West Nile virus

Primer for family physicians

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ABSTRACT

OBJECTIVE To provide primary care physicians with an understanding of West Nile virus in North America. This article focuses on epidemiology, clinical features, diagnosis, and prevention of infection.

QUALITY OF EVIDENCE MEDLINE and EMBASE searches revealed epidemiologic, surveillance, cohort, and outcome studies providing level II evidence. There were no randomized controlled trials of treatment. Recommended prevention and treatment strategies are based on level II and III evidence.

MAIN MESSAGE The mosquito-borne virus that first appeared on this continent in 1999 is now prevalent throughout North America. Most infections are asymptomatic. Fewer than 1% of those infected develop severe illness; 3% to 15% of those with severe illness die. While methods for controlling the mosquito population are available, we lack evidence that they reduce infection in the general human population. Family physicians have an important role in advising their patients on ways to prevent infection and in identifying patients who might be infected with West Nile virus.

CONCLUSION The general population is at low risk of West Nile virus infection. Prevention of infection rests on controlling the mosquito population and educating people on how to protect themselves against mosquito bites.

RÉSUMÉ

OBJECTIF Permettre au médecin de famille de mieux comprendre l'épidémiologie, les caractéristiques cliniques, le diagnostic et la prévention des infections par le virus du Nil occidental en Amérique du Nord.

QUALITÉ DES PREUVES Une recherche dans MEDLINE et EMBASE a permis de repérer des études épidémiologiques, prospectives, de surveillance et d'issues basées sur des preuves de niveau II. Aucun essai thérapeutique randomisé n'a été identifié. Les stratégies de traitement et de prévention préconisées reposent sur des preuves de niveau II et III.

PRINCIPAL MESSAGE Apparu pour la première fois sur ce continent en 1999, ce virus, qui est transmis par un moustique, est maintenant répandu dans toute l'Amérique du Nord. La plupart des infections sont asymptomatiques. Moins de 1% des personnes infectées développent une maladie grave et entre 3 et 15% de ceux-ci en meurent. Même s'il existe des méthodes de contrôle de la population de moustiques, il y a peu de preuves qu'elles réduisent l'infection chez l'humain. Le médecin de famille a un rôle important à jouer pour renseigner les patients sur les mesures préventives et sur l'identification des sujets à risque d'infection par le virus du Nil occidental.

CONCLUSION Le risque d'infection par le virus du Nil occidental est plutôt faible dans la population générale. La prévention repose essentiellement sur le contrôle de la population de moustiques en plus des conseils sur la façon de se protéger des piqûres.

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In 1999, detection of West Nile virus (WNV) in North America prompted public health authorities to anticipate a human outbreak of this mosquito-borne infection. Risk of being bitten by an infected mosquito is low, as is risk of serious health effects due to the virus. Nevertheless, the presence of a new mosquito-borne illness emphasizes the need to reduce risk of infection. Family physicians have an important role in advising their patients on ways to reduce this risk and in identifying patients who could be infected with WNV.

Quality of evidence

MEDLINE and EMBASE were searched from January 1999 to December 2003 using the key words ("West Nile virus" OR "West Nile fever") AND ("diagnosis" OR "epidemiology" OR "immunology" OR "virology" OR "mortality" OR "prevention and control") AND ("Canada" OR "North America"). We reviewed 92 articles containing relevant information on WNV in North America. These epidemiologic, surveillance, cohort, and outcome studies provide level II evidence. There are no randomized controlled trials of treatment; recommended prevention and treatment strategies are based on level II and III evidence.

Epidemiology

West Nile virus belongs to the Japanese encephalitis serogroup of *Flavivirus* that includes the St Louis encephalitis, Murray Valley encephalitis, and Kunjin viruses.[1] It was identified in the West Nile district of Uganda in 1937,[2] first appeared in the western hemisphere in New York City in 1999,[3] and is now found in much of the United States[4] and Canada.[5] People are infected by mosquitoes carrying the virus; peak incidence occurs in August and September.

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Ecology

West Nile virus is a single-stranded RNA virus that is maintained in a bird-mosquito-bird cycle.[6] In early spring in Canada, adult mosquitoes emerge from their aquatic stages and begin infecting birds. Both wild and domestic birds,[7] particularly corvine species, such as ravens, jays, and crows, can serve as viral reservoirs.

