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West Nile Virus in the United States

Author: **Stan Deresinski, MD, FACP**, Clinical Professor of Medicine, Stanford; Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center; Editor-in-Chief, *Infectious Disease Alert*.

Editor's Note—*West Nile virus was of no concern to residents of North America until the summer of 1999, when it seemingly inexplicably struck in Queens, NY.[1] The cases of encephalitis were thought to be due to a pathogen well known in the United States, St. Louis encephalitis (SLE) virus. SLE infection, like other arboviral diseases, occurs in the summer months when mosquitoes are active and, also like the outbreak in Queens, is most severe in the elderly. In addition, many of the patients had detectable antibody against SLE antigens. There was at least one puzzling observation, however, that did not fit with SLE—dead birds, especially crows and exotic birds in the Bronx Zoo. While birds are the natural reservoir for SLE virus, avian infection is seldom lethal. An initial thought was that SLE had perhaps mutated to a form more virulent to avians. Eventually, however, the startling discovery was made that the infections occurring that summer, both human and avian, were caused by a flavivirus related to SLE, West Nile virus (WNV). This relatedness was close enough to cause antigenic cross-reactivity and, thus, accounting for the falsely positive serological tests.*

The discovery that the infections were caused by WNV was both surprising and disquieting. Naturally acquired WNV infection had never before been detected in North America, a continent presumed to be protected by its surrounding oceans from the wayward flight of a migratory bird from across the Atlantic (patients with advanced cancer were deliberately infected with WNV at the Sloan-Kettering Institute in New York in the early 1950s, and several of these patients developed encephalitis [Southern]). In fact, we still do not know how the WNV made its way to this continent. Suggested means of transport have included a stowaway mosquito on an overseas transport, an infected migratory or storm-blown bird, in a viremic human, in an infected bird or mammalian pet, or by an (unlikely) act of bioterrorism.[2] Whatever the means, the virus had arrived in North America, a land mass heavily populated with birds and humans, none of which had previous immunologic experience with the virus. This immunologic naivete had predictably devastating consequences for wild and captive avian populations. While the birds were dying, so were humans, albeit in much smaller, but increasing numbers—from 7 deaths in 1999 to 284 in 2002. The approximately 2700 cases of WNV meningoencephalitis reported through 2002 made it the largest such epidemic ever documented anywhere in the world.

Virology

WNV is a member of the *Flaviviridae*, of which more than 70 have been described, with at least 13 capable of causing disease in humans. Other flaviviruses include the etiologic agents of tick-borne encephalitis, dengue, yellow fever, hepatitis C, and the closely related Japanese encephalitis and SLE viruses. Flaviviruses that affect humans are, with the exception of hepatitis C virus and GB virus, transmitted by the bite of mosquitoes or ticks.

WNV and other flaviviruses contain linear, positive-sense

single-stranded DNA comprised of approximately 11,000 nucleotides.[3] The open reading frame encodes 3 structural proteins and 7 nonstructural proteins. Electron micrography of the mature virion reveals an enveloped spherical capsid 40 nM to 60 nM in diameter, with icosahedral symmetry and small surface projections of E glycoprotein anchored in the viral membrane. The projecting E glycoproteins contain antigenic determinants recognized by hemagglutinating and neutralizing antibodies. It is believed that the E protein also interacts with host cell receptors during virion attachment. Penetration of the cell probably occurs by receptor-mediated endocytosis. Virion uncoating releases genomic RNA that then functions as messenger RNA, as well as a template for further RNA synthesis, via a minus-strand RNA intermediary. The open reading frame of the genomic RNA generates a large polyprotein that is then cleaved into constituent proteins. Assembled mature virions are transported to the cell membrane where they undergo vesicle fusion and are released from the cell.

Analysis of full-length genomes demonstrate 2 distinct WNV lineages.[4] One of these consists of enzootic strains present in Africa, while the other has wide distribution, including Africa, the Middle East, Eastern Europe and, now, North America. The Kunjin virus, present in Australia, closely related to WNV, is a subtype of the latter lineage.[5]

Epidemiology and Transmission (*see Tables 1 and 2*)

WNV was first isolated from the blood of a woman with an uncomplicated febrile illness residing in Uganda, near the West Nile, in 1937.[6] WNV infection has been described in Africa, Europe, the Middle East, west and central Asia, Oceania (sub-

Table 1. West Nile Virus in Humans in the United States—2002

STATE	Laboratory Positive Cases	Deaths
Alabama	49	3
Arkansas	43	3
California	1	
Colorado	14	
Connecticut	17	
Delaware	1	
District of Columbia	34	1
Florida	28	2
Georgia	44	7
Illinois	884	64
Indiana	293	11
Iowa	54	2
Kansas	22	
Kentucky	75	5
Louisiana	329	25
Maryland	36	7
Massachusetts	23	3
Michigan	614	51
Minnesota	48	
Mississippi	192	12
Missouri	168	7
Montana	2	
Nebraska	152	7
New Jersey	24	
New York	82	5
North Carolina	2	
North Dakota	17	2
Ohio	441	31
Oklahoma	21	2
Pennsylvania	62	7
Rhode Island	1	
South Carolina	1	
South Dakota	37	
Tennessee	56	7
Texas	202	13
Vermont	1	
Virginia	29	2
West Virginia	3	2
Wisconsin	52	3
Wyoming	2	
TOTALS	**4156**	**284 (6.8%)**

Source: http://www.cdc.gov/od/oc/media/wncount.htm.

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Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or e-mail: robin.mason@ahcpub.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Table 2. West Nile Virus: Possible Modes of Transmission

- Mosquito bite
- Blood transfusion
- Organ transplantation
- Transplacental
- Breast milk
- Direct inoculation (laboratory accident)
- Needle sharing

type Kunjin) and, most recently, North America.[7] Outbreaks of WNV infection in humans have occurred in recent years in Algeria in 1994, Romania in 1996-1997, the Czech Republic in 1997, the Democratic Republic of the Congo in 1998, Russia in 1999, the United States in 1999-2001, and Israel in 2000. Epizootics of disease in horses occurred in Morocco in 1996, Italy in 1998, the United States in 1999-2001, France in 2000, and in birds in Israel in 1997-2001 and in the United States in 1999-2002.

When WNV made its dramatic first appearance in North America in the summer of 1999, it accounted for 59 hospitalizations and 7 deaths.[1] Although the virus is transmitted vertically in mosquitoes, it was hoped that infected arthropods would not survive the cold northern winter. Unfortunately, this was not true, and the virus has caused infection in 4 consecutive transmission seasons in North America. Most human infections occur in summer or early autumn in temperate and subtropical zones, but year-round transmission has been documented in Florida.[8]

The transmission cycle of WNV involves mosquitoes and passerine birds (birds with the ability to hold on using claws), with mammals being accidental hosts.[9-12] While a variety of mosquitoes have been found to be infected by WNV (29 infected species have been identified in the United States through 2002), the most important vectors are those of the genus *Culex*, especially *C pipiens*, *C quinquefasciatus*, and *C restuans*, species that have an affinity for feeding on birds. The birds act as amplifying hosts and as reservoirs of virus. High-level viremia occurring during the course of the avian infection provides a reservoir, leading to infection of mosquitoes that feed on the firds. Some mosquitoes that bite both birds and humans serve as a bridge to the latter. More than 100 North American bird species have been found to be infected, with avian mortality highest in crows and other corvids, such as ravens and jays. Birds that survive the infection may acquire life-long immunity in the process.

