# CONSIDERATIONS CONCERNING THE WEST NILE VIRUS INFECTION

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***Abstract***

*The West Nile virus (WNV) is closely related to the Japanese encephalitis virus and the St. Louis encephalitis virus, which are found in the southeastern and Midwestern United States. These viruses are also mosquito-borne and have a similar life cycle in birds and mosquitoes and occasionally strike people. WNV is an RNA virus belonging to the genus Flavivirus within the family Flaviviridae. Sporadic cases and outbreaks of human and equine diseases were founded in the last years in US, Europe and in Romania. In 2010 41 patients with WNV infection were reported in Romania, with 2 lethal cases. The counties in which the infections developed were: Alba, Buzău, Cluj, Dolj, Galaţi, Ialomiţa, Mureş, Teleorman and Bucharest. In Romania there are different species of mosquitoes, but only Culex pipiens has been demonstrated to be vector for WNV. The best way to prevent West Nile virus infection is to avoid mosquito bites. Community spraying for mosquitoes may also prevent mosquito breeding. Testing of donated blood and organs is currently being evaluated.*

**Key words***: WNV, encephalitis, mosquito, Culex pipiens.*

## INTRODUCTION

### *BACKGROUND*

West Nile virus (WNV) was first identified in 1937 in Uganda in eastern Africa. The virus is commonly found in Africa, West Asia, and the Middle East. West Nile virus had not been previously reported in the U.S. prior to an outbreak in New York in September 1999. According to the U.S. Centers for Disease Control and Prevention (CDC), 48,961 confirmed and probable cases of West Nile virus disease were reported from 1999 to 2009. In Europe sporadic cases and outbreaks of human and equine diseases were founded in Russia (1962-1964), Belarus (1970), Ukraine (1980), Romania (1996-1997), Czech Republic (1997) and Italy (1998). The infection with WNV is transmitted from animals to humans by vectors (mosquitoes), and is manifested through fever, general signs of infection and nervous system inflammation, sometimes lethal.

## MATERIALS AN METHODS

### *ETIOLOGY AND EPIDEMIOLOGY*

The West Nile virus is an RNA virus. Image reconstructions and cryoelectron microscopy reveal a 45–50 nm virion covered with a relatively smooth protein surface. This structure is similar to the dengue fever virus;

both belong to the genus Flavivirus within the family Flaviviridae. The family contains 70 members, most of which are transmitted by mosquitoes and ticks. The genetic material of WNV is a positive-sense, single strand of RNA, which is between 11,000 and 12,000 nucleotides long; these genes encode seven non-structural proteins and three structural proteins. The RNA strand is held within a nucleocapsid formed from 12 kDa protein blocks; the capsid is contained within a host-derived membrane altered by two viral glycoproteins.

To date, the West Nile virus has been commonly found in humans, birds, and other vertebrate animals in Africa, Eastern Europe, West Asia, and the Middle East. Prior to 1999, the West Nile virus had not been recognized in the Western Hemisphere. The risk of infection is highest during mosquito season and does not lower until mosquito activity ceases for the season (when freezing temperatures occur). In temperate areas of the world, cases of West Nile virus infection occur primarily in the late summer or early fall. In southern climates where temperatures are milder, West Nile virus infections can occur year round.

The mosquito' species identified by epidemiologists as part of the "triad of the most important disease vectors" are Culex pipiens, involved in the transmission of the infection with WNV, Anopheles gambiae (which transmits malaria) and Aedes aegypti (transmitting yellow fever virus and dengue virus). Mosquito (from the Spanish or Portuguese meaning "little fly" is a common insect in the family Culicidae (from the Latin "culex" meaning midge or gnat. There are about 3,500 species of mosquitoes found throughout the world.

Culex pipiens quinquefasciatus is the most widely distributed mosquito in the world, and in terms of disease transmission to humans it's one of the three most important mosquito species. Although 43 different species of mosquitoes can carry the WNV, Culex species are the primary carrier of the virus. Cx. restuans and 93% of Cx. pipiens acquired blood from avian hosts; Cx. salinarius fed frequently on both mammals (53%) and birds (36%). Mixed-blood meals were detected in 11% and 4% of Cx. salinarius and Cx. pipiens, respectively.

