# West Nile Encephalitis

8

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## Introduction

West Nile virus (WNV) is a mosquito-borne illness found worldwide, with manifestations ranging from asymptomatic infection to neuroinvasive disease (WNND), characterized by encephalitis, meningitis, and acute flaccid paralysis. First isolated in Uganda, the virus has spread globally, and transmission has now been documented on all six inhabited continents. The public health impact of WNV is considerable, with greater than six million people estimated to have been infected in the United States alone. This vector-borne disease is propagated in nature between the mosquito vector and birds, while horses and humans act as incidental, dead-end hosts. Diagnostic tests are widely available, but detection of antibodies, antibody cross-reactivity with other flaviviruses, and virus isolation in biological samples continue to pose challenges to clinical diagnosis. With limited treatment options and no FDA-approved vaccines, decreasing one's personal vector exposure is the most effective way to prevent disease. This widespread disease continues to be an annual public health threat, resulting in high morbidity, prolonged sequelae, and excessive mortality, thus warranting further study to improve diagnostics, treatments, and prevention to increase patient quality of life.

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## Epidemiology

First isolated in 1937 in the West Nile district of Uganda, WNV was one of the first arthropod-borne viruses (arboviruses) to be identified [1]. Since the mid-1990s, there has been an increase in human and equine outbreaks coinciding to large culling of avian populations [2]. WNV was first detected in North America in 1999, during an epidemic of meningoencephalitis in New York City [3]. Following its introduction into North America, a rapid geographic spread occurred between 2000 and 2004 followed by annual outbreaks in endemic areas [4, 5]. To date, millions are estimated to have been infected with WNV in the United States [6]. Similar rapid geographic expansions have been documented in other naïve populations globally. Diagnosis of human WNV cases is complicated by the potential for cross-reactivity in regions where other flavivirus infections are endemic: dengue virus in South America, Kunjin virus in Australia, Japanese encephalitis in Asia, and St. Louis encephalitis in North America. Cost estimates indicate that up to $400,000 are spent caring for each individual suffering from WNV sequelae [7]. With a robust vector range and sustained annual transmission internationally, this infection continues to present a significant health concern.

## Transmission

*Culex* sp. mosquitoes are the principal vectors of WNV, with *Culex pipiens* (northern United States), *C. quinquefasciatus* (southern United States), and *C. tarsalis* (western United States) the most common in the United States [8–10]. However, these are not the only vectors, as the virus has been identified in at least 65 different mosquito species [9–11].

Birds are the natural reservoir and amplifying host, with WNV identified in over 300 different species. WNV is maintained through a bird-mosquito-bird transmission cycle. Dead-end hosts, such as horses and humans, can be infected through the bite of an infected mosquito but do not reach levels of viremia necessary for transmission back to the mosquito population. However, WNV can be transmitted from human-to-human through blood transfusions, organ transplant, intrauterine infection, and breastfeeding [12–16].

Transmission via organ transplantation was first reported in 2002 [17]. The same year in Toronto, community-acquired cases revealed an increased rate of WNND among transplant recipients (200/100,000 people) compared to the general population (5/100,000 people) [18]. In addition, chronically immune-suppressed solid organ transplant recipients have an increased risk for severe meningoencephalitis compared to the general population [19, 20].

The first intrauterine infection of WNV was documented when an infected mother gave birth to an infant with chorioretinitis and cerebral tissue damage [14]. Although the exact mechanisms involved in intrauterine infections remain unclear, mouse models indicate that infection of placental trophoblast cells can progress to infection of the embryo and that the timing of pregnancy plays a role [18]. Other

infected mothers have given birth to children without defects, although there is one report of premature birth [19, 21]. There is a clear risk of transmission between mother and child, but the extent of the risk and associated outcomes require further study. Multiple body fluids are potentially infectious during peak viremia, as documented by case reports of transmission from mothers to their infants via infectious breast milk [22].