Infection of migrating birds accounts for transport of the virus between distant geographic areas. The means by which WNV was first introduced into North America in 1999, however, remains a matter of conjecture. The WNV first detected in New York is genetically almost identical (99.8% nucleic acid and amino acid homology) to a virus isolated from a dead goose in Israel in 1998.[13]

In urban outbreaks, including that in New York City, risk factors for human infection were predictable: prolonged time spent out-of-doors, lack of regular use of mosquito repellent, having noticed mosquitoes in the home, and living in an apartment with a flooded basement.[14] In addition to its usual means of mosquito-borne transmission, WNV has also been transmitted by blood component transfusion, organ transplantation, direct percutaneous inoculation in laboratory accidents, and by transplacental passage.[15-19] During 2002, it was estimated that the maximum and mean risk of WNV transmission from donors in Queens were 2.7 (95% CI, 0.9-5.6) and 1.8 (95% CI, 1.4-2.2) per 10,000 donors, respectively, with the peak risk in late August and very low risk before August and after September.[16] A single case report has raised the possibility of transmission via breast milk.[17] Transmission as a result of needle sharing by injection drugs users is also considered a potential danger. There is otherwise no evidence of direct person-to-person transmission.

Clinical Aspects (*see Figure 1*)

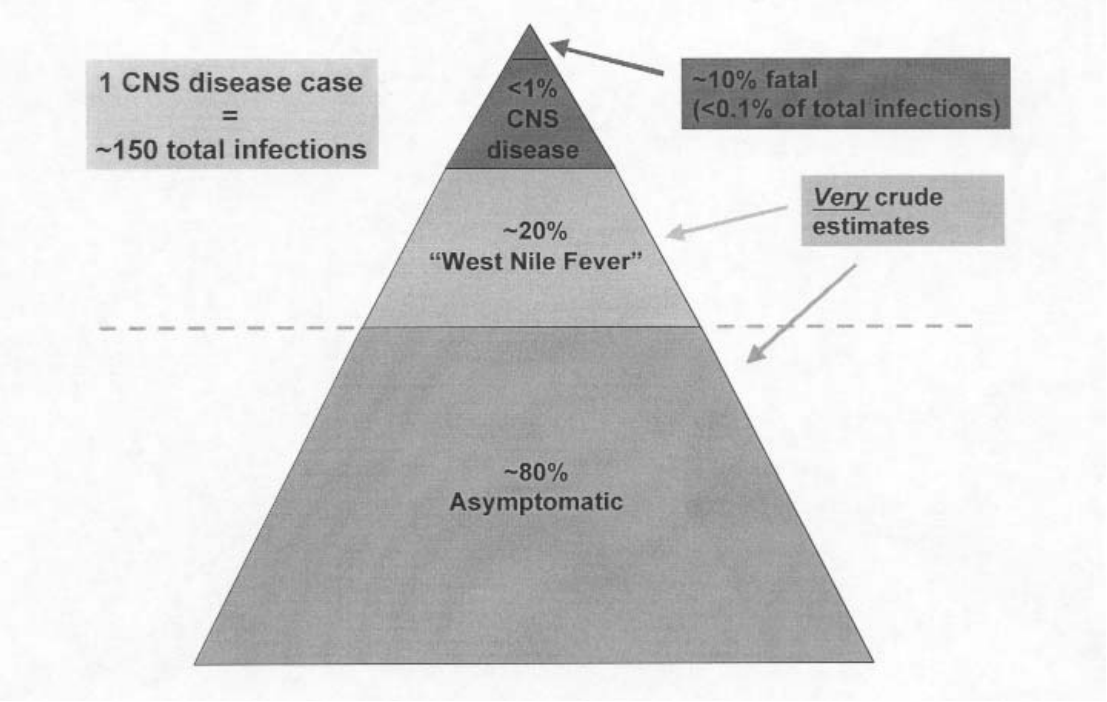
Most human cases of WNV infection are clinically inapparent, with only approximately one-fifth becoming symptomatic.[9-11] The incubation period for symptomatic cases is 2-14 days, although it is most often 2-4 days for febrile cases. Symptoms generally last 3-6 days. The onset of fever is typically abrupt, often reaching > 39° C, with mylagia and headache or ocular pain. Gastrointestinal symptoms, including anorexia, nausea, and vomiting may also occur. Rash may occur in up to one-fifth of cases and generalized lymphadenopathy in only approximately 5% of US cases. The rash is maculopapular or morbilliform and may involve the neck, trunk, arms, and legs. Both fever and lymphadenopathy occurred more frequently during previous outbreaks in Israel.

In the United States, approximately 1 in 150 patients have developed infection of the central nervous system (CNS). In patients with neurologic disease, the illness is often biphasic, with 1-7 prodromal days of febrile illness followed by manifestations of CNS infection. The risk of neurological involvement rises with increasing age, especially after the age of 50 years. In the initial New York experience, the risk of severe neurologic disease was 43 times greater in those 80 years or older compared to those younger than 20 years of age.[1] Encephalitis or meningoencephalitis is observed in approximately 60% of those with CNS involvement, while 16-40% have meningitis without an encephalitic component.[9-11]

The onset of CNS symptoms may occur simultaneously with, or within a few days after the onset of fever. Patients with mental status changes may progress to coma, a complication that may occur in 15% of those with encephalitis. Muscle weakness, resulting from myelitis, may be observed in one-half of patients, in some cases severe enough to suggest the presence of acute poliomyelitis or Guillian-Barré syndrome.[20] Respiratory failure may result. Less frequently observed have been ataxia, extrapyramidal signs, cranial neuropathies and polyradiculitis, and rhabdomyolysis. Tremors and myoclonus may be more frequent than previously reported.[21] Seizures may occur. Also uncommonly observed are optic neuritis, chorioretinitis, uveitis, and vitritis.[22-25]

Differentiation from Guillian-Barré syndrome may be made by clinical findings, electromyography, and nerve conduction

Figure 1. Clinical Spectrum of WNV Infection. CDC.



velocity studies, as well as by the presence of cerebrospinal fluid (CSF) pleocytosis in WNV infection (*see Table 3*). WNV infection may produce flaccid paralysis clinically indistinguishable from that caused by polioviruses, as a consequence of direct involvement of anterior horn cells.[26] Resultant weakness of thoracic muscles may lead to respiratory failure and need for mechanical ventilation.