Infected birds give the virus an opportunity to amplify, resulting in spread of infection to large numbers of bridge vectors. These bridge vectors include mosquitoes that bite both humans and birds, enabling the virus to pass from bird hosts to humans without direct contact between humans and birds. While the *Culex* genus of mosquito is the principal vector, bites from other mosquitos can lead to human infection also.[8] Many birds are found dead in a region shortly before human cases develop there.[9]

Clinical features

Most human WNV infections are asymptomatic. When symptoms do occur, the incubation period ranges from 2 to 14 days,[10] but might be as long as 21 days in organ-transplant recipients.[11] West Nile fever is a mild viral illness lasting 3 to 6 days, characterized by sudden onset of headache, myalgia, malaise, anorexia, nausea and vomiting, and sometimes an erythematous macular or papular rash. While the proportion of infected patients who develop West Nile fever is unknown, a household serologic survey in New York City suggested that approximately 20% of those infected with the virus developed the fever.[12]

Less than 1% of those infected with WNV develop severe illness, such as meningitis, encephalitis, or acute flaccid paralysis.[12] Movement disorders, such as tremor, myoclonus, and symptoms resembling those of Parkinson disease, might also

appear during acute illness with WNV.[13] Other neurologic manifestations attributed to WNV infection include cranial nerve abnormalities[13] and seizures.[14] **Table 1** lists common WNV symptoms.

Table 1. Common symptoms of West Nile virus infection

Fever
Weakness
Nausea
Vomiting
Headache
Altered mental status
Diarrhea
Rash
Cough
Stiff neck
Myalgia
Arthralgia

The case-fatality rate in humans with severe illness is 3% to 15%.[15] People with meningoencephalitis had a case-fatality rate of 9% during the 2002 WNV outbreak in the United States.[16] Advanced age is the most important risk factor for death; case-fatality rates can be as high as 29% for hospitalized patients aged 70 and older.[17] Risk of death is also greater in patients with encephalitis accompanied by severe muscle weakness and changes in level of consciousness and in patients with a history of diabetes mellitus or immunosuppression.[3,17] In 2002, the virus caused at least eight deaths in Canada.[18]

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

Data on patients hospitalized with WNV suggest substantial long-term morbidity. In New York and New Jersey in 2000, more than half those affected did not return to their functional level before discharge, and only one third were fully ambulatory.[19] Persistent symptoms included fatigue, memory loss, difficulty walking, muscle weakness, and depression.

Diagnosis

Diagnosis of WNV infection relies on a high index of clinical suspicion and laboratory testing. Patients with sudden, unexplained encephalitis or meningitis in late summer or fall in a WNV-endemic area should raise your suspicions. Patients' total leukocyte count can be normal or elevated.[3,17,19] Examination of cerebrospinal fluid often reveals lymphocytosis with elevated protein levels and normal glucose levels.[3,17,19] Computed tomography scan of the brain usually shows no evidence of acute disease, but magnetic resonance imaging might show focal lesions in the pons, basal ganglia, or thalamus, with enhancement of the leptomeninges, periventricular areas, or both.[10,13]

Definitive diagnosis of WNV infection is made by serologic testing. Detection of WNV immunoglobulin M antibody in a single serum or cerebrospinal fluid specimen confirms diagnosis. The antibody was detected in nearly 95% of cerebrospinal and 90% of serum samples of WNV-infected patients during the 1999 and 2000 outbreaks in New York City.[20]

Serologic testing is not straightforward. Patients recently vaccinated with yellow fever or Japanese encephalitis vaccines or recently infected with a related *Flavivirus* (dengue or St Louis encephalitis) might have false-positive results due to the close antigenic relationships among *Flavivirus*.[21] Even the presence of the antibody might not indicate acute infection because the antibody can persist for 6 months or more. A four-fold increase in antibody titre in serum samples from acute and convalescent patients confirms acute infection.[15]

Prevention

Risk of infection can be minimized in several ways. The first is by reducing the local mosquito population. Mosquitoes breed in standing pools of water, so draining pools of water and eliminating containers of standing water limit mosquito reproduction. Municipalities can apply larvicides to stagnant water to limit mosquito reproduction and spray insecticide to kill existing mosquitoes. In 2002 and 2003, the City of Winnipeg, Man, used a *Bacillus thuringiensis* subspecies larvicide and malathion insecticide to reduce the mosquito population. While there is no evidence this reduced the risk of WNV spread to humans, similar efforts reduced mosquito populations[22,23] and other mosquito-borne illness in other jurisdictions.[23,24]

The second way to reduce risk is to avoid mosquito bites. Avoid mosquito-infested areas, particularly at dawn and dusk when mosquitoes are most active. Physical barriers, such as long pants and sleeves, socks, and shoes, also protect against bites. Babies should be protected with nets since they are unable to defend themselves against mosquitoes. Permethrin-treated nets, shelters, and clothing prevent mosquito bites by killing mosquitoes on contact. Screens prevent mosquitoes from entering dwellings, reducing the risk of bites indoors. While electronic or carbon dioxide insect traps can decrease local mosquito populations, they do not prevent bites.