## Viral Characteristics and Pathogenesis

WNV is a member of the family *Flaviviridae*, genus *Flavivirus* (Fig. 8.1). Flaviviruses are positive-sense RNA viruses divided by their antigenic cross-reactivity into different serocomplexes. WNV is a member of the Japanese encephalitis serocomplex, which also includes St. Louis encephalitis virus, Japanese encephalitis virus, and Murray Valley encephalitis virus. The diversity of WNV strains has been studied in great detail, with four lineages being described [23–25], although lineage II strains are often attributed to severe neuroinvasive disease. The RNA genome is made up of structural genes C, prM, E, and nonstructural genes (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). These genes play different roles in the virus life cycle, virulence, and pathogenicity of infection.

Methods of immune evasion increase the pathogenicity of WNV. WNV enhances viral replication once in the host by blocking type-I interferons and evading the antiviral activity of IFN-stimulated genes (ISGs) [26, 27]. NS1, NS2A, NS4B, and NS5 may contribute to controlling this signaling cascade [28–30]. Interestingly, the IFN-inducible gene 20,50-oligoadenylate synthetase (OAS) has been shown to protect against flavivirus infection [31–33]. OAS is involved in the RNA decay pathway, known as the OAS/RNase L pathway, indicating it may promote antiviral activity of the immune system. Polymorphisms of OAS1 have indicated an increased

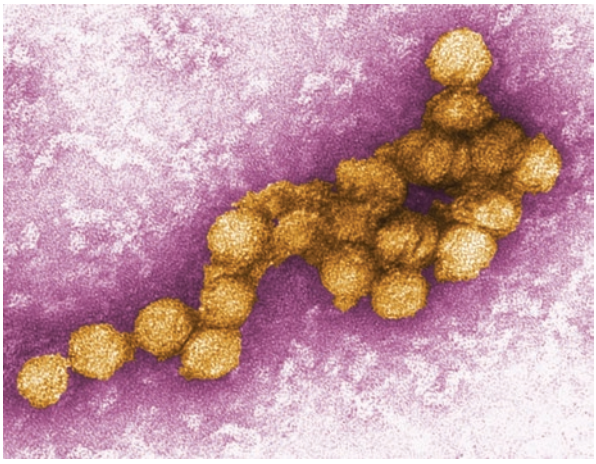

**Fig. 8.1** West Nile virions. Digitally colored transmission electron microscope (TEM) image of West Nile virions. Photo credit: Cynthia Goldsmith. Provided by CDC/P.E. Rollin

susceptibility to WNV infection in horses and humans [34, 35]. Identification of other viral and host factors that affect WNV infection is critical to understanding, preventing, and treating future infections.

## Pathology of Infection

After a blood meal, the mosquito vectors initiate host responses that drive the spread of infection. The mosquito injects saliva-containing virus within the dermis of the host, where the saliva acts as a potent enhancer of the host immune response, causing inflammation and edema. This drives the recruitment of leukocytes that become infected and allow for viral replication in additional target cells. Ultimately, virus migrates to the lymph nodes [36, 37]. Once in the lymph tissue, additional viral replication leads to viremia and infection of other organ systems (Fig. 8.2). Viremia peaks 2–4 days after infection and declines by the time of symptom onset [38], complicating the detection of viral particles for isolation and diagnosis. Viral persistence has been described in the kidneys and CNS [39–45]; however, the exact immune modulation is unknown.

Once in the brain, the virus directly infects neurons in nearly all regions but most commonly in the basal ganglia, thalamus, and brain stem (predominantly the medulla and pons) [46–48]. In cases of encephalitis and meningoencephalitis, the gross appearance of the brain is normal. Neuronal death, necrosis, mononuclear inflammation, and microglial nodules composed of lymphocytes and histiocytes are observed microscopically [47, 49]. Leptomeningeal mononuclear inflammatory infiltrates are present in cases of meningitis, with CD8 T lymphocytes the predominant inflammatory cell type in the nodules and infiltrates [48, 49]. Spinal cord infection primarily involves the ventral and dorsal gray and white matter, as well as the nerve roots, most commonly affecting the spinal cord anterior horn cells [47, 49–51]. Radiculitis caused by involvement of spinal and cranial nerve roots has also been documented [52].

