Lesson S27: PreAnesthetic Assessment of the Patient with Neuroinvasive West Nile Virus Infection.

Authored by: Elizabeth A.M. Frost MD, Clinical Professor of Anesthesia, Mount Sinai School of Medicine, New York, NY

Reviewed by: Ram Roth MD, Assistant Professor, Mount Sinai School of Medicine, New York, NY
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Practice Gaps

The West Nile Virus (WNV) can cause a severe neuroinvasive disease that can mimic other disorders which have significance for the anesthesiologist. Because this viral infection occurs sporadically, anesthesiologists may not be familiar with the presentation and anesthetic implications.

Objectives

At the end of the lesson, the participant will be able to:

1. Identify vertebrate hosts for WNV
2. Describe the life cycle of WNV in the mosquito
3. Identify the forms that the disease may take in humans
4. Describe the symptoms of neuroinvasive infection
5. Inform patients of risks of acquiring the infection
6. List common means for prevention
7. Draw up an anesthetic plan
8. List the differential diagnoses
9. Anticipate complications of neuroinvasive disease
10. List public health measures to control WNV infection

Case Presentation

An 80 year old woman was visiting her daughter in New York from Dallas. The day after her arrival she complained of a headache which she treated with acetaminophen. Over the next 3 days, she vomited repeatedly and had difficulty walking. When her condition deteriorated and she developed uncontrollable tremors, her daughter brought her to the emergency room (ER). The ER doctor called the anesthesiologist for help in establishing an airway and for central line placement.
West Nile Virus Infection: Introduction

The West Nile Virus (WNV), endemic in Africa, was first isolated in the United States in 1999 when a cluster of encephalitis cases were identified in New York City. Seven deaths were reported in the region at that time. As of September, 2012, West Nile virus infections in people, birds, or mosquitoes has been reported in 48 states.\(^1\) The Centers for Disease Control (CDC) has recorded a total of 2,636 cases of West Nile virus disease in people, including 118 deaths. Of these, 1,405 (53%) were classified as neuroinvasive disease (such as meningitis or encephalitis) and 1,231 (47%) were classified as non-neuroinvasive disease. This 2012 outbreak represents the highest incidence of West Nile virus disease cases reported to CDC since 2003. Two thirds of the cases have been reported from six states (Texas, Louisiana, South Dakota, Mississippi, Michigan, and Oklahoma) and 40 percent of all cases have been reported from Texas, specifically in areas just north of downtown Dallas.\(^2\)

History

The WNV was first isolated in 1937 from a woman in the West Nile district of Uganda. Closer examination of the relationship between the organism and the environment was performed in Egypt in the 1950’s. In 1957, WNV was isolated as the cause of an outbreak of severe neuroinvasive disease in elderly patients in Israel. Transmission to horses was identified in Egypt and France in the early 1960’s. The virus has been isolated in Africa, Europe and the Middle East, as well as in west and central Asia. Outbreaks of WNV encephalitis in humans have been recorded in Algeria in 1994, in Romania in 1996-1997, the Czech Republic in 1997, the Congo in 1998 and Russia in 1999. Major outbreaks were recorded in horses in Morocco in 1996 and in Italy in 1998. The virus was first identified in the United States in 1999 as the cause of encephalitis in both humans and in horses. Of 62 cases of severe human encephalitis, seven died. Encephalitis was first found in horses in Long Island, New York. The virus spread rapidly across the US with human disease documented now in all states except Hawaii and Alaska. Of note, the first cases of human and animal infection (horse) reported in 2012 were identified in Oregon.

Definition and Causation

West Nile virus is a zoonotic flavivirus, transmitted by blood sucking mosquitoes. The genus Flaviviridae comprises about 70 members, of which about 30 are found in southern, south-eastern and eastern Asia and Australasia. These include major pathogens such as Japanese encephalitis, West Nile, Murray Valley encephalitis), tick-borne encephalitis, Kyasanur Forest disease virus, and the dengue viruses.