American robin (Turdus migratorius) was the most common source of vertebrate blood for Cx. pipiens (38%) and Cx. restuans (37%). Crows represented <1% of the blood meals in Cx. pipiens and none in Cx. restuans. Human-derived blood meals were identified from 2 Cx. salinarius and 1 Cx. pipiens. Results suggest that Cx. salinarius is an important bridge vector to humans, while Cx. pipiens and Cx. restuans are more efficient enzootic vectors in the northeastern United States. The infected mosquito species vary according to geographical area; in the US Culex pipiens (Eastern US

and Europe), Culex tarsalis (Midwest and West US and Africa), and Culex quinquefasciatus (widely distribution in the world) are the main sources.

The mammals (horses, dogs, cats, bats, chipmunks, skunks, squirrels, and domestic rabbits) and the birds represent the reservoir of the WNV. In mammals the virus does not multiply as readily (i.e. does not develop high viremia during infection), and it is believed that mosquitoes biting infected mammals do not ingest sufficient virus to become infected, making mammals so-called dead-end infections.

People get WNV from the bite of a mosquito that is infected with the virus. Mosquitoes become infected by feeding on birds that are infected with the virus. The infected birds may or may not become ill. The birds are vectors, or intermediate carriers, of the virus, that is important for the virus' life cycle and transmission cycle. The infected mosquitoes then transmit the virus when they bite and suck blood from people and animals and, in the process, inject the virus into their victim. Mosquitoes carry the highest amounts of virus in the early fall, which is why the rate of the disease increases in late August to early September. The risk of disease decreases as the weather becomes colder and mosquitoes die off.

Among birds, crows (Corvus spp.) are most vulnerable to infection by the WNV. They are often killed by the virus. Although 17 species of birds have been found to be infected by the virus, the common dust-colored house sparrow (Passer domesticus) is probably a principal bird reservoir for the virus in New York. Sparrows can harbor the virus for five days or more at levels high enough to infect mosquitoes that bite them.

Although many people are bitten by mosquitoes that carry WNV, most do not know they've been exposed. Few people develop severe disease or even notice any symptoms at all. It is important to note that the West Nile virus is not contagious. It cannot be transmitted from person to person. A person cannot get the virus, for example, from touching or kissing a person who has the disease or from a health-care worker who has treated someone with the disease. Some studies reveal that WNV may be spread through blood transfusions and organ transplants. It is possible for an infected mother to spread the virus to her child through breast milk.

Humans are called a dead-end host for the virus, meaning one that can be infected but whose immune system usually prevents the virus from multiplying enough to be passed back to mosquitoes and then to other hosts. There also is no evidence that a person can get the virus from handling live or dead infected birds. However, avoiding skin contact when handling dead animals, including dead birds, is recommended. Gloves or double plastic bags should be used to remove and dispose of carcasses.

Ticks infected with the WNV have been found in Asia and Africa. Their role in the transmission and maintenance of the virus is uncertain.

However, ticks have not been associated in the transmission of the WNV in the New York outbreak from 1999.

In Romania there are different species of mosquitoes, as Culex theileri, Cx. torentium, Cx. hortensis, Cx. martinii, Cx. territans, Cx. lacticinctus. Only Culex pipiens has been demonstrated to be vector for WNV. Outbreaks of WNV infections in humans were described in 1996 and 1997, estimated at hundreds of cases, with 10% lethality. In 2010 41 patients with WNV infection were reported in Romania, with 2 lethal cases. The counties in which the infections developed were: Alba, Buzău, Cluj, Dolj, Galați, Ialomița, Mureş, Teleorman and Bucharest.

**PRELIMINARY RESULTS**

***CLINICAL ASPECTS***

The incubation period (the time from infection to the development of symptoms) is five to 15 days. In 41% of the cases, patients developed neuroinvasive disease (involvement of the brain and nervous system), the most severe form of WNV infection. Mild, flu-like illness is often called West Nile fever. More severe forms of disease, which can be life threatening, may be called West Nile encephalitis or West Nile meningitis, depending on what part of the body is affected. WNV is closely related to the Japanese encephalitis virus and the St. Louis encephalitis virus, which are found in the southeastern and Midwestern United States. These viruses are also mosquito-borne and have a similar life cycle in birds and mosquitoes and occasionally strike people.

A major difference is that St. Louis encephalitis is "silent" in birds, generally not killing them, so there is usually no warning before a human case occurs. With the West Nile virus (at least the American strain), birds, particularly crows, become ill or die and therefore offer an early warning system.

Risk factors for developing a more severe form of WNV infection include: conditions that weaken the immune system (such as HIV, organ transplants, and recent chemotherapy), older age, and pregnancy.