Exact pathogenesis of CNS invasion in humans is unknown. Originally, neurovirulence was thought to depend on initial viral spread prior to the establishment of an immune response. Other theories include endocytosis into the CNS across vascular endothelium, as was previously demonstrated [53, 54], and CNS entry by infection of olfactory neurons, which are unprotected by the blood-brain barrier (BBB) [55–57]. Other hypothesized entry routes include WNV-infected leukocyte migration through tight junctions; direct viral shedding through the choroid plexus, across the cerebral endothelial cell to the brain parenchyma [58]; and transportation through peripheral nerve axons in a retrograde fashion [55, 59]. Animal models suggest viral entry into the CNS is facilitated by peripheral production of tumor necrosis factor alpha, leading to increased permeability of the BBB [60]. Highly neurovirulent flaviviruses have been shown to exhibit an upregulation of genes involved in IFN signaling, T-cell recruitment, MHC class I and II antigen presentation, and apoptosis [61, 62].

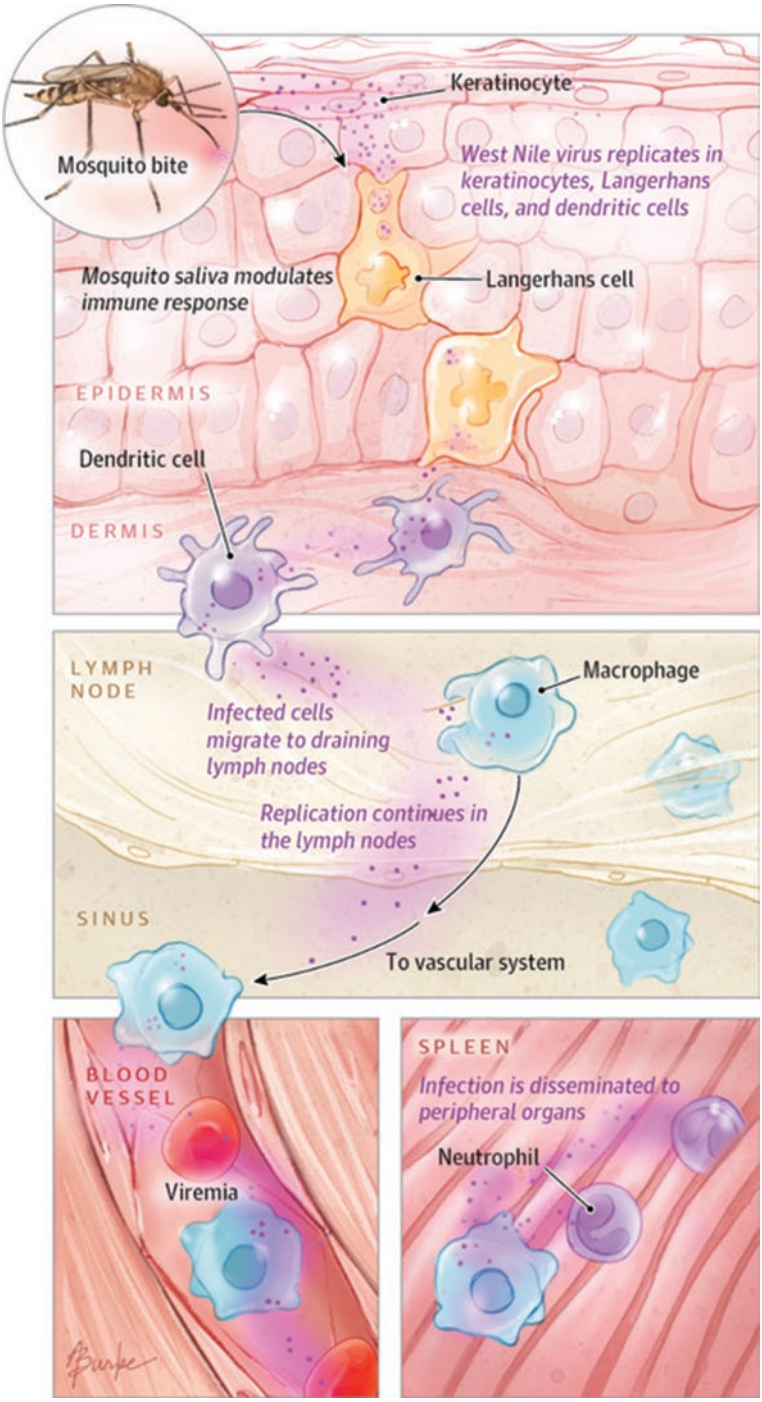


**Fig. 8.2** Pathogenesis of WNV infection. From West Nile Virus: Review of the Literature. Petersen LR, Brault AC, and Nasci RS. JAMA 2013;310(3):308–315. doi: https://doi.org/10.1001/jama.2013.8042