Birds are the primary vertebrate reservoir hosts for West Nile virus. Some bird species such as ravens, raptors and other birds of prey (falcons) are highly susceptible and develop deadly neuroinvasive disease while others have subclinical infection.\(^3\)

Arthropodborne viruses or arboviruses are transmitted to humans primarily through the bites of infected mosquitoes and ticks. Symptomatic infections most often manifest as a systemic febrile illness and, less commonly, as neuroinvasive disease (e.g., meningitis, encephalitis, or acute flaccid paralysis). West Nile virus (WNV) is the leading cause of domestically acquired arboviral disease in the United States. In 2011, CDC received reports of 871 cases of nationally notifiable arboviral diseases (excluding dengue); etiological agents included WNV (712 cases), La Crosse virus (LACV) (130), Powassan virus (POWV) (16), St. Louis encephalitis virus (SLEV) (six), Eastern equine encephalitis virus (EEEV) (four),
and Jamestown Canyon virus (JCV) (three). Of these, 624 (72%) were classified as neuroinvasive disease, for a national incidence of 0.20 per 100,000 population. WNV and other arboviruses continue to cause focal outbreaks and severe illness in substantial numbers of persons in the United States.4

Endemic arboviruses are nationally notifiable. The Centers for Disease Control and Prevention together with the US Geographical Survey, USDA Animal and Plant Health Inspection Service, State wildlife agencies, and State and local health and vector control agencies track WNV on a daily basis. WNV infections in humans, birds, mosquitoes, and nonhuman mammals are reported to CDC through ArboNET, an internet-based arbovirus surveillance system managed by state health departments and the CDC. 5,6

WNV is the leading cause of arboviral encephalitis in the United States. The viruses all share a common size (40-60nm), symmetry (enveloped, icosahedral nucleocapsid), nucleic acid (positive-sense, single stranded RNA, approximately 10,000-11,000 bases) and appearance in the electron microscope.

Arboviruses, such as WNV, propagate by transmission to non-human vertebrate hosts through the blood feeding habits of arthropods (e.g., mosquitoes, sand flies, ticks, and ceratopogonids). All arboviral encephalitides are zoonotic with a complex life cycle involving a non-human primary vertebrate host and a primary arthropod vector. Humans are not an integral part of the life cycle. They become incidental targets when human populations encroach on natural reservoirs of infection or when the virus is inadvertently carried to human populations by a secondary vector (Fig 1).

West Nile virus multiplies by ongoing transmission between adult mosquito vectors feeding on the blood of bird reservoir hosts. The cycle begins when infected mosquitoes carrying the virus in their salivary glands inject the virus into susceptible birds while acquiring blood. The injected bird becomes a reservoir of infection and can sustain an infectious viremia for 1 - 4 days after exposure. New mosquito vectors feed on viremic host birds and acquire the virus in their blood meal. Following an incubation period of 10 – 14 days, the virus is stored in the salivary glands of the mosquito and may be readily transmitted to other susceptible hosts to create additional reservoirs of infection.

Some 20 native bird species in the United States and bats have tested positive for virus by reverse transcriptase-polymerase chain reaction. Humans are not effective reservoirs of infection because levels of viremia are low-grade and transient.
Role of the Mosquito in Causation of WNV

Mosquitoes are two-winged insects that belong to the order of Diptera and are ubiquitous throughout the world with the exception of polar environments such as Antarctica. Bites to humans are usually from insects of the genera *Anopheles*, *Culex* and *Aedes*. In North America, there are about 170 species of mosquitoes. Five species of *Culex* are primarily responsible for transmission of WNV and can survive through the winter in the adult stage. *Culex pipiens*, isolated from July through September, is probably involved in early season enzootic transmission and late season epizootic amplification of the virus in wild bird populations. The prevalence of *Culex restuans* in June and July and isolates of WNV in early July suggest that this species may play an important role as an enzootic vector involved in early amplification of WNV virus among wild birds. Its involvement as a bridge vector to humans is not likely. *Culex salinarius* is the most frequently captured *Culex* species and is found mainly in August and September when virus activity is highest. Frequent isolations of WNV from this species in September when the majority of human cases are reported, combined with its abundance at this time of the year, demonstrates vector competence and broad feeding habits. Thus, *Culex salinarius* is a likely bridge vector to humans, horses and other mammals. The risk of human infection extends from early August through the end of October. As some *Culex* species hibernate throughout the winter months, the virus may survive with the mosquito, indicating that surveillance is necessary throughout the entire year.

