

West Nile Virus: A Review

In recent years, West Nile Virus (WNV) has emerged in temperate regions of Europe and North America, presenting a threat to public, equine and animal health. One year after recognizing its presence in Ontario's mosquitoes and birds, human cases of infection due to WNV have been reported.

As of October 7, 2002, the Ontario Ministry of Health and Long-Term Care has confirmed nine human cases of West Nile Virus infection, while further blood test results of 37 other probable cases are pending.¹

The virus was first recognized in the West Nile district of Uganda, in 1937. Since that time, it has been known to cause human outbreaks throughout much of Africa, Asia, the Middle East and Europe. It first appeared in North America in 1999. It is unknown how the virus made its way to this continent. However, because it first appeared in New York City, an international gateway, travel and commerce may have played a role.²

WNV has been known to cause infections associated with a broad range of symptoms. While about 80% of individuals infected with the virus do not develop symptoms, about 20% will develop a febrile illness, usually mild and lasting three to six days. About 1 in 150 infected persons will develop meningitis or encephalitis. Advanced age is an important risk factor for neurologic disease.³ Muscle weakness is another notable feature of this infection, attributable in some cases to involvement of anterior horn cells or motor neurons.⁴ The incubation period is typically between 3 to 15 days.


West Nile Virus is maintained in an enzootic cycle involving culicine mosquitoes and corvid birds (crows, ravens and jays). The virus will multiply in both hosts until the early fall. When conditions are right, mosquitoes that bite both humans and birds can become infected and pose a threat to humans. Human outbreaks in Israel and the United States have often been preceded by dramatic death rates in birds.

The risk of viral transmission in blood transfusion products and organ transplants is currently being

investigated by the Centre for Disease Control and Prevention. Blood transfusion services have been alerted to exclude individuals who may have early symptoms of West Nile virus infection.⁵

Physicians may order WNV testing of blood and cerebrospinal fluid, which is referred by MDS to the Toronto Public Health Laboratory. Cross reactivity amongst several viruses of the Flavivirus family (i.e. St Louis Encephalitis Virus and WNV) will often be reflected in initial serologic testing. For this reason, all positive assays, including seroconverted samples, are further tested at the National Microbiology Laboratory in Winnipeg, by plaque reduction neutralization assay.

There is no specific treatment for West Nile Virus infection. When necessary, affected individuals are hospitalized in order to receive intravenous fluids, respiratory support, and prevention of secondary infections.

Individuals may reduce their chances of becoming ill by protecting themselves from mosquito bites. When outdoors, application of a repellent containing DEET can be helpful. Products containing 10 to 50% DEET are sufficient under most conditions and can be reapplied according to the manufacturer's instructions. The American Academy of Pediatrics recommends that repellents containing no more than 10% DEET be used on children. DEET is not recommended for infants younger than 2 months of age. When possible, long-sleeved clothes and long pants treated with repellents should be worn. The number of places available for mosquitoes to lay their eggs should be limited by eliminating standing water sources from around homes. 

References

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3. Petersen LR, Hughes JM. *N Engl J Med* 2002; 347(16):1225 – 1226.
4. Leis AA et al. *N Engl J Med* 2002; 347(16).
5. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5137a5.htm>



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Deep Vein Thrombosis: investigation of inherited risk


Approximately 15-20% of the population has an inherited predisposition to venous thromboembolism (VTE) and identifying such patients is helpful for the purpose of VTE risk counseling and management. The most common genetic defects associated with VTE are the Factor V Leiden (FVL) and prothrombin mutation (PT) which occur in 2-7% and 1-4% of patients of European descent respectively.¹ Persons heterozygous for either of these mutations have a 3-5 fold increase in risk of thrombosis (1/250 affected persons per year) and in homozygotes the risk is significantly higher (50 fold). Due to the frequency of these hereditary risk factors it is not uncommon to find patients who carry more than one mutation (double heterozygotes), hence the need to screen for all defects.² A full thrombophilia screen will identify at least one defect in approximately 50% of all VTEs.