The case fatality rate among patients hospitalized in New York City in 1999 was 12%.[1] In New York, patients affected severely enough to warrant hospitalization during the initial outbreak in 1999, persisting morbidity was frequent. One year later, 67% reported persisting fatigue, 50% memory loss, 49% difficulty walking, 44% muscle weakness, and 38% suffered depression.[27]

Diagnosis (*see Table 4 and Figure 2*)

In North America, arbovirus infection, especially WNV and SLE, should be suspected in patients who develop otherwise unexplained encephalitis or meningitis during the summer or early autumn, especially if these infections are active in the community, or if the patient has traveled to an area with suspected or known arboviral activity.[7,10-12] This suspicion should be heightened in patients older than 50 years of age. The presence of significant muscular weakness should also suggest the diagnosis. The presence of WNV infection should also be considered in patients with nonspecific febrile illness in a setting of WNV activity.

The white blood count may be normal or elevated or low and anemia may also be present.[7,10-12] Hyponatremia, possibly due to inappropriate secretion of antidiuretic hormone may be seen, especially when encephalitis is present. When CNS infection is present, CSF examination generally demonstrates a lymphocyte-predominant pleocytosis, modest protein elevation, and normal glucose. The CSF may, however, have a neutrophilic predominance or may be acellular. Magnetic resonance imaging may demonstrate leptomeningeal and/or periventricular enhancement and, in some cases, high signal intensity lesions on T2 weighted images involving basal ganglia, findings consistent with the high frequency of movement disorders.[7]

The diagnosis of infection due to WNV may be made by detection of serum IgM antibody, by enzyme-linked immunosorbent assay, to viral antigens in serum or cerebrospinal fluid (CSF).[27-30] Detection in the CSF of IgM antibody against WNV antigens is highly consistent with acute CNS infection due to the virus. A negative test on a serum sample obtained within the first 14 days of illness should be repeated on a later sample. Falsely positive serum IgM antibody tests may occur in individuals recently infected with or vaccinated against related flaviviruses such as dengue, yellow fever, or Japanese encephalitis viruses. The use of the highly specific plaque reduction neutralization assay may assist in distinguishing between false and true positives. Care must also be taken because IgM antibody to antigens of WNV may persist for 6 or more months and, as a consequence, a positive test may only indicate a prior, probably asymptomatic infection.[28,30] The serological diagnosis of WNV infection is most confidently made in the presence of a fourfold or greater increase in serum neutralizing antibody titers upon testing acute and convalescent sera. Specimens are ideally obtained on the first day of illness and again after an interval of at least 3 weeks. In addition, the titers detected against WNV antigens should be at least fourfold higher than those to antigens of other appropriately selected flaviviruses, in order to assure specificity.

Successful cultivation of WNV from CSF or brain tissue has had a very low yield in US cases. In New York City cases, a polymerase chain reaction (PCR) assay has been reported to be positive in as many as 55% of CSF but in only 10% of serum samples.[28,30] PCR assays may be more successful when applied to brain tissue, in which viral antigen may also be detected by immunohistochemistry.

The neurological changes appear to result from CNS invasion, with viral proliferation in glial cells and neurons, together with a cytotoxic immunological response to viral antigens.[10] Tissue responses include diffuse perivascular lymphocytic inflammation and formation of microglial nodules, together with neuronal degeneration. Areas of involvement include the thalamus, the brain stem, and proximal spinal cord. Cases clinically resembling paralytic polio are characterized by death of anterior horn cells.[26]

Treatment

Treatment is symptomatic and supportive. No controlled trials of either adjunctive measures, such as the use of osmotic agents or corticosteroids in the presence of cerebral edema, or of antiviral agents have been reported. Passive

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Table 3. Differential Features of Some Causes of Acute Flaccid Paralysis

Clinical Findings	WNV Myelitis	Polio	Guillain-Barré Syndrome	
			AIDP*	AMAN**
Antecedent illness	No	No	Yes, in 2/3	Yes, in 1/3
Headache	Frequent	Frequent	Infrequent	Infrequent
Fever	Yes	Yes	No	No
Muscle tenderness	Yes	Yes	No	No
Meningismus	Yes	Yes	No	Frequent
Symmetrical weakness	Infrequent	Infrequent	Yes	Yes
EOM weakness	No	No	Yes	Yes
Facial nerve paresis	No	Occasionally	Frequent	Frequent
Bulbar weakness	Yes	Some	Frequent	Frequent
Sensory loss	No	No	Yes	No
Encephalitis	Yes	Infrequent	Rare	No
Residual weakness	Common	Common	Occasionally	Common
Laboratory findings				
WBC (peripheral)	Normal or decreased	Normal or increased	Normal	Normal
CSF Protein	Elevated	Elevated	Elevated	Elevated
CSF WBC	Elevated	Elevated	Normal	Normal

*Acute inflammatory demyelinating polyneuropathy.

**Acute motor axonal neuropathy.

Source: Solomon T, Vaughn DW. Pathogenesis and clinical features of Japanese encephalitis and West Nile virus infections. *Curr Top Microbiol Immunol.* 2002;267:171-194.

Table 4. Encephalitis or Meningitis, Arboviral (includes California serogroup, Eastern Equine, St. Louis, Western Equine, West Nile, Powassan) 2001 Case Definition

Clinical description

Arboviral infections may be asymptomatic or may result in illnesses of variable severity sometimes associated with central nervous system (CNS) involvement. When the CNS is affected, clinical syndromes ranging from febrile headache to aseptic meningitis to encephalitis may occur, and these are usually indistinguishable from similar syndromes caused by other viruses. Arboviral meningitis is characterized by fever, headache, stiff neck, and pleocytosis. Arboviral encephalitis is characterized by fever, headache, and altered mental status ranging from confusion to coma with or without additional signs of brain dysfunction (eg, paresis or paralysis, cranial nerve palsies, sensory deficits, abnormal reflexes, generalized convulsions, and abnormal movements).

Laboratory criteria for diagnosis

- Fourfold or greater change in virus-specific serum antibody titer; or
- Isolation of virus from or demonstration of specific viral antigen or genomic sequences in tissue, blood, cerebrospinal fluid (CSF), or other body fluid; or
- Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF by antibody-capture enzyme immunoassay (EIA); or
- Virus-specific IgM antibodies demonstrated in serum by antibody-capture EIA and confirmed by demonstration of virus-specific serum immunoglobulin G (IgG) antibodies in the same or a later specimen by another serologic assay (eg, neutralization or hemagglutination inhibition).

Case classification

Probable: an encephalitis or meningitis case occurring during a period when arboviral transmission is likely, and with the following supportive serology: 1) a single or stable (≤ twofold change) but elevated titer of virus-specific serum antibodies; or 2) serum IgM antibodies detected by antibody-capture EIA but with no available results of a confirmatory test for virus-specific serum IgG antibodies in the same or a later specimen.

Confirmed: an encephalitis or meningitis case that is laboratory confirmed

Comment

Because closely related arboviruses exhibit serologic cross-reactivity, positive results of serologic tests using antigens from a single arbovirus can be misleading. In some circumstances (eg, in areas where two or more closely related arboviruses occur, or in imported arboviral disease cases), it may be epidemiologically important to attempt to pinpoint the infecting virus by conducting cross-neutralization tests using an appropriate battery of closely related viruses. This is essential, for example, in determining that antibodies detected against St. Louis encephalitis virus are not the result of an infection with West Nile (or dengue) virus, or vice versa, in areas where both of these viruses occur.