Life Cycle of the Mosquito

Standing water is essential to the life cycle of the mosquito. The insect can live in salt or fresh water, and in the stagnant water found in discarded rubber tires or in holes of trees. There are four stages to the life cycle – eggs, larvae, pupae, adults. The female mosquito lays several hundred eggs on the surface of standing water or in an area that is prone to flooding. Desiccated eggs can remain viable
until the right conditions for hatching develop. The eggs of most species hatch in 2-3 days and the larvae feed on organic matter in the water for about a week before changing into pupae. The pupae continue to live in the water for another 2-3 days and then metamorphose into adult mosquitoes. Male mosquitoes feed on flower nectar and do not require blood meals. Only the females require blood to produce eggs. Feeding occurs approximately every three days and usually occurs at twilight, although some insects will feed during the day. A female mosquito will typically consume its own weight in blood.

Zoophilic mosquitoes have a preference for feeding on animals while anthropophilic mosquitoes prefer humans. In some species, seasonal switching allows for the proliferation of the virus in animal hosts. Mosquitoes are efficient vectors for a number of viruses, protozoa and helminths. However, they are not able to carry and transmit all blood-borne viruses. Human Immunodeficiency Virus (HIV) does not survive or replicate in mosquitoes and cannot be transmitted during subsequent feedings.

Malaria, a protozoan infection carried by mosquitoes, is responsible for about 3 million deaths annually throughout the world. Also transmitted are the arboviruses responsible for yellow fever, epidemic polyarthritis and several forms of encephalitis. Bancroftian filariasis, a disease of tropical and subtropical areas of the world, is caused by a nematode that is spread by mosquitoes.

**Epidemiology of Human Infection**

Since its discovery in New York City in 1999, WNV has caused seasonal epidemics of febrile illness and severe neurologic disease, usually during the months of July to September. From 1999 through 2004, more than 16,600 cases of WNV-related illnesses were reported in the United States, of which >7,000 were neuroinvasive disease and >600 were fatal. In 2005, a total of 2,744 cases of WNV disease in humans were reported, an increase from 2,359 cases reported in 2004. In 2011, arboviral disease seemed to be decreasing with a reported number of 871. As of September, 2012, there have been almost 3,000 cases reported of WNV. Underestimation is likely as many patients may have only mild symptoms. Overall, it is estimated that, in the United States, 3 million persons have been infected with the West Nile virus with the highest incidence rates in the central plains states (until this year when Texas reported more infection). These infections would equate to about 780,000 illnesses.

**Signs and Symptoms**

Only one of five persons bitten by an infected mosquito will acquire the virus. Once acquired, there are three possible presentations of illness.

**Severe Illness:** About one in 150 people infected with WNV develop severe illness. Symptoms include high fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness and paralysis. These symptoms may last several weeks, and neurological effects may be permanent. There is also a high prevalence of chronic kidney disease and progression of the disease over time. A study of 48 patients admitted to a rehabilitation facility after serious infection indicated some improvement may be seen after treatment for one year but in a subset of patients only moderate gains were accomplished.

**Symptomatic:** Up to 20 percent of people who become infected with WNV have symptoms such as fever, headache, and body aches, nausea, vomiting, and sometimes swollen lymph glands or a skin rash on the chest, stomach and back. Duration of symptoms ranges from a few
days to several weeks. Patients have frequently reported difficulty concentrating and neck pain or stiffness, with fatigue and muscle weakness lasting for more than one month.

**Mild symptoms or Asymptomatic:** Approximately 80 percent of people (about four out of five) who are infected with WNV have no symptoms or very mild flu like symptoms.

