West Nile Virus: Pathogenesis and Therapeutic Options

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West Nile virus, a member of the family Flaviviridae, has spread throughout the United States. With more than 9000 cases and 200 deaths in 2003, West Nile virus has become the most common cause of viral encephalitis in several states. West Nile virus encephalitis is a zoonosis. The life cycle of the virus includes mainly birds as hosts and mosquitoes as vectors. Humans are accidental hosts, insufficient to support the life cycle of the virus because of low-grade, transient viremia. However, human-to-human transmission through blood, organ transplantation, and lactation has been documented. The frequency of severe neurologic disease in the current epidemic suggests a more neuroviral strain of virus than the one classically associated with West Nile fever. Several neurologic manifestations have been described, but the most characteristic presentation is encephalitis with weakness. Magnetic resonance imaging scans may be normal initially, but a characteristic pattern of involvement of deep gray matter nuclei can be recognized. Although results of polymerase chain reaction may be positive in the cerebrospinal fluid early in the course of the disease, diagnosis is based on serologic tests. Possible cross-reactivity with other members of the genus flavivirus mandates caution when serologic testing results are interpreted. Thus far, no therapeutic intervention has shown consistent clinical efficacy in West Nile virus disease. Several approaches, including interferon-α2b and immunoglobulin with high titer against West Nile virus, offer promise based on animal models and limited clinical experience. New drugs with in vitro activity are being investigated, and a vaccine is being developed.


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Dr. Juan Gea-Banacloche (Infectious Diseases, Experimental Transplantation, and Immunology Branch, National Cancer Institute, National Institutes of Health [NIH], Bethesda, Maryland): A 55-year-old man with refractory chronic lymphocytic leukemia presented for evaluation to the Clinical Center, NIH, on 30 July 2002, 19 days after his third cycle of EPOCH-F (etoposide, prednisone, vincristine, cyclophosphamide, and fludarabine) chemotherapy. His temperature was 39.3 °C. The rest of his vital signs were normal. His history was unremarkable except for numerous mosquito bites during the previous weeks. Results of laboratory tests and imaging studies were unrevealing. The patient remained febrile (temperature, 39 °C to 40 °C) but clinically stable until day 5, when he reported leg weakness and diplopia. A magnetic resonance imaging (MRI) scan of the brain was normal. A lumbar puncture was performed (Table 1). Broad-spectrum antibiotics and acyclovir therapy were started. On day 6, the patient was drowsy, could not ambulate, and developed a coarse tremor. On day 7, he developed dysphagia and dysarthria and was transferred to the intensive care unit. Electromyographic studies showed mild axonal polyneuropathy. Findings on repeated lumbar puncture on day 7 were unchanged. Intubation was required for airway protection on day 8. On day 10, Maryland State Laboratory reported a positive result for West Nile virus on polymerase chain reaction (PCR) of the cerebrospinal fluid. Generalized flaccid weakness persisted. On day 14, the patient developed status epilepticus, which presented with flickering of the eyelids and tachycardia. Between days 15 and 21, intravenous immunoglobulin with a high titer against West Nile virus (Omr-IgG-am) was administered, without improvement. On day 23, a negative PCR result for West Nile virus in the cerebrospinal fluid was reported for the first time, but the patient never regained consciousness. Ventilatory support was discontinued on day 42.

West Nile virus belongs to the family Flaviviridae, a large family of positive-strand RNA viruses with 3 main genera (flavivirus, hepacivirus, and pestivirus). Among the more than 70 viruses in the genus flavivirus, several neurotropic and hepatotropic viruses that are important in human disease are transmitted by arthropods (dengue, Japanese encephalitis, yellow fever, and tick-borne encephalitis). West Nile virus belongs to the Japanese encephalitis serocomplex, which also includes Japanese encephalitis and St. Louis encephalitis, among others.

West Nile virus was associated with West Nile fever, a nonspecific febrile illness that was found in several countries in Africa and the Middle East, either in epidemics or as an endemic mild febrile illness (1). The association with high rates of encephalitis and death is relatively new (2–5) and suggests the presence of a new strain of virus.