**Symptoms**

Mild disease, generally called West Nile fever, has some or all of the following symptoms: abdominal pain, back pain, diarrhea, fever, and headache, lack of appetite, muscle aches, nausea, sore throat and vomiting. These symptoms usually last for 3 - 6 days.

With more severe disease, the following symptoms can also occur: confusion or change in ability to think clearly, loss of consciousness, muscle weakness, and stiff neck.

***LABORATORY STUDIES***

- The complete blood count (CBC) may show elevated or normal leukocytes values.

- In cases of encephalitis, hyponatremia may be present. The complication of syndrome of inappropriate ADH (SIADH) secretion is a possibility.
- Cerebrospinal fluid (CSF) analysis may reveal elevated protein and increased leukocyte levels, with predominant lymphocytes. Glucose levels are usually normal rather than decreased.
- Serologic testing to detect immunoglobulin M (IgM) antibodies is currently the best means of diagnosing WNV infection by using serum or CSF samples. False-positive results may occur because of the close relationship of the WNV to other flaviviruses. In light of this limitation, the plaque reduction neutralization test (PRNT) may help to identify false-positive MAC-ELISA results caused by cross-reactions by other flaviviruses.

***IMAGING STUDIES***

- In acute disease, computed tomography (CT) scans do not show any evidence of abnormalities.
- In an estimated one third of infected individuals, magnetic resonance imaging (MRI) scans show notable enhancement in the leptomeninges and periventricular areas.

***HISTOLOGICAL FINDINGS***

Autopsy findings in some patients with WNV infection reveal mononuclear inflammation that extensively involves the medulla, with some involvement of the cranial nerve roots. However, these findings are not diagnostic for the infection. Preliminary diagnosis is often based on the patient's clinical features, places and dates of travel (if patient is from a non-endemic country or area), activities, and epidemiologic history of the location where infection occurred. Laboratory diagnosis of WNV infections is generally accomplished by testing of serum or cerebrospinal fluid (CSF) to detect virus-specific IgM and neutralizing antibodies.

In fatal cases, nucleic acid amplification, histopathology with immunohistochemistry and virus culture of autopsy tissues can also be useful. Only a few state laboratories or other specialized laboratories, including those at CDC, are capable of doing this specialized testing.

***MEDICATION***

Because this illness is not caused by bacteria, antibiotics do not help treat WNV infection. Standard hospital care may help decrease the risk of complications in severe illness. Research trials are under way to determine whether ribavirin, an antiviral drug used to treat hepatitis C, may be helpful.

Ongoing research is being pursued into the direct treatment of WNV meningoencephalitis with interferon alpha and intravenous immunoglobulin G. GenoMed, a U.S. biotech company has found that blocking angiotensin II can treat the "cytokine storm" of West Nile virus encephalitis as well as other viruses.

***PROGNOSIS AND COMPLICATIONS***

In general, the likely outcome of a mild WNV infection is excellent. For patients with severe cases of WNV infection, the outlook is more uncertain. West Nile encephalitis or meningitis may lead to brain damage and death. Approximately 10% of patients with brain inflammation do not survive. Complications from mild WNV infection are extremely rare. Complications from severe WNV infection include:

- Permanent brain damage
- Permanent muscle weakness (sometimes similar to polio)

Other complications are**:**

- Pressure ulcers. Pressure ulcers are caused by prolonged pressure, shear forces, friction, and maceration. Means of preventing this complication include close monitoring of potential ulcer sites, frequent repositioning to reduce pressure on vulnerable areas, ensuring that adequate nutrition is provided, and cleaning and drying sites of perspiration, urine, or feces. Once a pressure ulcer develops and progresses, more severe complications (e.g, wound infection, bacteriemia, and osteomyelitis) may enter the clinical picture.
- Deep venous thrombosis. Elderly patients who are severely deconditioned because of WNV encephalitis may be predisposed to deep venous thrombosis (DVT). The inherent risk of having DVT is the development of a pulmonary embolus that can cause death. Risk factors for DVT may include, among others, decreased mobilization, a history of smoking, and a history of premorbid medical conditions, such as coronary artery disease, diabetes mellitus, hypercoagulopathy, and peripheral vascular disease.
- Pulmonary complications. Individuals with severe illness secondary to WNV infection are at increased risk of pulmonary complications in the rehabilitation setting. Individuals with encephalitis may have a decreased level of consciousness, or they may suffer from dysphagia related to their neurologic injury, predisposing them to aspiration pneumonia. Swallow evaluation can be performed to identify the problem and to help in implementing the appropriate diet and feeding techniques to decrease the risk of aspiration. Phrenic nerve palsy has been described. This complication could lead to decreased expansion of the lungs, further increasing the risk of atelectasis and nosocomial pneumonia.