Other non-neurologic clinical manifestations that may rarely occur during WNV infection include hepatitis, pancreatitis, myocarditis, rhabdomyolysis, orchitis, and ocular manifestations. A study in Tunisia found that among 29 patients hospitalized with WNV, 69% disease had chorioretinitis. Cardiac dysrhythmias have also been observed in some North American patients.

Signs of severe neuroinvasive illness such as meningitis, encephalitis and paralysis include stupor, disorientation, tremors, seizures, and coma. Death may occur as the virus replicates in the human body and crosses the blood brain barrier. The proportion of reported cases that are neuroinvasive disease is higher because cases of neuroinvasive disease are more likely to be reported than cases with mild or moderate symptoms.

Acute, asymmetric flaccid paralysis - similar to that seen with poliomyelitis occurs in approximately 13% of patients with neuroinvasive disease where WNV infects spinal motor neurons (anterior horn cells). Infection of the brainstem and high cervical spinal cord may cause diaphragmatic and intercostal muscle paralysis with resulting respiratory failure and sometimes death. Guillain-Barré syndrome has been infrequently reported and has occurred in an HIV-infected patient. Despite the poor physical condition of these patients, the return of mental health is generally favorable.

**Diagnosis**

Diagnosis of WNV infection is based on a high index of clinical suspicion, serologic test results and viral isolation. WNV, or other arboviral diseases such as St. Louis encephalitis, should be strongly considered in adults > 50 years who develop unexplained encephalitis or meningitis in summer or early fall. Year-round transmission is possible in some areas. Therefore, WNV should be considered in all persons with unexplained encephalitis and meningitis. If local health authorities are reporting outbreaks, the index of suspicion should be raised. Obtaining a recent travel history is also important.

Of interest, during an outbreak of meningitis and encephalitis in Arizona, record review indicated that only 28% (12 of 43) of patients aged < 50 years were tested for WNV compared to 71% (12 of 17) of patients > 50 years. Such lack of testing of younger patients likely contributes to inaccurate estimates of the WNV neuroinvasive disease burden.

West Nile virus testing for patients with encephalitis, meningitis, or other serious central nervous system infections can be obtained through local or state health departments who usually perform the test within 24 to 36 hours of submission. Detection of WNV-specific IgM antibody in CSF using MAC-ELISA is the most conclusive method to diagnose persons with WNV infection of the central nervous system (CNS). This test can be done with a CSF specimen obtained during initial clinical presentation. In neuroinvasive disease CSF analyses also reveals pleocytosis with lymphocyte predominance.

IgM antibody does not readily cross the blood-brain barrier, and thus IgM antibody in CSF strongly suggests acute CNS infection. *Serum* IgM antibody may persist for more than a year; as such,
physicians must determine whether or not the presence of serum antibody is the result of a prior WNV infection or related to the current clinical presentation.

If CSF is not obtained, acute and convalescent serum samples submitted at least 2 weeks apart may be used to make the diagnosis utilizing MAC-ELISA. If the acute sample is IgM-negative, then the illness is unlikely to be an acute WNV infection. If the specimen is IgM-positive and the illness is clinically compatible, then it may be a recent WNV infection. Other reasons for the positive test should be explored such as St. Louis encephalitis (SLE) virus, or recent infection with related flaviviruses (e.g., yellow fever, Japanese encephalitis, and dengue).

Common findings among patients in recent outbreaks are reported in Table 1. In peripheral blood, total leukocyte counts are mostly normal or elevated, with lymphocytopenia and anemia also occurring. Hyponatremia is sometimes present, particularly among patients with encephalitis. Examination of the cerebrospinal fluid (CSF) shows pleocytosis, usually with a predominance of lymphocytes. Protein is universally elevated. Glucose is normal. Computed tomographic scans of the brain generally do not show evidence of acute disease, but in about one-third of patients, magnetic resonance imaging indicates enhancement of the leptomeninges, the periventricular areas, or both.

