

Clinical manifestations, diagnosis, and treatment of West Nile virus infection

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INTRODUCTION — West Nile virus infection can lead to a wide range of clinical symptoms from asymptomatic disease to severe meningitis and encephalitis.

The clinical manifestations, diagnosis, and treatment of West Nile virus are discussed below. The epidemiology and pathogenesis of this infection is discussed elsewhere. ([See "Epidemiology and pathogenesis of West Nile virus infection"](#)).

CLINICAL MANIFESTATIONS — Most persons infected with the WN virus are asymptomatic, as symptoms are seen in only about 20 percent of infected patients. The typical incubation period for infection ranges from 2 to 14 days, although longer incubation periods have been observed among immunosuppressed hosts [1].

West Nile fever — The usual presentation is a self-limited febrile illness, called West Nile fever, which is indistinguishable from dengue fever and other viral grippes. The illness is characterized by fever, headache, malaise, back pain, myalgias, and anorexia persisting for three to six days. Eye pain, pharyngitis, nausea, vomiting, diarrhea, and abdominal pain can also occur.

Data from the 2002 outbreak in the United States suggested that rash appears in approximately one-half the patients with WN fever [2], which may be more frequent than with neuroinvasive disease [3]. The rash is typically maculopapular, involves the chest, back and arms, and generally lasts for less than one week ([show picture 1](#)). The rash is sometimes accompanied by complaints of dysesthesia and pruritis [4]. Generalized lymphadenopathy, although commonly reported in previous outbreaks, is rare in contemporary outbreaks.

Acute symptoms typically last three to ten days, but may have a more prolonged course as was demonstrated in a study of 98 patients with a diagnosis of WN virus [2]. Illustrated below are the common presenting clinical manifestations in this cohort with the median duration of symptoms:

Fatigue (96 percent; 36 days)

Fever (81 percent; five days)

Headache (71 percent; ten days)

Muscle weakness (61 percent; 28 days)

Difficulty concentrating (53 percent; 14 days)

Hospitalization was required in 30 patients for a median of five days; 79 percent missed work or school for a median of 10 days. At 30 days, 63 percent were symptomatic.

Neuroinvasive disease — WN virus infection can present as encephalitis, meningitis, or flaccid paralysis.

Encephalitis or meningoencephalitis are more common than meningitis in contemporary outbreaks [5-9]. Older age, alcohol abuse, and diabetes was associated with West Nile encephalitis in a retrospective study of 221 patients with West Nile virus infection, 65 of whom presented with encephalitis [10]. Encephalitis that is associated with muscle weakness and flaccid paralysis is particularly suggestive of WN virus infection [9]. Fever is present in at least 90 percent, with weakness, nausea, vomiting, and headache in approximately one-half of

patients. Other neurologic manifestations include tremor, myoclonus, and parkinsonian features such as rigidity, postural instability, and bradykinesia [11,12].

WN virus infection can also cause an acute flaccid paralysis syndrome. Paralysis from WN virus poliomyelitis is asymmetric and can occur without overt meningitis or encephalitis [12,13]. Although Guillain-Barré syndrome can occur [14,15], most paralysis results from an anterior horn cell process suggestive of poliomyelitis [12,13,16-20].

Cranial nerve abnormalities also may occur [11]. Facial paralysis appears to have favorable prognosis [CDC, unpublished data]. Dysarthria and dysphagia accompanied by acute flaccid paralysis indicates a high risk of impending respiratory failure [13]. Other neurologic complications with WN virus can include seizures [11], cerebellar ataxia [15], and optic neuritis [19].

WN virus infection infrequently causes other forms of weakness, including brachial plexopathy [13,21], radiculopathy, and a predominantly demyelinating peripheral neuropathy similar to Guillain-Barré syndrome [22,23]. (See "[Guillain-Barré syndrome in adults](#)").

It is imperative that appropriate diagnostic testing, including lumbar puncture, electromyography, and nerve conduction studies, be obtained before initiating therapies for Guillain-Barré syndrome or other inflammatory neuropathies. (See "[Diagnosis](#)" below).