Using mosquito repellent is the most effective way to prevent bites. N,N-diethyl-3-methylbenzamide (DEET) is a safe, effective insect repellent used by more than 200 million people worldwide each year.[25] Products with 10% to 35% DEET provide adequate protection under most conditions. High mosquito density, increased risk of disease transmission, or rapid repellent loss from skin surface (eg, due to bathing or water sports) requires higher concentrations of DEET. A combination of DEET-based repellents and permethrin-treated clothing is highly effective at reducing risk of mosquito bites.[26]

While children are thought to be more sensitive to the adverse effects of DEET, this has not been demonstrated in a large-scale population-based study.[27] Nevertheless, Health Canada and the Canadian Paediatric Society recommend against use of DEET on children 6 months or younger and suggest applying it only once daily on those aged 6 to 24 months and three times daily on children aged 2 to 12 years.[28] There is no evidence that use of DEET by pregnant or lactating women poses a health hazard to unborn babies or children who are breastfeeding.[29]

Immunization might be the ultimate way to prevent WNV infection. A variety of immunization strategies using killed WNV, live attenuated virus, and passive immunization are under investigation.[30] The most promising is a live attenuated recombinant vaccine that uses yellow fever as a vector for the WNV envelope genes to induce a protective immune response against WNV.[31] Immunization against related *Flavivirus*, such as Japanese encephalitis, does not protect against WNV.[32]

Public health officials must weigh the relative risks and benefits of mosquito control measures. The overall burden of disease in the general population is low, less than 1% of mosquitoes are infected, and less than 1% of infected humans become severely ill.[15] Widespread spraying of pesticide could elicit a negative response from the public due to fear of the pesticide itself,[33] and its efficacy at reducing human infection in the general population is unknown.

Treatment

Treatment of patients with WNV infection is primarily supportive. Interferon–alpha-2B and ribavirin are efficacious against WNV in vivo, but clinical trials using these agents have not been completed.[34]

Conclusion

Despite its recent arrival, WNV is now present throughout much of North America. Most infected patients are asymptomatic or develop mild, nonspecific clinical illness. The best ways to prevent infection are to reduce mosquito populations and use mosquito repellents. Investigations are under

way to develop a vaccine, but this is not yet available. Treatment of infected patients is supportive. Family physicians have a role in advising their patients about reducing risk of infection and identifying patients who might have WNV infection.

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EDITOR'S KEY POINTS

- West Nile virus, which belongs to the Japanese encephalitis group of Flaviviruses, has spread throughout large parts of Canada since it was first detected in North America in 1999.
- It is spread by a bird-mosquito-bird cycle, with a reservoir mostly in corvine species (eg, crows, ravens, jays), and the incidence peaks in August and September.
- Most human infections are asymptomatic or present as mild, nonspecific viral illness that lasts 3 to 6 days. Less than 1% of those infected develop severe symptoms: meningitis, encephalitis, paralysis, or other neurologic conditions. Case fatality is 3% to 15%. Advanced age and compromised immunity are the most important risk factors.
- Diagnosis is by serology; treatment is for symptoms and support. A human vaccine is under investigation. Reducing mosquito contact is the mainstay of prevention.

POINTS DE REPÈRE DU RÉDACTEUR

- Le virus du Nil appartient au groupe des *Flavivirus* de l'encéphalite japonaise. Depuis sa découverte en Amérique du Nord en 1999, il s'est propagé dans une grande partie du Canada.
- Il se propage via un cycle oiseau-moustique-oiseau, avec comme principal réservoir la famille des corvidés (par ex., corneilles, corbeaux, geais). L'incidence maximale se situe en août et septembre.
- Chez l'humain, l'infection est généralement asymptomatique ou prend la forme d'une affection virale légère d'une durée de 3 à 6 jours. Moins de 1% des sujets infectés développent des symptômes sévères : méningite, encéphalite, paralysie ou autres troubles neurologiques. Le taux de létalité est de 3 à 15%. Les principaux facteurs de risque sont le grand âge et l'immunodéficience.
- Le diagnostic repose sur la sérologie, et le traitement est essentiellement symptomatique et de soutien. Un vaccin humain est à l'étude. La principale mesure préventive consiste à réduire les contacts avec le moustique.

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