<table>
<thead>
<tr>
<th>TABLE 1: COMMON DIAGNOSTIC FINDINGS IN PATIENTS WITH WNV</th>
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<tr>
<td><strong>Blood</strong></td>
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<td>Total leukocyte count normal or elevated</td>
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<tr>
<td>Lymphocytopenia</td>
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<td>Anemia</td>
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<td>Hyponatremia</td>
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<td><strong>CSF</strong></td>
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<tr>
<td>Pleocytosis, with predominance of lymphocytes</td>
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<td>Protein elevated</td>
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<tr>
<td>Glucose normal</td>
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<td><strong>MRI</strong></td>
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<tr>
<td>Enhancement of leptomeninges, or periventricular areas, or both</td>
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National blood donor screening strategies for WNV RNA were implemented in 2003 using minipool nucleic acid-amplification testing (MP-NAT) based on pooled donor samples. To improve sensitivity of WNV detection, blood-collection agencies later implemented enhanced screening by individual donation NAT (ID-NAT), most often used when a given trigger threshold of positive MP-NAT results is reached during the WNV transmission season.\(^\text{16,17}\) The initial screening in 2003 yielded 944 confirmed viremic donors. MP-NAT yield peaked in August of that year with > 0.5% of donations positive for WNV RNA in 4 states. The average time viremia is detectable by MP-NAT was 6.9 days (95% confidence interval [CI] 3.0-10.7). In addition to preventing transfusion-transmitted WNV infection, donor screening can serve as a tool to monitor seasonal incidence in the general population. But universal blood screening for WNV has not been shown to be cost effective. The risk of transmitting WNV during transfusion of fresh frozen plasma and platelets is small. A substantial fraction (15%-25%) of WNV RNA positive blood donations collected in high incidence regions have shown low level viremia. Such donations may be missed by NAT screening and/or supplemental assays, especially when screening is performed on minipools (MPs). This has led to concern over the residual risk of WNV transmission from MP-NAT screened blood transfusions, with consequent consideration of targeted conversion to ID-NAT, reduced collections and frozen component recalls in high MP-NAT regions. There is also evidence that some very low-level viremic donations and follow-up specimens detected as WNV RNA positive by the screening NAT assays, may test negative on other types of assays that are currently used.\(^\text{18}\) Nevertheless, repeat testing should be done prior to any transplant, as transmission or even de novo infection leading to neuroinvasive infection can occur, especially in immunocompromised patients.\(^\text{19}\)
Many flaviviruses can produce symptoms of encephalitis, and therefore it is important to identify WNV and to differentiate it from the viruses such as those that cause Dengue fever, tick-borne and Japanese encephalitis so that prognosis can be determined and spread can be prevented. Of importance to the anesthesiologist is the recognition that these patients are often severely dehydrated with major electrolyte abnormalities, especially those related to kidney function. Hyponatremia can result in cerebral edema and increased intracranial pressure. Consent issues also arise in with obtunded patients.

**Risk Factors**

There is an increased risk of complications and severity of disease from WNV infection for those of advanced age or those with compromised immune systems. There is no evidence that pregnant women are at any greater risk of complication from the infection.

Of 1090 cases included in an analysis from several states between 2008-10, 708 (65%) were hospitalized and 641 (59%) had neuroinvasive disease. Five percent died. Chronic renal disease, history of cancer, alcohol abuse, diabetes and hypertension were independently associated with severity of illness. Only hypertension was associated with meningitis. Immune suppression was independently associated with death.

**Treatment**

Treatment for WNV infection is supportive consisting mostly of hydration, respiratory support (possibly with controlled ventilation), prevention of secondary infection, and control of hyperthermia. Increase in intracranial pressure can be managed with controlled ventilation, mannitol, furosemide, and mild hypothermia.