Other clinical features — Ocular manifestations, including chorioretinitis and vitritis, are commonly reported [24-28]. The chorioretinal lesions are multifocal with a "target-like" appearance. A prospective study of patients presenting to a hospital with WN virus infection in Tunisia found that 80 percent had multifocal chorioretinitis with mild vitreous inflammatory reaction [27]. Most patients were asymptomatic and symptoms were self-limited. Other reported ocular findings include iridocyclitis [25], occlusive vasculitis [29], and uveitis [30].

WN virus infection has been associated with many other less commonly reported complications including [18,31-38]:

- Rhabdomyolysis

- Myocarditis, which has been seen pathologically, but clinical correlation with cardiac dysfunction in humans has not been conclusively demonstrated.

- Hepatitis and pancreatitis

- Central diabetes insipidus

Laboratory findings — Total leukocyte counts in peripheral blood are mostly normal or elevated. In cases with signs of CNS involvement, the cerebrospinal fluid (CSF) usually demonstrates a pleocytosis often with a predominance of lymphocytes as well as an elevated protein concentration.

In a study of CSF samples from 334 patients with WN virus infection, the key findings were a CSF pleocytosis with increased protein and normal glucose [39]. The mean CSF nucleated cell count was similar for patients with meningitis and patients with encephalitis (226 and 227 per mm³, respectively). A neutrophilic predominance was present in a large proportion of patients with meningitis and patients with encephalitis (45 and 37 percent respectively). A small percentage of patients with meningitis and patients with encephalitis had normal (<5 per mm³) CSF cell counts (three and five percent, respectively).

Imaging — Computed tomography (CT) of the brain typically shows no evidence of acute disease [5,40-42]. In approximately one-third of patients who have mental status changes due to WN virus infection, magnetic resonance (MR) imaging shows enhancement of the leptomeninges, the periventricular areas, or both. Hyperintensity on T2-weighted MR images may be seen in regions such as the basal ganglia, thalami, caudate nuclei, brainstem, and spinal cord [1,6,43,44]. An initially normal MR can evolve to show evidence of deep gray matter involvement [43].

Electroencephalography — Electroencephalography (EEG) in patients with meningitis or encephalitis typically shows generalized, continuous slowing, which is more prominent in the frontal or temporal regions [45]. Patients with acute flaccid paralysis have electrodiagnostic studies showing normal sensory nerve action potentials (SNAPs) with compound motor action potentials (CMAPs) varying between normal and markedly decreased, depending on the degree of paralysis [17].

DIAGNOSIS — WN virus should be strongly considered in patients who have the onset of unexplained febrile illness, encephalitis and/or meningitis, or flaccid paralysis during mosquito season. Evidence of WN virus enzootic activity or other human cases, either locally or in a region where the patient has traveled, should raise the index of suspicion. Year-round transmission is possible in temperate climates.

In patients who present with a syndrome compatible with WN fever, we recommend serologic testing with EIA for the detection of IgM antibody to WN virus. A positive test in a patient with suggestive clinical features of the disease has a high predictive value for the diagnosis of WN virus infection, although false positive tests can occur. A negative test, however, does not rule out infection. ([See "Serologic testing" below](#)).

In patients who present with suspected meningitis, encephalitis, or acute flaccid paralysis, we recommend a lumbar puncture and testing of the CSF for detection of IgM antibody as well as serologic testing. Use of nucleic acid testing (NAT) in serum or CSF may be valuable in severely immunocompromised patients, who may have absent IgM antibody. ([See "Serologic testing" below](#) and [see "Viral isolation or nucleic acid testing" below](#)).

Serologic testing — The IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) is optimal for IgM detection because it is simple, sensitive, and applicable to serum and CSF samples. Testing of serum or CSF is available commercially, and also can be obtained through local or state health departments.

The timing of the IgM antibody response in patients with WN fever has not been completely determined. Among the 1999 and 2000 New York City patients for whom a CSF sample was available, 95 percent had demonstrable IgM antibody (90 percent within eight days of symptom onset) [46]. However, limited data suggest that many patients with West Nile fever do not have demonstrable antibody upon clinical presentation and can only be documented to have WN virus infection after convalescent-phase samples were obtained [4,47]. A rise in WN virus-specific neutralizing antibody titer in acute and convalescent sera is confirmatory of acute infection.