The first U.S. cases of West Nile virus natural infection occurred in 1999 in New York, New York (6). The number of human cases did not increase during 2000 and 2001, but the virus spread in animal reservoirs. In 2002, there were 4156 cases with 284 deaths (7). In 2003, there were more than 9000 cases and 220 deaths, and the disease has been identified in almost all parts of the United States (8) (Table 2).

Birds are the main reservoir of West Nile virus in nature; more than 200 species in the United States have been found to be infected. Several species of mosquitoes can acquire the virus after biting a bird with high-level viremia and may then transmit it to the next animals they...
Table 1. Diagnostic Test Results for the Patient*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 11</th>
<th>Day 14</th>
<th>Day 18</th>
<th>Day 23</th>
<th>Day 38</th>
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<tbody>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cells, ×10⁶/L</td>
<td>125</td>
<td>126</td>
<td>80</td>
<td>61</td>
<td>46</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Glucose level, mmol/L (mg/dL)</td>
<td>3.4 (62)</td>
<td>3.4 (62)</td>
<td>3.6 (64)</td>
<td>NA</td>
<td>2.4 (43)</td>
<td>3.3 (60)</td>
<td>3.3 (59)</td>
</tr>
<tr>
<td>Protein level, mg/L</td>
<td>590</td>
<td>1030</td>
<td>560</td>
<td>1320</td>
<td>890</td>
<td>730</td>
<td>1930</td>
</tr>
<tr>
<td>Reverse transcriptase PCR result</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reverse transcriptase PCR result</td>
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<td>–</td>
<td>NA</td>
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<td>–</td>
<td>NA</td>
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<tr>
<td>IgM result</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>IgG result†</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
</tbody>
</table>

* NA = not available; PCR = polymerase chain reaction; + = detectable signal by PCR or detectable West Nile virus–specific IgG or IgM; – = no detectable PCR signal or West Nile virus–specific IgG or IgM; † = equivocal PCR result.

Whether immunosuppression is a risk factor remains unclear (3).

The proportion of patients who develop disease after acquiring the virus is unknown. The commonly reported estimates (1 in 5 infected patients develops fever and 1 in 150 infected patients develops severe neurologic disease) come from serologic surveillance data from the New York epidemic (13). Of the cases reported in 2003, approximately 70% were reported as West Nile fever (milder disease) and 30% were reported as West Nile meningitis or encephalitis (8). Age older than 70 years seems to be the main risk factor for severe meningoencephalitis and death. Whether immunosuppression is a risk factor remains unclear (3).

Dr. Richard T. Johnson (The Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland): West Nile virus was first isolated from the blood of a febrile woman in the West Nile province of Uganda in 1937 (14). Subsequent investigations established that the virus in Africa cycled between culicine species of mosquitoes and various species of birds (15, 16). A mild dengue-like illness with fever, malaise, lymphadenopathy, and rash was thought to be the only manifestation of the infection. During outbreaks in the 1950s, patients occasionally had nuchal rigidity and pleocytosis, which first associated benign aseptic meningitis with West Nile virus. Encephalitis was not recorded (17).

The first documented cases of human encephalitis due to West Nile virus occurred in New York City in 1952, when 95 debilitated patients with advanced cancer were inoculated with an Egyptian strain on the premise that the virus might have an oncolytic effect. Encephalitis developed in 9 patients, virus was recovered from spinal fluid of 3 patients, and classic encephalitis was seen in 1 autopsy (18).

During the following decades, only few encephalitis cases were reported in Israel, India, and the Mediterranean region (19). A major change in neurovirulence was evident with the epidemics of West Nile virus encephalitis in 1996 in Bucharest, Romania (2), and in 1999 in Volgograd, Russia (4). The 2000 outbreak in Israel showed unprecedented high rates of encephalitis, a higher mortality rate, and more involvement of the elderly population (5), similar to the recent experience in the United States. Greater neurotropism and neurovirulence seem to have evolved in strains of West Nile virus circulating in the Middle East, Europe, and the United States. The virus reported in New York in 1999 closely resembles a recent Israeli isolate. In Central Africa, West Nile virus infections have been associated with fulminant hepatitis resembling yellow fever, suggesting the appearance of hepatotrophic strains in that region (20).