The seasonality of arboviral transmission is variable and depends on the geographic location of exposure, the specific cycles of viral transmission, and local climatic conditions. Reporting should be etiology-specific (see below; the 6 encephalitides/meningitides printed in bold are nationally reportable to CDC):

St. Louis encephalitis/meningitis

West Nile encephalitis/meningitis

Powassan encephalitis/meningitis

Eastern equine encephalitis/meningitis

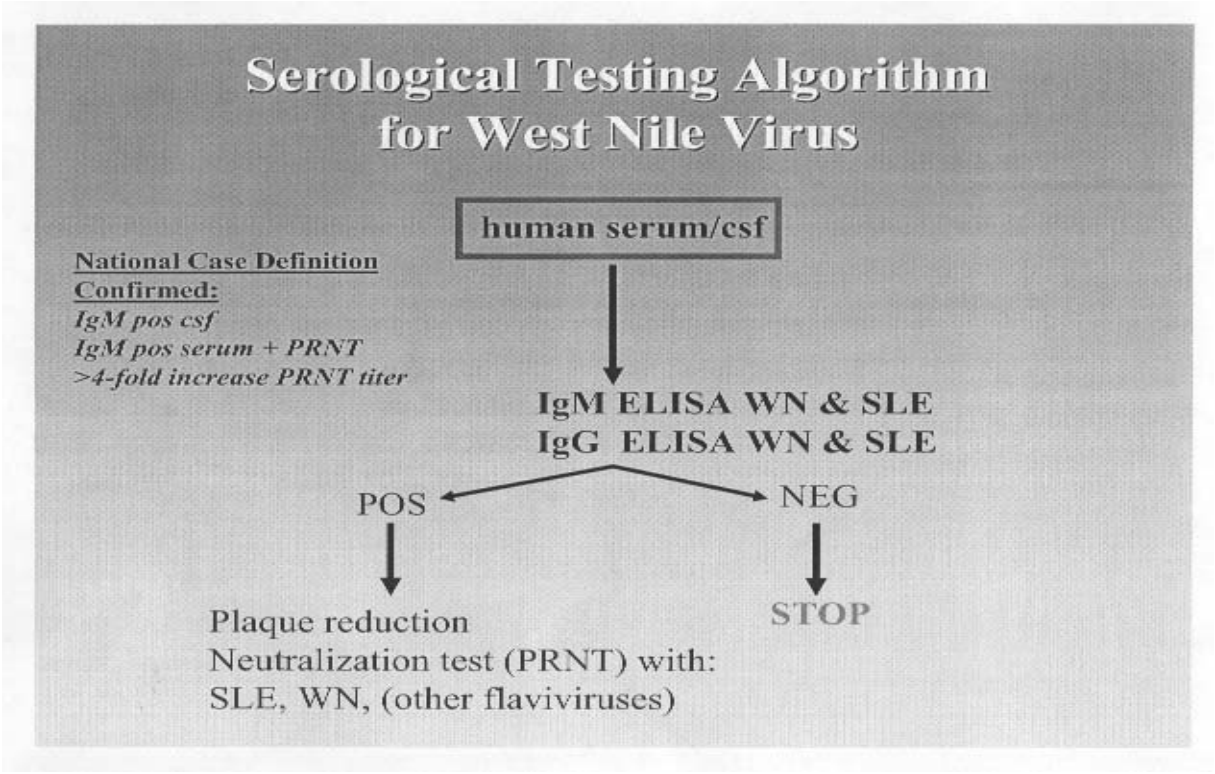
Western equine encephalitis/meningitis

California serogroup viral encephalitis/meningitis (includes infections with the following viruses: La Crosse, Jamestown Canyon, snowshoe hare, trivittatus, Keystone, and California encephalitis viruses)

Other viral CNS infections transmitted by mosquitos, ticks, or midges (eg, Venezuelan equine encephalitis/meningitis and Cache Valley encephalitis/meningitis)

Source: http://www.cdc.gov/epo/dphsi/casedef/encephalitiscurrent.htm.

Figure 2. Serological Testing Algorithm for West Nile Virus. CDC.



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immunization with WNV-immune serum protected hamsters from clinical illness and death when subsequently challenged with WNV.[31] Pooled intravenous immunoglobulin collected in Israel has been administered to WNV infected patients, but there is no data demonstrating its efficacy.[32,33]

Ribavirin and interferon α-2b each inhibit WNV replication and inhibit cytopathic effect in neural cells in vitro.[34,35] A multivariate analysis of 233 Israeli patients infected with WNV,[37] of whom received interferon α, found no evidence of survival benefit from this agent.[36] Interferon α-2a was ineffective in a randomized, placebo-controlled trial of treatment of Japanese encephalitis.[37] WNV is, as mentioned previously, very closely related to Japanese encephalitis virus. A randomized trial of interferon α therapy is underway, however. Several other small molecules, including mycophenolic acid, have been demonstrated to have in vitro activity against WNV.[38,39]

Prevention

While no vaccine is available for use in humans, an inactivated virus vaccine has received a license in the United States for use in horses.[40,41] A variety of experimental approaches to vaccine development have been reported, including the use of live attenuated chimeric vaccine backbone derived from yellow fever virus.[31,42] One of the patients who developed WNV infection by a laboratory accident had previously had dengue and had been vaccinated against yellow fever.[18] This suggests that immunity to these related viruses does not provide protection against WNV infection.

The most effective, and critical, means of prevention of WNV infection is a program of surveillance for arboviral surveillance and aggressive control of the mosquito serving as vectors within a region, together with education of the public. ArboNET is a cooperative WNV surveillance program involving CDC, 48 states, 5 cities, and the District of Columbia. This network accumulates and analyzes reports of WNV-infected mosquitoes, sentinel animals, dead birds, and ill humans and horses.[40,41,43] The lethality of WNV infection in crows and jays makes observations of die-offs of these *Corvidae* a potential early warning system for WNV activity. It has been reported that the detection of WNV infected dead birds prior to August 15 of both 2001 and 2002, was an early harbinger of the subsequent appearance of WNV disease in humans.[44]

Critical prevention measures include elimination of larval habitats, including such things as old tires, tin cans, and other containers that may accumulate water. Also considered in some instances is the spraying of insecticides to kill juvenile larvae and adult mosquitoes.[40] The combination of mosquito control methods selected for use in a control program depends on the type of mosquitoes to be controlled and the habitat structure. In emergency situations, wide area aerial spraying is used to quickly reduce the number of adult mosquitoes.

Personal protective measures are also of great importance (*see Table 5*). To avoid mosquito bites, one should wear long sleeves, long pants, and socks and apply DEET (N,N-diethyl-meta-toluamide) to exposed skin when outdoors, especially in the period from dawn to dusk. Extra protection

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Table 5. West Nile Virus: Repellent Use and Safety

Source: The CDC. Updated 10/04/02. http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm

Insect Repellent Use

Q. Why should I use insect repellent?

A. Insect repellents help people reduce their exposure to mosquito bites that may carry potentially serious viruses such as West Nile virus, and allow them to continue to play and work outdoors.