Recent studies noted a protective role of several innate immune response elements including alpha/beta interferon (IFN-alpha/beta), immunoglobulin M, gamma delta T cells, and complement. In laboratory mice infected with WNV, a lack of IFN-gamma production or signaling resulted in a rise in mortality from 30% (wild-type mice) to 90% (IFN-gamma(-/-) or IFN-gammaR(-/-) mice) and a decrease in the average survival time. The protective mechanism of IFN-gamma is likely to be antiviral in nature, thereby preventing viral dissemination to the CNS. Type I interferon (IFN) has also been shown to have a critical role in controlling WNV replication, spread, and tropism. Mice lacking both the interferon-induced, double-stranded-RNA-activated protein kinase (PKR) and the endoribonuclease of the 2',5'-oligoadenylate synthetase-RNase L system (PKR(-/-) x RL(-/-)) were highly susceptible to subcutaneous WNV infection, with a 90% mortality rate compared to the 30% mortality rate observed in congenic wild-type mice. PKR and RNase L may contribute to IFN-mediated protection in a cell-restricted manner and control WNV infection in peripheral tissues and some neuronal subtypes.

Anecdotal reports, supported by rodent studies, have indicated the presence of anti-WNV antibodies in intravenous immunoglobulin assists in the recovery from neuroinvasive disease. A humanized anti-WNV mAb, derived from plants can also block viral fusion. In one patient, who developed WNV after a liver transplant, infusion of hyperimmune plasma and gamma globulins prevented the development of a neuroinvasive disease.
Prevention

Preventive measures consist of community-based mosquito control programs to reduce vector populations, personal protective measures to reduce the likelihood of being bitten by infected mosquitoes, and the underlying surveillance programs that characterize spatial and temporal patterns to best target interventions and resources. The easiest and best way to avoid acquisition of WNV is to prevent mosquito bites. Prevention guidelines include the following:29

1. When outdoors, wear long sleeved shirts and pants or long skirts.
2. Wear a hat with a shade over the brow.
3. Spray skin and clothing with insect repellent.
4. Restrict outdoor activity at dawn, dusk and during the evening.
5. Use nets to cover babies in strollers.
6. Remove all pools of standing and stagnant water.
7. Keep storm drains free of debris.
8. Drill holes in the bottom of garbage containers to avoid accumulation of rain water.
9. Chlorinate swimming pools.
10. Maintain the integrity of window and door screens.

There is no evidence that WNV is transmitted from infected live or dead birds. Carcasses should be carefully removed and disposed into double plastic bags in accordance with local protocols. Infection in domestic animals is low and there is no evidence linking transmission of WNV by dogs and cats (although the virus was identified in one dead cat in New York). The disease is not spread from one animal to another, or from one person to another. While cats or dogs could conceivably become contaminated by eating carcasses of infected birds, such a sequence has not been identified. Infected animals are likely to have a full recovery. Horses vaccinated against eastern equine encephalitis, western equine encephalitis, and Venezuelan equine encephalitis are not protected against WNV infection. The extent to which duck and other wild game are susceptible to WNV infection is unknown but surveillance studies continue in collaboration with the US Geological Survey National Wildlife Center, Madison, Wisconsin.

In conjunction with active surveillance, insecticide spraying programs have been established in affected areas. The spraying agent, Malathion®, was first used but was found to induce respiratory difficulties in susceptible individuals. In 2000, a safer synthetic neurotoxin, Anvil®, was employed. Daily schedules of spraying times and areas are circulated to allow the public the opportunity to stay indoors.

Several visual, thermal and olfactory factors stimulate the attraction of mosquitoes to a host. Daytime feeding insects are oriented to the host by dark colored clothing. Such visual stimuli enable flight orientation, especially at far distances. Byproducts of human metabolism (over 100 volatile substances) are present in human breath, with carbon dioxide and lactic acid being most attractive to mosquitoes. Carbon dioxide can be detected by mosquitoes at up to 100 feet. Other chemoattractants include volatile compounds derived from sebum, eccrine and apocrine sweat and the cutaneous microfloral actions on these secretions. Floral fragrances, perfumes, soaps, lotions and shampoos also can increase the likelihood of being bitten. Skin temperature and moisture are also attractive. Propensity to bite around the head or feet may be due to local temperature and eccrine sweat gland output. Mosquitoes are generally not attracted to anhydrotic individuals.
There seems also to be a gender and age preference with men bitten more frequently than women, adults more than children (except for the very old), and larger people more often than thinner ones (perhaps because of greater relative heat and carbon dioxide production).