After a female mosquito takes an infected blood meal, West Nile virus penetrates the gut; replicates in tissues, often including the nervous system; and then invades and replicates in the mosquito’s salivary glands. This noncytopathic infection of mosquitoes is lifelong. During subsequent feedings, the mosquito injects virus-laden saliva into the warm-blooded host. Virus may initially infect local fi-
broblasts, vascular endothelial cells, or cells of the reticuloendothelial system (21). This extraneural infection leads to viremia, which is the probable route for invasion of the central nervous system. Viremia is also essential to provide an infected blood meal to the next mosquito. Clinical disease is not observed in most avian infections; the massive deaths of crows during the past 3 years in the United States also indicate a change in the neurovirulence of the virus.

The human incubation period of West Nile virus is 2 to 14 days. Approximately 20% of infected patients develop a mild febrile illness with malaise, myalgias, headache, and lymphadenopathy; few patients develop a maculopapular rash. About 1 in 150 patients develops meningitis or encephalitis. The mean age of patients with encephalitis in 2002 was 56 years, and the mean age of decedents was 79 years. Stiff neck and altered mental status are the most common neurologic findings. Seizures are relatively rare (<5%), and flaccid paralysis is common (about 10%). Immunocytochemical staining of brains of patients with the related Japanese encephalitis showed infection that was limited to neurons scattered throughout the brain but with greater intensity of infection in the basal ganglia, thalamus, and brainstem (22). Older studies have shown inflammation and neuronophagia in anterior horns of the cord, explaining the flaccid paralysis (23, 24). The intense weakness and flaccid paralysis in West Nile virus infections were initially thought to represent an axonal form of the Guillaume-Barré syndrome (3). The observations of asymmetry of paralysis, preserved tendon reflexes, and electrophysiologic studies support the localization to the anterior horn cells (25). The finding of a paralytic poliomyelitis syndrome has seldom been seen with West Nile virus but is well described with other flavivirus infections, such as Japanese encephalitis and St. Louis encephalitis (26–28).

A neurovirulent strain of West Nile virus has spread across the United States and established natural cycles in a wide variety of mosquitoes and birds. This virus will probably be with us for future generations; rates of human disease, however, cannot be predicted. As with St. Louis encephalitis in North America, rates of disease may alternately increase and decrease in the future; in contrast, as with Japanese encephalitis in parts of southeast Asia, high rates of seasonal disease may recur yearly.

Dr. Anto Bagic (Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland): Up to 30% of patients with West Nile virus central nervous system infection may have seizures (29), although seizures have not been reported as a presenting sign (30). The patient described in this paper developed seizures after 2 weeks of fever, and his 2 initial electroencephalograms on days 8 and 10 were nonspecific. On day 14, subtle flickering of the eyelids and tachycardia prompted an electroencephalogram that demonstrated polymorphic delta activity, consistent with status epilepticus. The electroencephalographic changes persisted despite standard doses of lorazepam and phenytoin, which are first- and second-line antistatus drugs. The patient progressed into a prolonged and refractory status epilepticus (31), a syndrome associated with considerable mortality (32).

Nonconvulsive status epilepticus may be mistaken for a postictal state or psychiatric disorder (33). It can occur de novo or emerge from a partially treated convulsive status epilepticus and is more likely to become refractory (34). The risk for central nervous system injury is related to duration of seizure activity, age, and systemic complications (33–35).

A later MRI scan in this patient showed subcortical changes affecting the deep gray matter structures, including the thalamus (Figure 1), a reported possible source of this kind of electroencephalographic activity (36). High-dose propofol was required to break the electrical status and retain a burst suppression electroencephalographic pattern, and 3 classic antiepileptic drugs (phenytoin, carbamazepine, and valproic acid) were required for maintenance.

Seizures are not early manifestations of West Nile virus encephalitis, unlike in Japanese encephalitis and many other viral syndromes. The incidence, presentation, therapy, and prognosis of status epilepticus during West Nile virus encephalitis are unknown (37), but the disorder may develop during the course of West Nile virus infection and represents a therapeutic challenge. Early diagnosis may be facilitated by close clinical monitoring, early electroencephalography, and a low threshold for electroencephalographic monitoring (33, 38, 39).