Clinicians should also bear in mind that IgM antibody to WN virus may persist for six months or longer. Since most infected persons are asymptomatic, residents in endemic areas may have detectable IgM antibody from previous WN virus infection that is unrelated to their current clinical illness [48].

False positive ELISA — False positive ELISA testing can occur due to recent immunization with particular vaccines (yellow fever or Japanese encephalitis) or due to infections with other related flaviviruses (eg, St. Louis encephalitis, dengue) [49]. The plaque reduction neutralization test (PRNT), the most specific test for the arthropod-borne flaviviruses, can help distinguish false positive results of MAC-ELISA or other assays (eg, indirect immunofluorescence, hemagglutination inhibition). The PRNT may also help distinguish serologic cross-reactions among the flaviviruses, although some degree of cross-reaction in neutralizing antibody may still cause ambiguous results.

Viral isolation or nucleic acid testing — It is also possible to isolate WN virus or to detect viral antigen or nucleic acid in CSF, tissue, blood, or other body fluids, although the low sensitivities of these methods preclude their use as routine screening tests. Viral culture of CSF or brain tissue in humans has had very low yield among patients in the United States; nucleic acid amplification testing such as real-time PCR has been positive in up to 55 percent of CSF samples and 10 percent of serum samples [46].

Nucleic acid test (NAT) screening of blood donors using newly developed investigational screening assays was introduced in 2003 [50]. In one study, the analytical sensitivity of this approach was effective in testing of individual samples, but was compromised by the use of minipool donations, particularly in the setting of low-level viremia [51]. In contrast, the false positivity and unit discard rate for blood donations screened by individual NAT was higher than for minipool screening [52]. (See "[Laboratory testing of donated blood](#)", section on West Nile virus).

DIFFERENTIAL DIAGNOSIS — The differential diagnosis in patients with a non-specific febrile illness is extensive and includes other viral infections, such as dengue viral infection in the appropriate endemic areas. The differential diagnosis in patients with central nervous system involvement include other arthropod-borne illnesses, such as St. Louis encephalitis, and other causes of encephalitis, such as herpes simplex virus type 1. (See "[St. Louis encephalitis](#)" and see "[Clinical presentation and diagnosis of dengue virus infections](#)" and see "[Epidemiology of dengue virus infections](#)" and see "[Herpes simplex virus type 1 encephalitis](#)").

TREATMENT — Treatment of WN virus infection is supportive. Controlled studies to evaluate specific therapies for WN virus infection have not been completed. Uncontrolled studies or case reports suggesting treatment efficacy should be cautiously interpreted, since the clinical course and outcomes with WN virus neuroinvasive disease are highly variable [12,53].

Interferon — The rationale for the use of alfa interferon is based upon evidence of efficacy against WN virus in vitro and in animal models [54-56].

Two patients with serologic confirmation of WN virus infection, who presented with deteriorating mental status and progression to coma, were treated with standard [interferon alfa 2b](#) within 72 hours of presentation [57]. Rapid neurologic improvement was demonstrated in both patients within 48 hours of initiation of therapy. It remains unclear if the change in clinical status was due to interferon or to spontaneous improvement, which has been documented in untreated WN virus infection [12]. In addition, two patients receiving interferon alfa 2b and [ribavirin](#) for hepatitis C infection developed WN fever after mosquito exposure [58].

Ribavirin — The antiviral agent [ribavirin](#) has demonstrated in vitro activity against WN virus, but therapeutic efficacy has not yet been demonstrated in animal models. Ribavirin increased mortality in Syrian golden hamsters when administered two days after inoculation [55].

During an outbreak in Israel, [ribavirin](#) was used in an uncontrolled, non-blinded fashion in some patients with WN virus neuroinvasive disease [59]. Ribavirin appeared to be ineffective and possibly detrimental.

Clinical trials in progress — The following randomized, double-blind, placebo-controlled trials are currently underway for the treatment of acute WN virus infection:

A phase I/II randomized, placebo-controlled trial to assess the safety and efficacy of intravenous immunoglobulin G (Omr-IgG-am) containing high anti-West Nile virus antibody titers in patients with, or at high risk for progression to West Nile virus (WNV) encephalitis and/or myelitis. Sponsored by: National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health.