Screen for thrombophilia in the following groups:³

1. First episode of idiopathic VTE at 50 years or younger.
2. A history of 2 or more episodes of recurrent thrombosis, especially if unprovoked.
3. Thrombosis in an unusual site e.g.: cerebral, mesenteric, upper limb etc.
4. Positive family history with one or more first degree relatives with a documented history of idiopathic VTE.
5. Women who develop thrombosis in pregnancy or following recent institution of a hormonal agent.
6. Women who have an unexplained recurrent pregnancy loss.

Timing of Investigations

There is little rationale to perform complete testing upon initial presentation with an acute VTE since these findings do not affect acute management and may be spuriously abnormal. Tests not affected by anticoagulants or the acute inflammatory state of a VTE include fasting homocysteine, molecular studies, antiphospholipid antibody studies and APCR. Protein S and C, antithrombin and Factor VIII should only be measured in the absence of coumadin or after resolution of acute inflammatory effects.

These tests should be ordered as a group of tests rather than individually, however since only one of these tests is covered by OHIP (Antithrombin), this battery of tests will incur a charge to the patient. Some of these costs may be covered by private insurance. 

References

1. Dr. Sheppard. J. Activated protein C resistance: The most common risk factor for venous thromboembolism. *Am Board Fam Pract.* 2000; 13(2):111-115.
2. U Seligsohn and A Lubetsky. Genetic Susceptibility to Venous Thrombosis. *N Engl J Med.* 2001; 344 (16): 1222-1231.
3. J Hirsh and A Lee. How we diagnose and treat deep vein thrombosis. *Blood.* 2002; 99:3102-3110.



A substantial fraction of venous thromboembolic events are due to mutations in genes that directly affect coagulation.

“Thrombophilia is finally being appreciated by the medical community.”

Douglas A Triplett, MD.

Thrombophilia Investigations suggested include:

	Hereditary	Acquired	Prevalence	Incidence in VTE
Antithrombin	●	●	1/2000	1-2%
Protein C	●	●	1/2000	1-2%
Protein S	●	●	1/2000	1-2%
Fasting homocysteine	●	●	5-7%	15%
Activated protein C resistance	●	●	4-15%	15-20%
Factor V Leiden	●		4-15%	10-15%
Prothrombin G20210A mutations	●		2-4%	6-8%
Antiphospholipid Antibodies		●	2-5%	5-15%

The Bleeding Time

The medical literature clearly documents that pre-operative bleeding time performed as a screening test lacks clinical benefit. The bleeding time in isolation is not a predictor of surgical bleeding and conversely a normal bleeding time does not exclude the possibility of excessive hemorrhage. Furthermore the test is subjective and technically difficult to standardize.

The patient's individual or family history is of prime importance in assessing the possibility of a hemorrhagic disorder. When this history indicates the need for further investigation it is advisable not to rely on the bleeding time alone but rather to undertake a clinical and laboratory assessment at a facility with access to the necessary specialized resources.

Because of the evidence in the literature, MDS will not perform bleeding time estimation at our laboratory facilities.

References

1. Preoperative Bleeding Time Lacks Clinical Benefit: *Archives of Surgery* 1998; 133: 134-139.
2. MDS Topics in Laboratory Medicine: #77 October 1993.
3. The Bleeding Time Does Not Predict Surgical Bleeding. *Blood* 1992; 77: 12.

More On HPV Testing

In a previous MDS LabNews, the causal association between Human Papillomavirus (HPV) and cervical neoplasia was discussed. Also reviewed were the results of the National Cancer Institute's ALT Study, which supported the use of HPV testing in women positive for ASCUS (atypical cells of undetermined significance), to accurately and rapidly identify those who would be at significantly increased risk of cervical intraepithelial neoplasia.¹

It now appears that HPV testing has become the preferred diagnostic approach for specific groups of women with abnormalities on cytological exam. In the April 2002 issue of JAMA, the American Society for Colposcopy and Cervical Pathology published evidence-based guidelines for the management of women with all cytological abnormalities.² Whenever possible and permitted by the insurer, reflex HPV testing is the preferred approach for further investigation of women with ASCUS. Women with ASCUS who test positive for high risk HPV DNA should be referred for colposcopic evaluation. Women with ASCUS

who test negative for high-risk HPV DNA can be followed up with repeat cytological testing at 12 months, since the negative predictive value of an HPV test for HSIL (high-grade squamous intraepithelial lesions) is extremely high.