Dr. John A. Butman (Diagnostic Radiology Department, Clinical Center, NIH, Bethesda, Maryland): Progressive involvement of gray matter structures developed over 5 weeks in this patient (Figure 1). On day 5 of fever, MRI scan was normal. By day 8, a subtle focus of T2 hyperintensity was present in the left thalamus. By day 10, this lesion was more conspicuous and a new symmetric hyperintensity was present in the substantia nigra. By day 18, several symmetric foci were present in the thalamus, substantia nigra, pons, and dentate nuclei of the cerebellum. Finally, by day 36, abnormalities extended to the red nuclei and globus pallidus. No clear abnormalities were evident in the cerebellar or cerebral cortical gray matter. Parenchymal or meningeal enhancement after intravenous contrast administration was not present. There was no evidence of acute ischemia or hemorrhage. Only deep gray nuclei were involved; there was no evidence of white matter involvement. On day 36, magnetic resonance spectroscopy, the technique that allows assessment of brain biochemistry, demonstrated a relatively normal metabolite spectrum in occipital gray matter but a selective destruction of neurons in the globus pallidus and thalamus with no reactive gliosis, inflammation, or necrosis.

Magnetic resonance imaging allows detection of acute ischemia, mass lesion, and disruption of the blood–brain barrier.
Early in the course of encephalitis, however, MRI findings may be normal. Conversely, specific patterns of brain lesions can strongly suggest some forms of encephalitis. For instance, herpes simplex characteristically causes limbic encephalitis, which involves medial temporal lobes and insula but spares the basal ganglia (40). Enteroviruses have a predilection for brainstem structures (41). Magnetic resonance imaging findings in Japanese encephalitis and St. Louis encephalitis, which are members of the same serogroup of flaviviruses as West Nile virus, share characteristics with this case. Japanese encephalitis is the most fulminating of these diseases, commonly presenting with gray matter abnormalities on MRI scan (42). The thalamus is the most frequent site of involvement, followed by the midbrain, although all gray matter structures may be involved. The St. Louis encephalitis virus is the least aggressive, and the only MRI findings are bilateral lesions in the substantia nigra (midbrain) (43). This distribution of lesions is remarkably similar to the findings in this case. Although MRI evidence of meningitis in West Nile virus has been reported, these reports have not described abnormal signals in brain parenchyma that would indicate encephalitis. In the 1999 New York outbreak, 13 MRIs were performed in 37 patients with encephalitis; 5 of these showed meningeal or periventricular enhancement (3). No acute brain parenchymal lesion was identified. These MRIs may have been performed too early in the course of the disease. Early parenchymal lesions may have been masked in the presence of ischemic changes, which were seen in 4 of the 13 MRI scans.

Several MRI sequences were used, but fluid-attenuated inversion recovery imaging depicted the lesions most clearly. This MRI sequence is sensitive to increases in tissue water, which typically represent edema (cytotoxic or vasogenic) or gliosis. Restriction of diffusion, a marker of ischemia, was not seen in this case. Contrast-enhanced T1-weighted imaging, sensitive to breakdown of the blood–brain barrier, did not reveal any meningeal or parenchymal enhancement. Less commonly used, but relevant to encephalitis, are gradient-echo T2*–weighted sequences, which are sensitive to minute quantities of blood products, such as the petechial hemorrhage that occurs in herpes simplex encephalitis. Again, such hemorrhage was not evident in this case.

The distribution of brain lesions in this patient was remarkably similar to that seen with other viruses of the Japanese encephalitis complex of the flavivirus. Knowledge of this potentially disease-specific pattern of brain involvement may lead to MRI detection of West Nile virus encephalitis at earlier stages of the disease. It is also important to recognize the delayed nature of the imaging findings. The initial MRI scan was normal, and the abnormalities from days 8 and 10 were subtle. It was not until day 18 that the MRI scan clearly revealed the extent of encephalitis. The slow evolution and subtle nature of findings may explain the lack of previous imaging documentation of
gray matter involvement in West Nile virus encephalitis. The inflammatory response was possibly blunted in this patient because of immunosuppression, minimizing the pathologic alterations that lead to detectable signal abnormalities on MRI scan.