## Acute Clinical Features

Incubation time ranges from 2 to 14 days, with an estimated 80% of human cases remaining asymptomatic. Approximately 20% develop West Nile fever (WNF), generally a mild febrile illness [63, 64]. Less than 1% of patients progress to neuroinvasive disease, which includes West Nile meningitis (WNM), West Nile encephalitis (WNE), and WNV-associated acute flaccid paralysis (AFP) [64, 65]. The frequency of neuroinvasive cases varies based on region [66], with North Dakota having the highest percentage of neuroinvasive clinical cases compared to febrile or asymptomatic cases [67]. The inherent bias of syndromic surveillance reporting in the United States makes it challenging to elucidate the exact percentage of neuroinvasive versus febrile or asymptomatic cases.

### West Nile Fever

WNF can range from a mild flu-like illness to a severe, debilitating illness lasting for months. Symptoms include headache, fatigue, fever, myalgia, chills, rash, and emesis [64, 68, 69]. Most symptoms of acute infection resolve within days, but some patients describe symptoms more than 6 months after infection [70]. It is theorized that febrile patients with long-term sequelae may have presented with subclinical neurologic disease that was misclassified upon initial examination. Rash typically presents in younger patients, persists 5–14 days after symptom onset [71, 72], and is usually nonpruritic, morbilliform, and maculopapular over the torso and extremities while sparing the palms of hands and soles of the feet [71]. Less common symptoms include eye pain, arthralgia, diarrhea, and lymphadenopathy [68, 69]. WNF has a higher incidence among younger individuals [68, 69] and females [69] than the other clinical forms of disease.

### West Nile Neuroinvasive Disease

Progressing from a general, febrile illness, WNND leads to severe symptoms and death in approximately 10% of WNND cases. Previous serosurveillance studies have found age to be the most important host risk factor for the development of WNND [73, 74]. Advanced age greatly increases the risk of WNND, especially encephalitis, with a risk of 1:50 in those 65 years or older [67]. Additional risk factors for WNND are found in Table 8.1, with hypertension, immune suppression, and male gender being the most commonly reported after advanced age.

#### West Nile Meningitis

WNM clinically manifests with abrupt onset of fever, headache, nuchal rigidity, and photophobia, but these symptoms are not distinguishable from other causes of meningitis. Other symptoms include nausea, emesis, myalgia, muscle jerking, and tremors [43, 44]. For patients with severe meningeal symptoms, some patients may need hospitalization for pain control due to severe headaches or antiemetics and

**Table 8.1** Risk factors for WNND and mortality

| Risk factors | References |
|---|---|
| *Neuroinvasive disease risk factors* | |
| Increased age | [73–84] |
| Male sex | [67, 73, 81, 82, 84] |
| Diabetes | [77–79, 84] |
| Hypertension | [77, 78, 81, 84, 85] |
| Cardiovascular disease | [77, 78, 81] |
| Alcohol abuse | [77–79] |
| Chronic renal disease | [77, 78, 81, 83] |
| Chronic obstructive pulmonary disease | [77, 78] |
| Solid organ transplant | [17, 86] |
| Cancer | [77, 78, 83] |
| Immunosuppression | [79, 81, 83] |
| Chemokine CCR5 receptor deficiency | [87] |
| SNP in the *OAS1* gene | [88] |
| *Mortality risk factors* | [73–84] |
| Increased age | [67, 73, 81, 82, 84] |
| Neuroinvasive disease | [77–79, 84] |
| Male sex | [77, 78, 81, 84, 85] |
| Hypertension | [77, 78, 81] |
| Diabetes | [77–79] |
| Cardiovascular disease | [77, 78, 81, 83] |
| Chronic renal disease | [77, 78] |
| Previous stroke | [17, 82] |
| Chronic obstructive pulmonary disease | [77, 78, 83] |
| Hepatitis C | [79, 81, 83] |
| Alcohol abuse | [87] |
| Immunosuppression | [88] |
| Cancer | [73–84] |
| Anemia on admission | [67, 73, 81, 82, 84] |
| Change in level of consciousness | [77–79, 84] |
| Chemokine CCR5 receptor deficiency | [77, 78, 81, 84, 85] |

rehydration for nausea and vomiting [89]. WNM makes up the largest percentage of WNND cases in younger age groups (age <65 years) [43, 44, 66].