**Insect Repellents**

**Chemical Repellents**

A single bite from an infected insect can result in disease transmission; therefore, it is essential to know which repellent products can be relied on to provide predictable and prolonged protection. DEET-based (N,N-diethyl-m-toluamide) repellents were historically the gold standard of protection. DEET was developed in the 1930s by the U.S. Department of Agriculture and registered for use by the general public in 1957. Over 200 million persons now use DEET-containing repellents annually worldwide. In the past 45 years, people have applied DEET more than 10 billion times. The CDC recommends DEET, picaridin, and PMD (p-menthane 3,8-diol - oil of lemon eucalyptus extract) to protect against West Nile virus. DEET remains the most effective. The CDC and WHO recommends DEET repellents in concentrations ≥ 30% and picaridin in concentrations of 20% for travelers going to malaria endemic areas.

Repellents have marked species variation and consist solely of topical preparations that may have adverse effects such as skin irritation. Effective repellents have appropriate volatility and maintain an effective vapor concentration on the skin without evaporating too quickly. Factors that contribute to the effectiveness of repellents include the frequency and uniformity of application, organism susceptibility, and the host’s activity and level of attractiveness to the biting insect. Repellents all become less effective in the rain, as the individual sweats, as the environmental temperature rises, and as wind increases. Higher concentrations of DEET provide longer-lasting protection, but as the concentration of applied DEET climbs above 50%, each incremental increase provides relatively less additional protection. Extended-release formulations, however, have made it possible to reduce the concentration of DEET without sacrificing duration of action. DEET is most effective against mosquitoes and ticks, less so against gnats, black flies, biting flies, fleas, and mites. It has no effect against bees and wasps.

Until recently, non-DEET repellents did not provide protection for durations similar to those of DEET-based repellents. Nearly 100% protection can be achieved when longer-duration repellents are used in combination with permethrin-treated clothing. Permethrin is an insecticide that is chemically related to natural pyrethrum. It kills mosquitoes and ticks, but is nontoxic for human use. The unfounded fear of “DEET toxicity” prevents many people from using repellents properly. DEET may have more side effects (such as skin irritation) than non-DEET repellents. Low-concentration (5% to 15%) DEET, picaridin, and biological repellents are acceptable for preventing nuisance bites. The American Academy of Pediatrics has recommended that repellents used for children contain not more than 10% DEET.

**Plant Derived Repellents**

Long before the advent of synthetic chemicals, people used plant-derived substances to repel mosquitoes. Most plant-based insect repellents currently on the market contain essential oils from one of the following plants: citronella, cedar, lemon eucalyptus, peppermint, lemon grass, geranium, and soybeans. Citronella is the most common botanical oil found in natural repellents. When compared
with DEET, however, citronella and most other essential oils give only short-lasting protection, lasting anywhere from minutes to less than 2 hours. Exceptions are the soybean oil-based and lemon eucalyptus repellents which give 90 to 120 minutes of protection. Note: Although it is "natural," p-menthane-3, 8-diol (PMD, above) is now prepared synthetically.32

Consumers perceive natural repellents as a safer alternative to chemical repellents, despite DEET’s safety and effectiveness. Others reasons cited include a dislike of the odor and DEET’S adverse effects on synthetic fabrics and plastics. The true safety profile of natural repellents has yet to be determined. Plant-derived repellents are not inherently safe. Citronella, for example, caused the death of a 21-month-old child after ingestion of only one ounce of the oil. Drinking eucalyptus oil has also caused poisonings and fatalities.

Electronic Devices

Ultrasonic, handheld devices that are advertised to emit sounds that repel mosquitoes are not effective. Similarly, larger devices that are hung in gardens and back yards (bug zappers) to attract and electrocute insects are ineffective against mosquitoes.33,34 Of the insects killed by these instruments, only about 0.1% are female mosquitoes. Many beneficial insects are killed by such devices.