Dr. Patrick R. Murray (Microbiology Section, Department of Laboratory Medicine, Clinical Center, NIH, Bethesda, Maryland): Diagnosis of West Nile virus infection is currently based on serologic tests and detection of viral RNA by nucleic acid amplification (Figure 2). Alternative tests include viral culture, immunohistochemical stains, and antigen-capture enzyme-linked immunosorbent assay (ELISA).

West Nile virus can grow in suckling mice; chick embryo cells; and various primary cell lines of human, primate, swine, and mosquito origin. Growth of the virus is detected by plaque development or a cytopathic effect, and the virus is confirmed by using specific monoclonal antibodies. Culture is useful for screening mosquitoes and infected birds, but the level of viremia in humans is low and of short duration. Virus can be detected during the first few days of illness, but it has rarely been detected in patients with meningoencephalitis (44). Viral antigen immunosassays and immunohistochemical tests are available for detecting West Nile virus; however, the antigen tests are insensitive in human infections and the immunohistochemical test reagents are not readily available (45).

In the case presented, both reverse transcriptase PCR and serologic tests were performed with serum and cerebrospinal fluid samples (Table 1). Various nucleic acid amplification tests have been developed, including reverse transcription PCR, TaqMan (Roche Molecular Systems, Alameda, California) real-time PCR, and nucleic acid sequence–based amplification (46–49). These assays are typically more sensitive than viral culture, but in human disease their results are generally negative by day 3 to 5 of the illness, when viral-specific antibodies are detectable. Our patient is unusual because positive PCR results were detected in both serum and cerebrospinal fluid at day 14.

Given the low sensitivity of these tests, diagnosis of West Nile virus infection in humans is usually based on serologic characteristics. The 2 most common tests are IgM antibody capture (MAC) ELISA and IgG direct ELISA (50). The IgM antibody capture ELISA is more sensitive than other IgM tests; it detects antibodies in cerebrospinal fluid 3 to 5 days into the clinical illness and 3 or more days earlier than detectable serum antibody (50). The IgG antibody generally appears about 5 days after the IgM antibodies. Several factors complicate the interpretation of the serologic results. The most important factor is related to the taxonomic complexity of the genus flavivirus (51). The presence of cross-reactive antigens, particularly in the Japanese encephalitis complex, necessitates confirmation of all positive serologic test results with viral neutralization studies. Many laboratories can perform screening tests for viral antibodies; however, neutralization tests require a Biosafety Level 3 facility (which involves a double-door access zone,

Figure 2. Schematic of virologic and serologic tests in West Nile virus encephalitis.

Solid lines represent the more common results; broken lines represent reported ranges. The shaded box is an example of a typical patient. Incubation period is usually 5 to 14 days (median of 10 days in cases acquired after blood transfusion). Viremia has usually resolved by the time symptoms begin, but it may last up to 11 days in some immunocompromised patients. Results of polymerase chain reaction (PCR) in the cerebrospinal fluid are positive very early in the course of encephalitis and only for a short period. In most patients, the PCR test result is already negative during the symptomatic phase when viral specific antibodies are detected, although this may vary depending on the method used. In the patient described, the result was still positive 2 weeks into his illness. Serologic responses follow: IgM and IgG in the cerebrospinal fluid first and later in the serum, at approximately 1- to 2-day intervals each. Many patients will not show a positive result for IgG in the cerebrospinal fluid (lighter line). A typical patient (shaded box) will have results that are either positive for PCR (if sampled very early) or positive for IgM in the spinal fluid (occasionally), depending on the duration of symptoms. The serologic responses may persist for months.
biological safety cabinets, special training, and protective garments) to grow the virus and perform specific neutralization tests for the most common flaviviruses. Although the level of antibody response can indicate the flavivirus most likely responsible for infection, patients infected with St. Louis encephalitis may react more strongly with West Nile virus antigens than with the homologous antigen (52). Immunofluorescence assays may present less cross-reactivity than ELISA (53), but definitive diagnosis requires testing against antigens from more than one virus and, in some cases, viral neutralization studies. Finally, IgM antibodies may persist for a prolonged time. In a study of patients with West Nile virus meningoencephalitis, serum IgM was detectable in 77% of the patients at 12 months after infection (44). Other studies have reported detectable antibodies in patients infected with West Nile virus at 500 days after infection (54). Of interest, our patient did not have detectable IgM antibodies until day 38, presumably because of his compromised immunologic status.