## West Nile Encephalitis

WNE can present with a wide range of symptoms, including those described in WNF, and with altered mental status (i.e., confusion, disorientation, and/or coma) lasting more than 24 h, which is the primary clinical indicator for encephalitis. The most common symptoms include fever (84–95%), altered mentation or somnolence (59–100%), fatigue (27%), myalgia (27%), headache (41–83%), stiff neck (19–49%), rash

(19–39%), vomiting (23–47%), diarrhea (19%), abdominal pain (17%), dizziness (12%), blurred vision (12%), slurred speech (17%), and weakness (22–55%) [66, 85, 90]. An abnormal neurological exam is found in almost all patients [85]. Seizures (10%), hypo- or hyperreflexia [44, 72, 75], neuromuscular weakness (59%), AFP (13%), loss of consciousness (20%), and somnolence (23%) can occur, sometimes requiring intubation and ventilator support for patient survival [85, 90]. Patients diagnosed with WNE have a mortality rate of approximately 15–18.6% [67, 68].

### Acute Flaccid Paralysis

AFP occurs in 5–15% of patients with WNND, presenting as a poliomyelitis-like (anterior myelitis) or a Guillain-Barre-like syndrome (GBS) [44, 91, 92]. Paralysis can present more symmetrically, sometimes resulting in quadriplegia if there is extensive spinal cord involvement, and can be associated with areflexia or hyporeflexia without sensory deficits [44, 93, 94]. The poliomyelitis-like presentation is the most common form of WNV AFP (84%) and is caused by viral injury to lower motor neurons, leading to an asymmetrical paralysis and possibly permanent weakness or paralysis [93]. Nerve conduction studies revealed axonopathy with no significant demyelination [44, 95] or pronounced anterior horn cell or motor axonal injury [90, 96]. Spinal MRI may reveal anterior horn damage or ventral root enhancement [90, 93, 95]. Symptoms of AFP usually develop abruptly, with pain presenting in affected limb prior to symptom onset [44, 93, 97]. Approximately 80% of cases with AFP also present with encephalitis or meningitis [93]. Parkinsonian-like symptoms and bowel/bladder dysfunction have also been described [44, 96, 98]. When innervations to the respiratory muscles are involved, including the diaphragm and intercostal muscle, paralysis can result in respiratory failure. Consequential endotracheal intubation may last for months [90, 93, 96]. MRI findings reveal enhancement of the cauda equina and lumbosacral nerve roots and increased intensity of the spinal cord [44, 46, 97, 99, 100].

The Guillain-Barre-like presentation occurs less commonly (13%) [93] and radiculopathy-associated WNV infection very rarely. Weakness associated with the Guillain-Barre-like presentation is characterized by ascending and more symmetric weakness, pain in affected limb prior to weakness onset, and sensory and autonomic dysfunction [93, 98]. Weakness onset and nadir appear to occur later in the disease process compared to the poliomyelitis-like presentation [93], and nerve conduction studies reveal a predominantly demyelinating sensorimotor neuropathy [93].

## Outcomes and Sequelae

Hospital stays are variable for those with WNV infection, but for WNND, this can last from days to months, depending on the degree of impairment, and some patients require discharge to long-term care or rehabilitation facilities [101, 102]. Among those with WNND, only 25–68% patients are discharged home [79]. Case fatality

ranges from 4.3 to 47.6% [44, 46, 66, 72, 74–77, 79, 80, 85, 90, 93, 97, 102–108] and appears to be more common in the elderly [104] and among those with WNND, especially WNE [106]. The most common sequelae are found in Table 8.2. Overall, survival analysis indicates that recovery plateaus after the second year, with WNE patients having the worst outcome [106].