Q. When should I use mosquito repellent?

A. Apply repellent when you are going to be outdoors and will be at risk for getting bitten by mosquitoes.

Q. What time of day should I wear mosquito repellent?

A. Many of the mosquitoes that carry the West Nile virus are especially likely to bite around dusk and dawn. If you are outdoors around these times of the day, it is important to apply repellent. In many parts of the country, there are mosquitoes that also bite during the day, and these mosquitoes have also been found to carry the West Nile virus. The safest decision is to apply repellent whenever you are outdoors.

Q. How often should repellent be reapplied?

A. Follow the directions on the product you are using in order to determine how frequently you need to reapply repellent. Sweating, perspiration or getting wet may mean that you need to re-apply repellent more frequently. If you are not being bitten, it is not necessary to re-apply repellent. Repellents containing a higher concentration of active ingredient (such as DEET) provide longer-lasting protection.

Q. Should I wear repellent while I am indoors?

A. Probably not. If mosquitoes are biting you while you are indoors, there are probably better ways to prevent these bites instead of wearing repellent all the time. Check window and door screens for holes that may be allowing mosquitoes inside. If your house or apartment does not have screens, a quick solution may be to staple or tack screening (available from a hardware store) across the windows. In some areas community programs can help older citizens or others who need assistance.

Q. How does mosquito repellent work?

A. Female mosquitoes bite people and animals because they need the protein found in blood to help develop their eggs. Mosquitoes are attracted to people by skin odors and carbon dioxide from breath. Many repellents contain a chemical, N,N-diethyl-m-toluamide (DEET), which repels the mosquito, making the person unattractive for feeding. DEET does not kill mosquitoes; it just makes them unable to locate us. Repellents are effective only at short distances from the treated surface, so you may still see mosquitoes flying nearby. As long as you are not getting bitten, there is no reason to apply more DEET.

Q. Which mosquito repellent works the best?

A. The most effective repellents contain DEET (N,N-diethyl-m-toluamide), which is an ingredient used to repel pests like mosquitoes and ticks. DEET has been tested against a variety of biting insects and has been shown to be very effective. The more DEET a repellent contains the longer time it can protect you from mosquito bites. A higher percentage of DEET in a repellent does not mean that your protection is better-just that it will last longer. DEET concentrations higher than 50% do not increase the length of protection.

Q. How does the percentage of DEET in a product relate to the amount of protection it gives?

A. Based on a recent study:

- A product containing 23.8% DEET provided an average of 5 hours of protection from mosquito bites.
- A product containing 20% DEET provided almost 4 hours of protection
- A product with 6.65% DEET provided almost 2 hours of protection
- Products with 4.75% DEET and 2% soybean oil were both able to provide roughly 1 and a half hour of protection.

Choose a repellent that provides protection for the amount of time that you will be outdoors. A higher percentage of DEET should be used if you will be outdoors for several hours while a lower percentage of DEET can be used if time outdoors will be limited. You can also re-apply a product if you are outdoors for a longer time than expected and start to be bitten by mosquitoes. (For more information, see Table 1: Fradin and Day, 2002. See Publications page.)

Table 5 continued. West Nile Virus: Repellent Use and Safety

Source: The CDC. Updated 10/04/02. http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm

Q. Why does CDC recommend using DEET?

A. DEET is the most effective and best-studied insect repellent available. (Fradin, 1998). Studies using humans and mosquitoes report that only products containing DEET offer long-lasting protection after a single application.(Fradin and Day, 2002. See Publications page.)

Q. Are non-DEET repellents effective (eg, Skin-So-Soft, plant-based repellents)?

A. Some non-DEET repellent products which are intended to be applied directly to skin also provide some protection from mosquito bites. However, studies have suggested that other products do not offer the same level of protection, or that protection does not last as long as products containing DEET. A soybean-oil-based product has been shown to provide protection for a period of time similar to a product with a low concentration of DEET (4.75%) (Fradin and Day, 2002. See Publications page.).

People should choose a repellent that they will be likely to use consistently and that will provide sufficient protection for the amount of time that they will be spending outdoors. Product labels often indicate the length of time that protection that can be expected from a product. Persons who are concerned about using DEET may wish to consult their health care provider for advice. The National Pesticide Information Center (NPIC) can also provide information through a toll-free number, 1-800-858-7378 or http://npic.orst.edu/.

Q. I'm confused. None of the products in the store says "DEET."

A. Most insect repellents that are available in stores are labeled with the chemical name for DEET. Look for N,N-diethyl-m-toluamide or, sometimes, N,N-diethly-3-methylbenamide. Choose a repellent that offers appropriate protection for the amount of time you will be outdoors. A higher percentage of DEET should be used if you will be outdoors for several hours while a lower percentage of DEET can be used if time outdoors will be limited.

Using Repellents Safely

Q. Is DEET safe?

A. Yes, products containing DEET are very safe when used according to the directions. Because DEET is so widely used, a great deal of testing has been done. When manufacturers seek registration with the US Environmental Protection Agency (EPA) for products such as DEET, laboratory testing regarding both short-term and long-term health effects must be carried out. Over the long history of DEET use, very few confirmed incidents of toxic reactions to DEET have occurred when the product is used properly. (From the National Pesticide Information Center [NPIC], EPA re-registration eligibility decision. See http://npic.orst.edu/factsheets/DEETgen.pdf.)

Q. What are some general considerations to remember in order to use products containing DEET safely?

A. Always follow the recommendations appearing on the product label.

- Use enough repellent to cover exposed skin or clothing. Don't apply repellent to skin that is under clothing. Heavy application is not necessary to achieve protection.
- Do not apply repellent to cuts, wounds, or irritated skin.
- After returning indoors, wash treated skin with soap and water.
- Do not spray aerosol or pump products in enclosed areas.
- Do not apply aerosol or pump products directly to your face. Spray your hands and then rub them carefully over the face, avoiding eyes and mouth.

Q. How should products containing DEET be used on children?

A. No definitive studies exist in the scientific literature about what concentration of DEET is safe for children. No serious illness has arisen from use of DEET when used according the manufacturer's recommendations. The American Academy of Pediatrics has recommended that a cautious approach is to use products with a low concentration of DEET, 10% or less, on children aged 2-12. Most guidelines cite that it is acceptable to use repellents containing DEET on children older than 2 years. Other experts suggest that it is acceptable to apply repellent with low concentrations of DEET to infants older than 2 months.

Repellent products that do not contain DEET are not likely to offer the same degree of protection from mosquito bites as products containing DEET. Non-DEET repellents have not necessarily been as thoroughly studied as DEET, and may not be safer for use on children.

Table 5 continued. West Nile Virus: Repellent Use and Safety

Source: The CDC. Updated 10/04/02. http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm

Parents should choose the type and concentration of repellent to be used by taking into account the amount of time that a child will be outdoors, exposure to mosquitoes, and the risk of mosquito-transmitted disease in the area. Persons who are concerned about using DEET or other products on children may wish to consult their health care provider for advice. The National Pesticide Information Center (NPIC) can also provide information through a toll-free number, 1-800-858-7378 or http://npic.orst.edu.

Always follow the recommendations appearing on the product label when using repellent.

