Monath TP. Japanese encephalitis vaccines: current vaccines and future prospects. *Curr Top Microbiol Immunol* 2002; 267:105-38.
- 89.** Shlim DR, Solomon T. Japanese encephalitis vaccine for travelers: exploring the limits of risk. *Clin Infect Dis* 2002;35: 183-8.
- 90.** Inactivated Japanese encephalitis virus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1993; 42(RR-1):1-15.
- 91.** Solomon T. Vaccines against Japanese encephalitis. In: Jong EC, Zuckerman JN, eds. *Travelers' vaccines*. Hamilton, Ont., Canada: B.C. Decker, 2004:219-56.
- 92.** Monath TP. Prospects for development of a vaccine against the West Nile virus. *Ann N Y Acad Sci* 2001;951:1-12.

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