Contact: Walla Dempsey, Tel. (301) 496-7453, e-mail: wdempsey@niaid.nih.gov

Website: www.clinicaltrials.gov/show/NCT00068055

A randomized double-blinded, placebo-controlled trial of alpha-interferon (Alferon) therapy for West Nile meningoencephalitis (Protocol WN-102).

Contact: James J. Rahal, MD, Tel. (718)-670-1525, email: JJR9002@nyp.org

Website: www.nyhq.org/posting/rahal.html

An exploratory study of the safety, tolerability, pharmacokinetics and potential effectiveness of AVI-4020 injection in patients presenting with presumptive acute neuroinvasive West Nile virus (WNV) disease.

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Website: www.clinicaltrials.gov/ct/show/NCT00091845

PROGNOSIS — Serious adverse outcomes are limited to the patients who develop neuroinvasive disease [9]. Older age is the most important predictor of neuroinvasive disease [7,9]. Increased severity of neuroinvasive disease may also be seen in immunosuppressed patients, such as solid organ transplant recipients [13,60,61].

In a review of almost 3000 patients with neuroinvasive disease in the United States in 2002, the case fatality rate was 2 percent in patients with meningitis and 12 percent in patients with encephalitis, with or without meningitis [62]. The median age of patients with encephalitis was higher than that in patients with meningitis (64 versus 46 years). Mortality was significantly associated with advanced age. Severe muscle weakness and a deterioration in the level of consciousness among patients with encephalitis are risk factors for death.

Data are limited on the long-term prognosis of patients with neuroinvasive WN virus infection [12,63]. One study evaluated self-perceived health outcomes among 40 New York City residents who developed meningitis or encephalitis during the 1999 WN virus epidemic and survived [63]. At twelve months, only 37 percent achieved a full recovery, which was most likely to occur in patients less than 65 years of age. Long-term neurologic sequelae included muscle weakness, loss of concentration, confusion, and light-headedness. These sequelae were still present in many patients at 18 months. These outcomes are similar to those seen with St Louis encephalitis. (See ["St. Louis encephalitis"](#)).

The long-term functional outcome of patients with WN virus poliomyelitis has not been fully characterized. Preliminary data indicate most patients have incomplete recovery of limb strength resulting in profound residual deficits [12,13,64,65]. Quadriplegia and respiratory failure are

associated with high morbidity and mortality, and recovery is slow and invariably incomplete [66].

INFECTION DURING PREGNANCY — A causal relationship between WN virus and fetal abnormalities has not been proven. In 2002, there was a single report of a woman who had WN virus encephalitis during the 27th week of her pregnancy and subsequently delivered a term infant with chorioretinitis and laboratory evidence of congenitally acquired WN virus infection [67].

To determine the frequency of West Nile virus infections during pregnancy, specific West Nile antibodies were measured in cord blood from 549 infants after a community-wide epidemic of disease [68]. Newborn growth parameters, Apgar scores, and hearing test results were recorded and demographic data were collected from the pregnant women through self-administered questionnaires. Four percent of cord blood samples tested positive for West Nile virus-specific IgG antibodies, but none were positive for IgM antibodies. There were no significant differences between infants of seropositive and seronegative mothers with respect to birth outcomes.

The Centers for Disease Control (CDC) also established a registry to track these pregnancies [69]. During 2003 and 2004, 77 women infected with West Nile virus during pregnancy were followed in 16 states [70]. A total of 71 women delivered 72 live infants; 4 women had miscarriages and two had elective abortions. Of 72 infants followed to date, none had conclusive laboratory evidence of congenital West Nile virus infection. Seven infants had major malformations, but four of these were unlikely to be related to West Nile virus based on the timing of the infections. However, it was concluded that the possibility of congenital infection among newborns with negative serology cannot be ruled out due to the unknown sensitivity of IgM in this clinical setting.

The CDC has made the following recommendations [67,71]:

Pregnant women should take precautions to protect themselves from bites from potentially infected mosquitoes (eg, avoid being outdoors at dawn and dusk, wear protective clothing, use insect repellants containing DEET). (See "[Insect bites](#)", section on Pregnancy).