- When using repellent on a child, apply it to your own hands and then rub them on your child. Avoid children's eyes and mouth and use it sparingly around their ears.
- Do not apply repellent to children's hands. (Children tend to put their hands in their mouths.)
- Do not allow young children to apply insect repellent to themselves; have an adult do it for them. Keep repellents out of reach of children.
- Do not apply repellent to skin under clothing. If repellent is applied to clothing, wash treated clothing before wearing again.

Using repellents on the skin is not the only way to avoid mosquito bites. Children and adults can wear clothing with long pants and long sleeves while outdoors. DEET or other repellents such as permethrin can also be applied to clothing (don't use permethrin on skin), as mosquitoes may bite through thin fabric. Mosquito netting can be used over infant carriers. Finally, it may be possible to reduce the number of mosquitoes in the area by getting rid of containers with standing water that provide breeding places for the mosquitoes.

Q. Is DEET safe for pregnant or nursing women?

A. There are no reported adverse events following use of repellents containing DEET in pregnant or breastfeeding women.

Q. Are there any risks due to using repellents containing DEET?

A. Use of these products may cause skin reactions in rare cases. If you suspect a reaction to this product, discontinue use, wash the treated skin, and call your local poison control center. There is a new national number to reach a Poison Control Center near you: 1-800-222-1222.

If you go to a doctor, take the product with you. Cases of serious reactions to products containing DEET have been related to misuse of the product, such as swallowing, using over broken skin, and using for multiple days without washing skin in between use, for example. Always follow the instructions on the product label.

Repellents and Schools

Q. Should parents spray insect repellent on their children before they go to school?

A. Whether children spend time outside during the school day should determine the need for applying repellent. Because most schools in the United States have air conditioning, children's exposure to mosquitoes during the school day is not likely to be high. If children will be spending time outdoors (for example, in recreational activities, walking to and from school), parents may wish to apply repellent. Mosquito repellent containing DEET is the most effective in providing long-lasting protection from mosquito bites.

Q. Should children be given repellent to use during the day?

A. The age and maturity of the child should be taken into account before giving repellent to children for their own use. As with many other chemicals, care should be taken that DEET is not misused or swallowed. Parents should find out if a child will be outside during the school day, and should discuss proper use of the product with their children. Parents should also consult local officials to obtain policies and procedures specific to bringing repellent to school.

More information

Q. Where can I get more information about repellents?

A. For more information about using repellents safely please consult the EPA Web site: http://www.epa.gov/pesticides/citizens/insectrp.htm or consult the National Pesticide Information Center (NPIC), which is cooperatively sponsored by Oregon State University and the US EPA. NPIC can be reached at: http://npic.orst.edu/ or 1-800-858-7378.

Continued from page 59

may be gained by treating clothes with repellents containing permethrin or DEET. It is also important to limit mosquito breeding grounds by eliminating standing water around the home.

Standard procedure has always required that donors of blood components be in good health at the time of donation, thus excluding the 20% of individuals with WNV infection who become symptomatic. Individuals with diagnosed WNV infection should defer donation until at least 14 days after resolution of the illness and at least 28 days after the onset of symptoms, whichever is the later date. In the absence of current or recent symptoms, an IgM positive antibody test result alone should not be grounds for deferral. Other *Flaviviridae* are known to be inactivated by heat or solvent detergent treatments used to prepare plasma derivatives.

The FDA has provided recommendations for donor deferral, and for product quarantine and retrieval related to reports of post-donation illnesses in the donor, or WNV infection in recipients of blood.[45] Because four-fifths of infections are asymptomatic, such measures may have limited effectiveness and there is a need for effective screening tests. Such tests would also be applied to organ donors. Finally, WNV is classified as a BSL3 agent and appropriate protective measures must be used in laboratories processing potentially affected specimens.

Cases of WNV infection must be reported to their local public health authority.

Conclusion

The introduction of WNV into North America provided a striking lesson in the globalization of infectious diseases. It can be expected that the infection will continue to spread through large parts of the western hemisphere, causing increasing disability and death. This highlights the need for improved public health structures in both developed and lesser developed countries, as well as the need for development of therapeutics.

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Physician CME Questions

33. Which of the following is correct?
    a. West Nile virus (WNV) has been endemic in North America for 2 decades.
    b. The normal WNV transmission cycle requires only mosquitoes and birds.
    c. WNV, like the viruses that cause dengue fever and yellow fever, is a flavivirus.
    d. WNV is a DNA virus.

34. Which of the following is correct?
    a. In North America, WNV is transmitted only during the summer and early autumn.
    b. Transfusion of contaminated blood products may lead to transmission of WNV infection.
    c. Human-to-human transmission of WNV results from aerosolization of WNV during coughing.
    d. Most human WNV infections are clinically inapparent.

35. Which of the following is correct?
    a. The usual incubation period of WNV is 10-21 days.
    b. Approximately one in 150 human WNV infections in the United States affect the central nervous system.
    c. The young are the most vulnerable to central nervous system infection with WNV.
    d. Muscle weakness in WNV infection is the result of an acute myositis.

36. Which of the following is correct?
    a. WNV infection may, in some cases, resemble acute poliomyelitis.
    b. The peripheral WBC is invariably elevated in WNV infection.
    c. Most cases of central nervous system infection due to WNV are accompanied by a predominantly neutrophilic CSF pleocytosis.
    d. Most cases of central nervous system infection due to WNV are accompanied by a marked decrease CSF glucose concentration.

37. Which of the following is correct?
    a. The diagnosis of infection due to WNV may be made by detection of IgM antibody, by enzyme-linked immunosorbent assay, to viral antigens in serum or CSF.
    b. The absence of detectable antibody against WNV in the first 14 days of illness eliminates WNV infection from diagnostic consideration.
    c. Recent yellow fever vaccination does not cause serological cross reactivity with WNV antigens.
    d. WNV is readily recoverable in tissue culture of CSF from almost all patients with central nervous system infection due to WNV.

38. Which of the following is correct?
    a. DEET is not effective in repelling the kinds of mosquitoes that carry WNV.
    b. IgM antibody to WNV may persist for 6 or more months.
    c. Parrots and parakeets are the kinds of birds that are the predominant target of WNV.
    d. Humans are the only mammals infected by WNV.