Management of the Case

Supplemental oxygen at 2 liters was provided and the patient was obtunded. The anesthesiologist gave midazolam 2 mg in divided doses to control the patient’s tremors. Mask ventilation was initiated the administration of propofol 30 mg and rocuronium 30 mg. She was admitted to the intensive care unit. Electrolyte evaluation showed severe hyponatremia (119mEq/l), hyperkalemia (6.8mEq/L), BUN of 80mg/dl and creatinine of 3.8 mg/dl. She was hydrated with several liters of Plasmalyte® solution. She was found to be febrile and a cooling blanket was applied. Sedation was maintained with small amounts of midazolam (0.5mg/hour). MRI indicated increased intracranial pressure which was initially managed with diuretics and appropriate ventilation. However, as ICP increased, a hemicraniectomy was performed. A bispectral analysis (BIS®) monitor was used. Renal function deteriorated further and the patient was dialyzed. After 14 days, the patient showed some improvement in cerebral function. All sedation was discontinued and after 4 hours, and the BIS® reading was 95. The patient became increasingly responsive and proceeded to be extubated. Although she made substantial recovery over the next 5 weeks, weakness persisted in all extremities and renal function remained impaired.

Summary

Physicians should consider West Nile virus infection when evaluating febrile patients who have unexplained neurologic symptoms, muscle weakness, or erythematous rash occurring during late spring through early fall, or throughout the year in warm climates. West Nile virus infection has no characteristic findings on routine laboratory tests, although anemia, leukocytosis, or lymphopenia may be present. Testing for IgM antibody to West Nile virus in serum or cerebrospinal fluid (samples from the acute and convalescent phases, submitted at least two weeks apart) is the most common diagnostic method.
References

POST-TEST

1. **Infection with WNV was first recognized:**
   a. In the Nile valley of ancient Egypt
   b. After isolation in the US in 1999
   c. Following an outbreak in Romania in 1996
   d. From a single case in Uganda in 1937

2. **A true statement about WNV:**
   a. It is a zoonotic flavivirus
   b. Humans are the primary vertebrate reservoir
   c. It affects all birds equally
   d. Infection in humans most often results in neuroinvasive disease

3. **Regarding mosquitoes:**
   a. They do not live in salt water
   b. Approximately 170 species have been identified in North America.
   c. The Culex species transmits WNV but does not survive winter months.
   d. There are 6 stages to their life cycle

4. **The most effective mosquito repellents are:**
   a. DEET-based sprays
   b. Citronella candles
   c. Cedar chips
   d. Bug zappers

5. **Vaccination of horses will not protect against:**
   a. Western equine encephalitis
   b. Eastern equine encephalitis
   c. Venezuelan equine encephalitis
   d. West Nile virus infection
6. **Factors that increase the likelihood of being bitten by a mosquito include:**
   
a. Wearing white clothing during the day
b. BMI of 20
c. Using floral fragrances
d. Female gender

7. **Anesthetic consideration in the care of patients with neuroinvasive disease requires:**
   
a. Correction of hyponatremia
b. Recognition of possible long term renal impairment
c. Identification and treatment of increased intracranial pressure
d. All of the above

8. **The life cycle of WNV is best described:**
   
a. Mosquitoes acquire the virus initially from infected birds and then inject it into humans which are an integral part of the life cycle.
b. Infected mosquitoes inject the virus to susceptible host birds. Other mosquitoes then feed on the reservoir bird, become infected and transmit the virus to humans.
c. An incubation period for the virus is necessary in the salivary glands of the mosquito of 2-5 days before it can by injected into humans.
d. Incubation within horses is necessary for long term survival of the virus.

9. **Human infection with WNV:**
   
a. May be contracted from domestic animals
b. Usually occurs in late September
c. Causes only mild symptoms in the vast majority of people
d. Results in death in 75% of cases

10. **Regarding treatment of severe WNV infection:**
    
a. Treatment is mostly supportive
b. Gamma interferon may have an early antiviral role
c. Neurologic impairment may be permanent
d. All of the above