Dr. Amy Guillet Agrawal (Infectious Diseases and Critical Care Department of Critical Care Medicine, NIH, Bethesda, Maryland): Thus far, no drug has been shown to be clinically effective for West Nile virus disease, and the standard is supportive care only. Candidate therapies include ribavirin, interferon-α2b, and high-titer anti–West Nile virus immunoglobulin. Ribavirin is active against many RNA and DNA viruses in vitro, including the flaviviruses hepatitis C, dengue, yellow fever, and Japanese encephalitis viruses (55). It has clinical efficacy in hepatitis C and Lassa fever. In vitro data on ribavirin for West Nile virus show activity only at very high doses in Vero cell lines (56) or oligodendroglia (55). Given that cerebrospinal fluid levels are 70% of serum levels after oral administration, high intravenous dosing (ribavirin, 4 g/d) would be required to achieve barely adequate cerebrospinal fluid concentrations (55). Ribavirin has been largely unsuccessful in animal models of central nervous system infections, despite in vitro activity against the causative viruses (56). In the 2000 West Nile virus outbreak in Israel, the effect of ribavirin on human West Nile virus infection was assessed retrospectively in 233 cases (5). The drug was given orally, so it probably did not achieve “active” cerebrospinal fluid concentrations. Ribavirin was used in 11% of patients who survived and 45.4% of patients who died. The association between use of ribavirin and a poorer outcome was thought to represent a marker for sicker patients because the effect disappeared in multivariate analysis. Nevertheless, it did not have a strikingly beneficial effect.

Interferon-α has broad antiviral activity in vitro and immunostimulatory effects in vivo (57). Although it does not cross the blood–brain barrier, interferon-α has been considered to be a possible therapy for flaviviral encephalitis. Interferon-α has been shown to have in vitro activity against West Nile virus in a Vero cell model (58), where it was therapeutic when applied to cells 1.5 hours after infec-

tious challenge at concentrations easily attainable in serum in humans. It has not been evaluated in an animal model of West Nile virus. Studies in mice infected with St. Louis encephalitis showed therapeutic effect. There was a 60% survival rate when interferon was given at 24 and 48 hours after infectious challenge but no benefit if the first dose was given 5 days after challenge. Survival in controls was 5% (59).

Two human trials for arthropod-borne flaviviruses have occurred, and one trial is ongoing. One trial was an open-label study of interferon-α during an outbreak of St. Louis encephalitis (Rahal J. Personal communication). The first 17 patients were treated with supportive care only, and 15 subsequent patients were given interferon-α2b (3 million IU/d for 2 weeks). No deaths were reported in either group, and the mean neurologic score in the treated group improved by week 3. The study had important limitations (unblinded, nonrandomized, and non–placebo-controlled study with limited follow-up), but it has encouraged the design of an open-label study examining the effect of interferon-α2b versus supportive care in West Nile virus and the possibility of a larger double-blind study of interferon-α3 versus placebo for future outbreaks.

The second study examined the effect of interferon-α2b in Japanese encephalitis in children in Vietnam (60). In a double-blind, placebo-controlled study, interferon-α, 10 million IU/m² daily, was equivalent to placebo in terms of mortality or functional outcome.

Interest in immunoglobulin was sparked by case reports in the literature about the 2000 West Nile virus outbreak in Israel. A 70-year-old woman with chronic lymphocytic leukemia who had become comatose from West Nile virus encephalitis recovered within several days of receiving intravenous immunoglobulin. The intravenous immunoglobulin used was subsequently found to have titers of 1:1600 against West Nile virus. (In contrast, U.S. donor source intravenous immunoglobulin was found to have undetectable titers [61].) In a second case, a patient with immunosuppression after lung transplantation and obturation from West Nile virus encephalitis was successfully treated with the high-titer anti–West Nile virus intravenous immunoglobulin (62). Although these results are anecdotal and the intravenous immunoglobulin from Israel did not produce clinical improvement in our patient, immunoglobulin use for West Nile virus is biologically plausible. Immune serum was frequently used successfully in the preantibiotic era to treat infectious diseases. Antibody is still used in certain viral illnesses, such as Junin virus—the agent of Argentine hemorrhagic fever (63)—chronic echorivus meningoencephalitis in hypogammaglobulinemic patients (64–66), and disseminated vaccinia after smallpox vaccination (67).