Answers: 33. (c); 34. (d); 35. (b); 36. (a); 37. (a); 38. (b)

In Future Issues:

SARS—

Michele Barry, MD

PHARMACOLOGY WATCH

Pneumococcal Vaccine Ineffective at CAP Prevention

Pneumococcal vaccine protects older adults from developing pneumococcal bacteremia but does not prevent community-acquired pneumonia (CAP), according to a new study from Group Health Cooperative in Seattle. The study reviewed records of more than 47,000 adults aged 65 and older who were followed for more than 3 years. During that period 1428 were hospitalized with CAP, 3061 were diagnosed with outpatient pneumonia, and 61 had pneumococcal bacteremia. Prior receipt of the pneumococcal vaccine was associated with a reduction in the risk of pneumococcal bacteremia (HR 0.56; 95% CI, 0.33-0.93), but an increased risk of hospitalization with CAP (HR, 1.14; 95% CI, 1.02-1.28). The pneumococcal vaccination did not change the risk of outpatient CAP (HR, 1.04; 95% CI, 0.96-1.13), or the combined outcome of inpatient and outpatient CAP (HR, 1.7; 95% CI, 0.99-1.14). The authors point out that these results are consistent with those of 4 meta-analyses, which also showed no reduction of CAP with the pneumococcal vaccine. They state, however, that the reduction in pneumococcal bacteremia, which is also consistent with results of other studies, is reason enough to administer the vaccine (*N Engl J Med*. 2003;348:1747-1755). A separate study in the same issue suggests that vaccinating children with pneumococcal vaccine may also benefit adults. Using CDC surveillance statistics, a dramatic reduction in invasive pneumococcal disease was found between the years 1998 and 1999 and the year 2001, one year after the licensing of the protein-polysaccharide conjugate vaccine with the largest decline in children younger than the age of 2, when a 69% reduction was seen. A reduction in disease rates for adults and, especially young adults, was also noted over this time period. Interestingly, the 35% reduction in penicillin-resistant pneumococcus was also noted over the same timeframe (*N Engl J Med*. 2003; 348:1737-1746).

Flu Vaccine Limits Hospitalization

The influenza vaccine is highly effective at preventing hospitalization and death during the influenza season. A recent study reviewed the records of more than 140,000 adults aged 65 and older during the 1998-1999 and 1999-2000 influenza seasons, during which 55.5% and 59.7%, respectively, were immunized. The flu vaccine was associated with a reduction in the risk of hospitalization for cardiac disease (reduction of 19% during both seasons [$P < 0.001$]), cerebrovascular disease (reduction of 16% during the 1998-1999 season [$P < 0.018$] and 23% during the 1999-2000 season [$P < 0.001$]), and pneumonia or influenza (reduction of 32% during the 1998-1999 season [$P < 0.001$] and 29% during the 1999-2000 season [$P < 0.001$]) and a reduction in the risk of death from all causes (reduction of 48% during the 1998-1999 season [$P < 0.001$] and 50% during the 1999-2000 season [$P < 0.001$]). The subgroups were well matched for major medical illnesses. The authors point out the extraordinary effectiveness of the influenza vaccine, which has also been seen in other studies, but they also point out that the national rate of vaccination against influenza was only 63% of adults older than the age of 65 in 2001 (*N Engl J Med*. 2003;348:1322-1332).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Verapamil Not Up To Competition

Controlled-onset extended-release (COER) verapamil "is not equivalent to atenolol or hydrochlorothiazide in preventing cardiovascular disease-related events" is the conclusion of the CONVINCE trial (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints). The study was terminated early by the sponsor for "commercial reasons." CONVINCE was initially designed to test the hypothesis that control of early morning blood pressure might reduce cardiovascular mortality given that acute myocardial infarction (MI), cardiovascular event-related death, and stroke all have their highest incidence during the early morning hours (6 AM to noon). More than 16,000 patients were randomized to receive COER verapamil or either of atenolol 50 mg or hydrochlorothiazide 12.5 mg. Other antihypertensives were added if needed. The main outcome was stroke, MI, or cardiovascular related death. Blood pressure control was virtually identical between the 2 groups. There were fewer myocardial infarctions in the COER verapamil group, but more strokes, and cardiovascular deaths were similar (hazard ratios: MI 0.82, CVA 1.15, CV death 1.09, all-cause mortality 1.08). Both groups had more cardiovascular deaths between 6 AM and noon (COER verapamil 99/277, atenolol or HCTZ 88/274). The authors state that low-dose thiazide diuretics and/or beta blockers remain first-line therapy for hypertension, a recommendation that is in line with the recent Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (*JAMA*. 2003;289:2073-2082).

International Companies Unite Against SARS

As researchers move closer to identifying the etiologic agent of SARS, several international drug companies are collaborating to develop a vaccine. GlaxoSmithKline has announced it is working with France's Institut Pasteur along with several other pharmaceutical companies to develop a vaccine. The SARS vaccine would have a massive worldwide market, and traditionally companies would compete to bring a product to market. But partially under urging from US government officials, companies such as Merck, Wyeth, Chiron, Baxter, J&J, and others have committed to collaborating in this important effort. Scientists involved in this process warn, however, that this process will likely take years.

New FDA Comissioner Brings Controversy

The pharmaceutical industry is still analyzing whether Mark McClellan, the FDA's new Commissioner, is friend or foe. The 38-year-old Commissioner has hit the floor running but has generated controversy in the process. Harvard trained as a physician and economist, McClellan was teaching medicine and economics at Stanford, and advising the Bush administration on health-care economics when he was tapped to head the FDA. The new Commissioner has pleased the pharmaceutical industry by pledging to speed the new drug evaluation process. But a new proposal to force drugmakers to switch some prescription drugs to over-the-counter (OTC) status is strongly opposed by the industry. Dr. McClellan confirmed to the *Washington Post* in late April that forced switches are being "actively considered." The controversy centers on nonsedating antihistamines. Schering-Plough recently took loratadine (Claritin) OTC with urging from the FDA. Now 2 competitor drugs, Aventis's fexofenadine (Allegra) and Schering-Plough's cetirizine (Zyrtec) are under consideration for forced switches to OTC status. Both these drugs have several years of lucrative patent protection during which time they are unlikely to pursue OTC status on their own. All 3 drugs are sold OTC in many other countries and are considered safer than current OTC antihistamines. The price of most drugs drop significantly when they are available OTC, a fact that is not lost on pharmaceutical companies or consumer groups. Opposing the powerful pharmaceutical lobby has never been politically savvy, but Dr. McClellan may choose to court an even more powerful lobby—the American health care consumer.

Janssen: 'Dear Doctor' Letter for Risperidone

Janssen pharmaceuticals has issued a "Dear Doctor" letter concerning its antipsychotic medication risperidone (Risperdal). The letter warns health-care providers about a possible increased risk of stroke among elderly patients taking the drug. "Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients (mean age, 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo." Risperidone is approved for treatment of schizophrenia, but it is commonly used off label to treat delusional or aggressive behavior in elderly patients with dementia. ■

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Detection of Alzheimer's Disease and Dementia in the Preclinical Phase

Source: Palmer K, et al. *BMJ*. 2003; 326:245-247.

Alzheimer's disease (AD) is the most common form of dementia in America, but often escapes clinical attention until symptoms compromise quality of life, activities of daily living, or safety. Interventions might be enhanced by early detection of AD, but little investigation of early detection techniques has been done.

Palmer and colleagues evaluated 1435 persons aged 75-95 years who were without dementia at baseline. All persons underwent evaluation at baseline, 3 years, and 6 years with 3 different tools; subjects were asked, "Do you currently have any problems with your memory?" Additionally, each subject underwent mini-mental status examination, and neuropsychological testing assessed cognitive function.

At follow-up, almost 20% of survivors had dementia. All 3 screening tools, if positive, increased relative risk of AD. Having a memory complaint at baseline doubled the relative risk of subsequent dementia, and cognitive impairments increased relative risk of dementia by 2- to 5-fold.