Physicians who are interested in further investigating women with ASCUS may order high risk HPV testing by calling the MDS Customer Care Centre at 416-675-2215 or 1-866-MDS-TEST (1-866-637-8378).

The OHIP Schedule of Benefits does not cover the cost of this test but it may be reimbursed by private insurance plans.

References

1. National Cancer Institute of Canada: *Canadian Cancer Statistics*, 1999.
2. Wright TC, Cox JT, Massad LS, Twigg LB, Wilkinson EJ. 2001 Consensus Guidelines for the Management of Women With Cervical Cytological Abnormalities. *JAMA* 2002;287:2120-2129.

Cardiac Markers (CK-MB)

Community laboratories do not have the mandate to provide 'stat' testing for patients who may require urgent medical intervention. Such patients should receive diagnostic investigation in institutions equipped to undertake such intervention immediately if required on the basis of test results or clinical indicators.

MDS therefore does not offer cardiac markers including CK-MB (CK-2) on an urgent basis. We are able to undertake CK-MB measurement, reported as CK index, as an elective procedure for patients with a clinical possibility but low probability of myocardial infarction.

Please be sure to confine your ordering of CK-MB to this clinical situation and provide MDS with a 24-hour contact number. Periodically we generate test results suggestive of myocardial infarction and in such circumstances you will be contacted immediately. If you order CK-MB you must take the responsibility to be available to receive the result and provide contact information.

Please note that markedly elevated total Creatine Kinase is not an uncommon result at community laboratories, is usually of skeletal muscle origin and does not suggest a life-threatening situation. We therefore have no critical value for total CK.

When you wish to exclude myocardial infarction as an unlikely possibility in differential diagnosis you must specifically order CK-MB index and appreciate the analysis can be provided only as an elective procedure.



Reference Range Updates

Effective October 21st, 2002, revised reference values for quantitation of serum immunoglobulins and urine microalbumin will be implemented. Reference intervals for these analytes were revisited during validation studies completed for new instrumentation. Microalbumin (all ages) levels of up to 30 mg/L may be expected in the reference population. For the immunoglobulins, age stratification intervals for children and newborns are equivalent to those currently in use at The Hospital for Sick Children in Toronto. The new ranges follow:

Immunoglobulin G	
0 – 12 months	2.30 – 14.10 g/L
1 – 3 yrs.	4.50 – 14.30
4 – 6 yrs.	5.00 – 14.60
7 – 9 yrs.	5.70 – 14.70
10 – 13 yrs.	7.00 – 15.00
14 – 19 yrs.	7.20 – 15.80
> 20 yrs. (adults)	7.00 – 16.00

Immunoglobulin A	
0 – 12 months	up to 0.80 g/L
1 – 3 yrs.	0.20 – 1.00
4 – 6 yrs.	0.30 – 2.00
7 – 9 yrs.	0.30 – 3.10
10 – 13 yrs.	0.50 – 3.60
14 – 19 yrs.	0.50 – 3.50
> 20 yrs. (adults)	0.70 – 4.00

Immunoglobulin M	
0 – 12 months	up to 1.40 g/L
1 – 3 yrs.	0.20 – 1.50
4 – 6 yrs.	0.20 – 2.10
7 – 9 yrs.	0.30 – 2.10
10 – 13 yrs.	0.30 – 2.40
14 – 19 yrs.	0.20 – 2.60
> 20 yrs. (adults)	0.40 – 2.30



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Your comments and
suggestions are welcomed.
Please contact us at:

Medical Support
Department
100 International Blvd.,
Toronto, Ontario
M9W 6J6

Toll-free: (877) 849-3637
Fax: (416) 213-4090
www.mdsdx.com