## CONCLUSIONS

### *REHABILITATION PROGRAM*

The program of rehabilitation consists in physical therapy, occupational therapy and speech therapy. Brain injury from WNV encephalitis or meningitis can result in cognitive, gross motor, and fine motor delays. Because infected patients have varying degrees of functional deficits, treatment programs must be individualized. Comprehensive rehabilitation using a team consisting of a physiatrist, nurse, physical therapist, occupational therapist, speech therapist, social worker/case manager, and neurophysiologist achieves best outcomes.

The physical therapist can partially address the problems of increased muscle tone, weakness, decreased sensation, and poor endurance. Mobility training, transfer training, and gait training are usually implemented, with range of motion and proper positioning attended to as well. Physical therapists are also important in providing exercises for muscle reeducation and for the improvement of strength, endurance, coordination, and balance, with the goal of returning the patient to independent function.

Occupational therapy focuses on the activities of daily living, including bathing, dressing, feeding, and hygiene maintenance. Occupational therapists provide a program to maximize the use of the arms and hands with functional activities; they also address the cognitive issues that affect daily independent function.

Patients may develop dysarthria, dysphagia, or aphasia. A structured speech therapy program may improve their ability to swallow, help them recover speech and language function, and prevent complications, such as aspiration pneumonia.

### *PREVENTION*

The best way to prevent West Nile virus infection is to avoid mosquito bites. Community spraying for mosquitoes may also prevent mosquito breeding. Testing of donated blood and organs is currently being evaluated. There are currently guidelines.

## REFERENCES


1. Tsai TF, Popovici F, Cernescu C, Campbell GL, Nedelcu NI (1998). West Nile encephalitis epidemic in southeastern Romania. Lancet 352 (9130): 767–71.
2. Sejvar JJ, Haddad MB, Tierney BC, et al. (2003). Neurologic manifestations and outcome of West Nile virus infection. JAMA 290 (4): 511–5.
3. Tsai TF, Vaughn DW, Solomon T. (2005). Flaviviruses (yellow fever, dengue, dengue hemorrhagic fever, Japanese encephalitis, West Nile encephalitis, St. Louis encephalitis, tick-borne encephalitis). In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, Pa: Elsevier Churchill Livingstone;chap 149.

4. Bleck TP. (2007). Arthropod-borne viruses affecting the central nervous system. In: Goldman L, Ausiello D, eds. *Cecil Medicine*. 23rd ed. Philadelphia, Pa: Saunders Elsevier;chap 406.
5. Hayes EB, Komar N, Nasci RS, Montgomery SP, O'Leary DR, Campbell GL (2005). Epidemiology and transmission dynamics of West Nile virus disease. Emerging Infect. Dis. 11 (8): 1167–73.
6. Taylor RM, Hurlbut HS, Dressler HR, Spangler EW, Thrasher D, Fonseca DM, et al. (2004). Emerging vectors in the Culex pipiens complex. Science 303 (5663): 1535–8.
7. Spielman A, et al. (2004). Outbreak of West Nile Virus in North America. Science 306 (5701): 1473–5.
8. Centers for Disease Control and Prevention (CDC) (2002). Intrauterine West Nile virus infection - New York, 2002. MMWR Morb. Mortal. Wkly. Rep. 51 (50): 1135–6.
9. Schneider BS, Soong L, Girard YA, Campbell G, Mason P, Higgs S (2006). Potentiation of West Nile encephalitis by mosquito feeding. Viral Immunol. 19 (1): 74–82.
10. Hayes EB, Gubler DJ (2006). West Nile virus: epidemiology and clinical features of an emerging epidemic in the United States. Annu. Rev. Med. 57: 181–94.
11. Deas, Tia S; Bennett CJ, Jones SA, Tilgner M, Ren P, Behr MJ, Stein DA, Iversen PL, Kramer LD, Bernard KA, Shi PY (2007). In vitro resistance selection and in vivo efficacy of morpholino oligomers against West Nile virus. Antimicrob Agents Chemother 51 (7): 2470.
12. Hayes EB, Sejvar JJ, Zaki SR, Lanciotti RS, Bode AV, Campbell GL (2005). Virology, pathology, and clinical manifestations of West Nile virus disease. Emerging Infect. Dis. 11 (8): 1174–9.