Recovery of neurological deficits is variable among affected individuals, but persistent weakness and functional disability are common, which usually requires physical rehabilitation. Limb strength appears to improve within the first 6–8 months [111, 118], and generally, those presenting with less weakness during clinical presentation have a more rapid and complete recovery of muscle strength [93]. Patients presenting with WNE and over the age of 50 usually have a prolonged or poor recovery time [106]. In the 1999 New York outbreak, only 37% achieved full recovery at 1 year [110]. Some also report a possible occurrence of relapse or delayed-onset of AFP symptoms from WNV infection [119]. Neuromuscular, depression, and cognitive long-term outcomes have been noted several years postinfection, particularly among those with neuroinvasive disease [45, 100, 120]. Excessive mortality has also been documented among those in a Colorado cohort, in which those diagnosed with WNV patients had 2.0 standard mortality ratios at 4 years postinfection, indicating two times greater prevalence of death than the average population [78]. Individual prognosis for improvement is difficult to predict, but new evidence for patient outcomes for WNND continues to emerge.

Ocular manifestations have also been identified in WNV infection, but ocular involvement usually has a self-limited course. Bilateral multifocal chorioretinitis is the most common ocular manifestation, occurring in nearly 80% of patients with severe systemic disease, but other ocular findings include anterior uveitis, retinal vasculitis, optic neuritis, and retinal scarring [116]. Retinopathy is seen more in the elderly and those with encephalitis, and it is associated with a great likelihood of

**Table 8.2** Common sequelae of WNV infection

| Condition | References |
|---|---|
| Abnormal reflexes | [45, 109] |
| Altered mental status | [44, 104, 106, 110–112] |
| Ataxia | [93, 106, 111, 113] |
| Balance disturbance | [43, 112] |
| Debilitating fatigue | [43, 44, 106, 110–112] |
| Depression | [43, 106, 110–112] |
| Dizziness | [106, 110, 112] |
| Headache | [43, 44, 93, 106, 110–112] |
| Insomnia | [43, 110, 112] |
| Language disorder | [112, 114, 115] |
| Myalgias and/or arthralgias | [43, 44, 106, 110–112] |
| Ocular manifestations | [43, 109, 116] |
| Renal insufficiency | [40, 85, 117] |
| Tremors | [43–45, 93, 111–113] |

abnormal reflexes, poorer learning, greater dependence for activities of daily living, and a lower quality of life [109].

Hepatitis [121], pancreatitis [122], myocarditis [123], autonomic dysfunction [98], neuropsychiatric symptoms (depression, anxiety, and apathy) [106, 124], and rhabdomyolysis [97] have also been attributed to WNV infection. Renal insufficiency has been noted in 12% of acutely infected WNE patients [125], and one study observed that 40% of patients went on to develop chronic kidney disease years postinfection, with neuroinvasive WNV being significantly associated with any stage of chronic kidney disease based on multivariate analysis [40]. Studies detecting viral RNA in human urine after infection have yielded contradictory results [39, 126–130], but this may be due to the low levels of virus excretion, the time points of urine collection, and the need for more sensitive diagnostic methods.

## Diagnosis

Diagnosis of WNV infection can be a challenging process, as the clinical symptoms are generally nonspecific; however, seasonality can be an indicator based on peak transmission, but incidence has been documented year-round in the United States [131]. In 2003, clinical criteria for assessing patients with suspected WNND were released [44]. For WNM, criteria include signs of meningeal inflammation, evidence of acute infection characterized by fever or hypothermia, and/or CSF pleocytosis. For WNE, criteria include encephalopathy defined by depressed or altered consciousness, lethargy, and/or personality changes lasting at least 24 h and at least two symptoms evident of CNS inflammation including fever or hypothermia, increased peripheral leukocyte counts, CSF pleocytosis, acute demyelination, focal neurological deficits, and seizures. AFP criteria include acute onset of limb weakness with clear progression over 48 h, asymmetry of weakness, absence of pain, numbness in affected limbs, CSF pleocytosis and raised protein levels, and/or spinal cord MRI with increased signal in the anterior gray matter. Even with this information on WNND criteria, many cases go unidentified.