Although using all 3 tools had a high predictive value if positive, the tools are too insensitive for routine employment, since only 18% of persons who ultimately developed dementia were identified using this 3-step process. That we can identify, with some reliability, a subgroup of persons likely to progress to dementia is promising. For broader applicability, more sensitive screening tools will be required. ■

Shoe Design and Plantar Pressures in Neuropathic Feet

Source: Praet S, et al. *Diabetes Care*. 2003;26:441-445.

Clinicians have tried a variety of maneuvers to reduce the incidence and effect of neuropathic foot ulcers in an attempt to reduce their subsequent morbidity. Since a substantial proportion of diabetics will ultimately develop distal sensory neuropathy and be at risk of foot ulcers, learning which type of footwear might help minimize the consequences of this neuropathy is of great importance. The most commonly used orthopedic shoe for diabetic neuropathy is the "rocker bar" variety (RB shoe), others suggest that a simple extra depth shoe, which is typically less expensive, more cosmetically pleasing, and more readily accessible, may be equally effective.

Praet and colleagues studied 10 diabetic women suffering from peripheral sensory neuropathy, but without evidence of foot deformity or ulceration. Women were tested in 3 categories of shoes: Category A were simple popularly styled traditional shoes, category B were extra depth shoes, and category C were specially crafted (based upon plaster casts of feet) shoes with rocker bottoms.

Overall, only the RB shoes effectively reduced forefoot pressure more than traditional "over the counter" footwear. Praet et al acknowledge that choosing footwear for any one individual diabetic remains a difficult choice and that shoe-specific pressure measurements in different types of footwear may be the best alternative for some patients, especially for those who balk at use of the less cosmetically acceptable RB shoes. ■

TSH in Assessment of Hypothyroidism

Source: Meier C, et al. *BMJ*. 2003; 326:311-312.

Although there is good agreement that thyroid stimulating hormone (TSH) is the most appropriate indicator of hypothyroidism, it is little understood whether absolute levels of TSH correlate either with degree of tissue effect of hypothyroidism, or levels of thyroid hormone. Meier and colleagues used a composite of clinical score, ankle reflex time, CK, and total cholesterol as markers of what they term "thyroid hormone action at the tissue level." They then correlated TSH with thyroid hormone levels and tissue parameters.

The correlation of tissue parameters and TSH was weak. This review suggests that there is a poor correlation between levels of TSH and clinical or metabolic severity of hypothyroidism. Meier et al have no quarrel with the sensitivity and diagnostic accuracy of TSH to discern the presence or absence of hypothyroidism. Rather, they hypothesize that once TSH is maximally stimulated, no further increase will occur, despite progressively greater degrees of hypothyroidism. Meier et al suggest that thyroxine treatment should be guided by clinical signs and thyroid hormone concentrations, rather than solely by TSH concentration. ■

Oral Vitamin D3 Supplementation on Fractures and Mortality

Source: Trivedi DP, et al. *BMJ*. 2003;326:469-472.

Despite recent enhanced clinician and public awareness, prevention and treatment goals for osteoporosis (OSPS) remain inadequately fulfilled. A variety of lifestyle and pharmacologic tools have been applied to OSPS management, including Vitamin D (VitD) supplementation, with some, albeit inconclusive, success.

This trial was a pilot study using VitD (cholecalciferol) supplementation in a British senior citizen population (age range, 65-85) solicited by mail (n = 2686) to participate in a placebo-controlled trial lasting 5 years. Unusual in this trial was the dosing methodology, which administered a single 100,000 IU VitD capsule once every 4 months for 5 years—not once daily, but once (total capsules administered in 5 years = 15). Participants were instructed to take the capsule they received in the mail immediately upon receipt, and respond by mail on a form indicating that they had indeed taken the medication.

Compared to placebo, the treatment group had a 22% lower rate for first fracture (any site) and a 33% lower hip, wrist, forearm, or vertebrae fracture rate. The parathyroid hormone concentrations did not differ significantly between active VitD and placebo, despite a 40% higher VitD level in the former.

Ultimately, the 100,000 IU dose of VitD is approximately equivalent to 800 IU per day, which has been used in other trials. However, the convenience, lack of toxicity, and monetary savings (in the United Kingdom, 3 capsules of 100,000 IU vitD costs less than 1 pound) provide intriguing stimuli for a larger trial. ■

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Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

Source: Rowbotham M, et al. *N Engl J Med*. 2003;348:1223-1232.

Neuropathic pain (NPP) is often described as "opioid resistant," based upon some limited human and animal studies. On the other hand, parenteral opioid analgesia has produced success in NPP. Although data on postherpetic neuralgia indicate a degree of efficacy with opioid analgesia, other NPP syndromes are not well studied in prospective, blinded studies.

Because of the ethical boundary of administering placebo to patients suffering chronic pain, a study was performed comparing 2 different dosing levels of levorphanol, a potent mu-opioid agonist, for patients (n = 100) suffering chronic NPP, in a double-blind fashion. Patients were administered either 0.15 mg or 0.75 mg capsules, and allowed to titrate up to as many as 7 capsules 3 times daily (levorphanol has a 6-8 hour duration of analgesia). The primary outcome of the study was degree of pain reduction; secondary outcome was time to pain relief. The study period was 8 weeks duration.

As perhaps might be intuitive, high-strength levorphanol reduced pain to a significantly greater degree than in the lower-strength group, despite the option available to patients of up-titrating their medication dose. Encouragingly, both groups did report levorphanol efficacy (pain reductions, 21% and 36%). Contrary to popular wisdom, tolerance to opioid analgesia was not evidenced. Additionally, the magnitude of pain reduction in the high-strength group was similar to that achieved with other more traditionally used NPP tools like tricyclic antidepressants and gabapentin.

Clinicians who have excluded opioid analgesia as an effective tool in NPP may need to consider these data in their decision process. ■

Tacrolimus Ointment vs. Topical Corticosteroids in Atopic Dermatitis

Source: Ellis C, et al. *J Am Acad Dermatol*. 2003;48:553-563.

For several decades the mainstay of management of atopic dermatitis (AD) has been corticosteroids (CSD), usually administered topically. When AD is mild-moderate, low, and mid-potency, CSD often suffices, but more severe disease may require high-potency agents, or even systemic therapy. Since CSD can produce both local effects like skin atrophy and systemic effects such as hypothalamic-pituitary suppression, chronic administration requires a degree of caution. Recently, a class of topical immunomodulator agents (IMA), exemplified by tacrolimus (Protopic) and pimecrolimus (Elidel), has been offered for clinical use as an alternative to CSD and appears to be equally efficacious. There are no serious side effects of IMA, and they have been demonstrated to be both safe and effective in children as young as 2 years, with minimal side effects.

For patients with moderate-to-severe AD, the cost of treatment was similar for either high-potency CSD and IMA for a 4-week treatment regimen. For short-term treatment (2 weeks), IMA is more cost effective than CSD because there is less requirement for secondary interventions. If lower potency and less costly CSD are used efficaciously, the cost efficacy of IMA becomes less favorable. The combination of safety, efficacy, and cost has important therapeutic implications for the role of IMA in AD. ■