Animal data indicate an important role for humoral immunity in controlling West Nile virus infection. In a model with cyclophosphamide-treated mice, immune serum given up to 6 days after West Nile virus challenge was more protective than splenocytes given at day 4, suggesting...
that antibody-mediated immunity may be more important than cellular immunity in this setting (68). More recent animal studies also support the importance of antibody-mediated immunity. A B-cell knockout mouse model is exquisitely susceptible to West Nile virus—one plaque-forming unit constitutes the LD50 (the dose that will cause the deaths of 50% of the animals in 1 experiment). Specific immunoglobulin given 1 day before and 1 day after lethal (100 plaque-forming units) infectious challenge is protective in 100% of these mice, in contrast to 0% survival in controls (69). In wild-type mice, immune serum given after inoculation with 100 plaque-forming units of West Nile virus produces 84% survival if the injection is given at 24 hours and 50% survival if it is given at 5 days, versus 14% survival in control animals who received either no treatment or nonimmune globulin (70). Other investigators inoculated 4- to 5-week-old BALB/c mice intraperitoneally with a lethal challenge of 100 plaque-forming units of West Nile virus. One injection of Omr-IgG-am (intravenous immunoglobulin) produced 95% survival if given at 4 hours after inoculation and 64% survival if given at day 1. When several injections were given, a dose-dependent effect was seen—3 daily injections led to 92% survival. All untreated mice died (71).

In summary, the in vitro data for ribavirin suggest an effect at high doses, animal data show it has disappointing results when used for other neurotropic viruses, and human experience has been anecdotal but not promising. Interferon-α2b is active against West Nile virus in vitro, there are no data in animal models of West Nile virus, and the more rigorous trial in humans for another neurotropic flavivirus is not encouraging. Intravenous therapy with high-titer immunoglobulin for West Nile virus is biologically plausible because of its efficacy in other viruses and the seeming importance of humoral immunity in animal models. Animal data are very preliminary but encouraging, and human experience is anecdotal.

Agents with more potency must be identified. A screening program sponsored by the National Institute of Allergy and Infectious Diseases is ongoing (56). A total of 34 compounds have been screened, and thus far 6 compounds have been identified that have in vitro activity against West Nile virus with minimal toxicity: 2-thio-6-azauridine, mycophenolic acid, 6-azauridine triacetate, cyclopenitocytosine, pyrazofurin, and 6-azauridine. These compounds are inhibitors of cellular enzymes that are involved in nucleotide synthesis. Each met the criteria of a median effective concentration (EC50) of 10 μg/mL or less and a selectivity index (ratio of the toxic to effective concentration) of 10 or more. These compounds will now be studied in animal models of West Nile virus infection (56). An antisense compound, AVI-4020 (AVI BioPharma, Portland, Oregon), has been found safe in a handful of human participants and should undergo further testing this year.

Finally, several human vaccines for West Nile virus are being developed, and one vaccine, ChimeriVax (Acambis, Cambridge, United Kingdom) (72), entered clinical trials in late 2003. However, even if a safe and effective vaccine is found, vaccinating large segments of the population may not be cost-effective, so there will probably always be a need for effective therapies.Currently, an open-label trial of interferon-α2b is ongoing, and a placebo-controlled, double-blind, multicenter trial using high-titer intravenous immunoglobulin began recruitment in 2003 by the Collaborative Antiviral Study Group of the National Institutes of Health.


59. Brooks TJ, Phillpotts RJ. Interferon-alpha protects mice against lethal infection with St Louis encephalitis virus delivered by the aerosol and subcutaneous routes. Antiviral Res. 1999;41:57-64. [PMID: 10321579]


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