Pregnant women with meningitis, encephalitis, acute flaccid paralysis, or unexplained fever in an area of ongoing WN virus transmission should have serum tested for antibody to WN virus. If laboratory tests indicate recent infection with WN virus, the infection should be reported to the local or state health department, and the woman should be followed to determine the outcome of her pregnancy.

If WN virus infection is diagnosed in pregnancy, care is supportive. An ultrasound examination of the fetus to screen for abnormalities should be considered no sooner than two to four weeks after onset of symptoms.

Amniotic fluid, chorionic villi, or fetal serum can be tested for evidence of WN virus infection. However, the sensitivity, specificity, and predictive value of these tests to evaluate fetal WN virus infection are not known, and the clinical consequences of fetal infection have not been determined. In cases of spontaneous or induced abortion, testing of all products of conception for evidence of WN virus infection is advised to document the effects of WN virus infection on pregnancy outcome.

Screening asymptomatic women for WN virus infection is not recommended because there is no treatment and the consequences of infection during pregnancy have not been well-defined.

Clinical evaluation is recommended for infants born to mothers known or suspected to have WN virus infection during pregnancy ([show table 1](#)). Further evaluation should be considered if any clinical abnormality is identified or if laboratory testing indicates that an infant might have congenital WN virus infection ([show table 2](#)).

Patients can be enrolled in the CDC registry by calling 970-221-6400.

PREVENTION — Prevention of infection includes personal protection measures, mosquito control programs, and blood donor screening. It is important to drain standing water where mosquitoes are likely to breed. In a case control study examining risk factors, only spending increased amounts of time outdoors and the presence of flooded basements correlated with infection [[72](#)].

Personal protection measures — Personal protection measures to avoid mosquito exposure is a mainstay of prevention. A variety of insect repellants are available. ([See "Insect bites"](#), section on Insect repellants).

Blood donor screening programs — Blood donor screening for WN virus has greatly reduced, but not eliminated, the risk of transfusion transmission [[73-75](#)]. WN virus infection should be considered in recent transfusion recipients with unexplained, compatible illness. ([See "Laboratory testing of donated blood"](#), section on West Nile virus).

Vaccine development — There has been great interest in a WN virus vaccine and studies of different vaccines in animals suggest efficacy. Three equine WN virus vaccines have been licensed in the United States: an inactivated vaccine, and a recombinant canarypox virus vaccine expressing the prM/E proteins of a 1999 WN virus isolate, and a DNA vaccine. In addition, live attenuated virus vaccine utilizing chimeric viruses (bearing genes of WN virus on a backbone of dengue virus) appears effective in monkeys [[76](#)], while immunization with WN virus-like particles induced sterilizing immunity in mice [[77](#)]. Human vaccines are unlikely to be available for at least several years.

SUMMARY AND RECOMMENDATIONS

WN virus is found worldwide and is associated with a febrile illness that occasionally causes neuroinvasive disease, particularly in the elderly or immunosuppressed host. ([See "Clinical manifestations" above](#)).

WN fever is characterized by fever, headache, malaise, back pain, myalgias, and anorexia. A maculopapular rash appears in approximately one-half of patients.

WN virus infection can present as encephalitis, meningitis, or an acute asymmetric flaccid paralysis. Encephalitis that is associated with muscle weakness and flaccid paralysis is particularly suggestive of WN virus infection. Other neurologic manifestations include tremor, myoclonus, and parkinsonian features such as rigidity, postural instability, and bradykinesia. ([See "Clinical manifestations" above](#)).

In patients who present with a syndrome compatible with WN fever in mosquito season, we recommend serologic testing with EIA for the detection of IgM antibody to WN virus. In patients who present with suspected meningitis, encephalitis, or acute flaccid paralysis, we recommend a lumbar puncture and testing of the CSF for detection of IgM antibody

as well as serologic testing. In cases with signs of CNS involvement, the CSF usually demonstrates a pleocytosis often with a predominance of lymphocytes as well as an elevated protein concentration. ([See "Diagnosis" above](#)).

The treatment of WN virus infection is supportive. Controlled studies to evaluate specific therapies for WN virus infection have not been completed. ([See "Treatment" above](#)).

Personal protection measures include the use of mosquito repellents; general programs to protect public health include mosquito control programs and blood donor screening. No human vaccine is yet available. ([See "Prevention" above](#)).

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