Diagnosis requires recognition of a combination of clinical features and positive laboratory tests. If WNV is suspected, patient serum and/or cerebrospinal fluid should be tested for IgM and IgG antibodies to WNV using an FDA-approved enzyme-linked immunosorbent assay (ELISA). Generally, a patient being $IgM^+$ and $IgG^-$ can be an indicator of acute infection versus past infection; yet, extended IgM antibody titers have been well documented within the first year postinfection [132–135] and possibly up to 8 years postinfection [136]. Diagnostics are commercially available in the United States, and some health departments offer reference testing for clinicians. Processing these samples can take up to 7 days if using a referral laboratory, delaying a timely diagnosis while continuing unnecessary empirical antibiotic and acyclovir treatment. In addition, antibodies may not be present at the time of symptom onset for WNF cases. In fact, one study identified that only 58% of WNF cases had detectable IgM levels when they presented to the

clinic at the onset of symptoms [137]. Additional studies have identified that 90% of WNND cases have detectable IgM antibodies in the CSF within 8 days of symptom onset; however, there are rare accounts of patients that never develop IgM antibodies [136]. The laboratory test most commonly used to detect WNV antibodies is the IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) [138], but other FDA-approved methods, like the lateral-flow IgM strip assay, can provide rapid, simpler means of diagnosis with less training and instrumentation [139].

It is important to note that although detection of antibodies provides evidence of WNV infection, it can also be an indication of a cross-reaction with another endemic flaviviruses, such as St. Louis encephalitis virus, dengue virus, Kunjin virus, and/or Japanese encephalitis virus. Travel history should be considered to determine potential cross-reactive flavivirus species. To determine the specific flavivirus causing infection, plaque reduction neutralization assays (PRNTs) can be done in reference laboratories. In some cases, PRNTs can be used to diagnose an acute infection if a fourfold or greater change is detected from acute and convalescent samples. However, using PRNTs for acute infection can delay diagnosis as it can take at least 5 days to perform depending on the capacities of the laboratory. Other diagnostics include viral cultures and PCR to detect virus in whole blood, serum, or CSF, but it is unlikely that a patient would present with clinical disease when these samples would still have detectable virus levels. Physicians should be aware that blood banks in the United States test for viremia via polymerase chain reaction (PCR) in asymptomatic blood donors, and patients might receive their blood bank results prior to symptom onset. Detailed information regarding testing through reference laboratories can be found on the CDC's website.

## Treatment and Prevention

Currently, there are no FDA-approved treatments or vaccines for WNV infections in humans, although an equine vaccine is available. Current management focuses on supportive care. Anecdotal reports of effective alternative agents have been reported, including antiviral agents, immunomodulating agents, angiotensin-receptor blockers, and nucleic acid analogues. Given the lack of random controlled trials and varied outcomes in case reports and animal models, there are no official recommendations to use such agents in clinical practice [58, 140]. Ribavirin was used during an outbreak of WNV in Israel but was associated with a higher risk of death; however, this experimental intervention was only used in severe cases [76]. The use of intravenous immunoglobulin (IVIG) containing high anti-WNV antibody in patients with WNND led to improvement, even in cases where IVIG was administered several days after onset of symptoms [141], but randomized, placebo-controlled trials are lacking. The use of corticosteroids for WNND remains controversial, but previous studies have shown intravenous steroids administered during acute infection may have led to a shorter clinical syndrome with decreased recovery time [142] or a decrease in mortality [79].

Preclinical vaccines tested in animal models have explored the success of DNA-vectored vaccines, live chimeric/recombinant vaccines, live-attenuated vaccines, inactivated whole virus vaccines, and recombinant subunit vaccines [143]. DNA, live chimeric, and recombinant subunit vaccines have made it to phase I and phase II clinical trials, but when and if these will be licensed and available to the general public remains to be seen. Tracking of the status of these vaccines can be done at https://clinicaltrials.gov/.

**Conclusions**

Without a preventative vaccine or therapeutic options available, WNV will continue to be a significant threat to public health. WNV has resulted in more than 41,000 reported clinical cases of disease and more than 1900 deaths since its introduction into the United States in 1999 [144]. It is estimated that greater than three million people in the United States have been infected [6]. Although many advancements have been made, many gaps in the understanding of the pathology, diagnostics, management, and prevention of the WNV disease process still exist. With continued study and research into these challenges, we can continue to work toward the goal of controlling future epidemics and improving morbidity and mortality associated with WNV infections worldwide.

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