

## **CURRENT DEVELOPMENTS IN MEDICINE AND PUBLIC HEALTH**

### **West Nile virus epidemic: contemporary challenge for public health in the western hemisphere**

#### **Introduction**

West Nile (WN) virus has emerged in recent years in temperate regions of Europe and North America, presenting a threat to public, equine, and animal health. The most serious manifestation of WN virus infection is fatal encephalitis in humans and horses, as well as mortality in certain domestic and wild birds.

#### **History**

West Nile virus was first isolated from a febrile adult woman in the West Nile District of Uganda in 1937. The ecology was characterized in Egypt in the 1950s. The virus became recognized as a cause of severe human meningoencephalitis in elderly patients during an outbreak in Israel in 1957. Equine disease was first noted in Egypt and France in the early 1960s. The first appearance of WN virus in North America in 1999, with encephalitis reported in humans and horses, and the subsequent spread in the United States may be an important milestone in the evolving history of this virus. In the U.S. from 1999 through October 18 2002, WN virus has been documented in almost all fifty states.

#### **Transmission cycle**

West Nile (WN) virus is amplified during periods of adult mosquito blood-feeding by continuous transmission between mosquito vectors and bird reservoir hosts. Infectious mosquitoes carry virus particles in their salivary glands and

infect susceptible bird species during blood meal feeding. Competent bird reservoirs will sustain an infectious viraemia for 1 to 4 days after exposure, after which these hosts develop life-long immunity. A sufficient number of vectors must feed on an infectious host to ensure that some survive long enough to feed again on a susceptible reservoir host. People, horses, and most other mammals are not known to develop infectious-level viraemias very often, and thus are probably "dead-end" or incidental-hosts. West Nile virus has been detected in dead birds of at least 110 species.

#### **Clinical features**

**Mild Infection:** Most WNV infections are mild and often clinically unapparent. Approximately 20% of those infected develop a mild illness (West Nile fever). The incubation period is thought to range from 3 to 14 days. Symptoms generally last 3 to 6 days. Reports from earlier outbreaks describe the mild form of WNV infection as a febrile illness of sudden onset often accompanied by non-specific constitutional symptoms.

#### **Severe infection**

Approximately 1 in 150 infections will result in severe neurological disease. The most significant risk factor for developing severe neurological disease is advanced age. Encephalitis is more commonly reported than meningitis. Myocarditis, pancreatitis, and fulminant hepatitis have been described.

#### **Clinical suspicion**

Diagnosis of WNV infection is based on a high index of clinical suspicion and

obtaining specific laboratory tests. WNV, or other arboviral diseases such as St. Louis encephalitis, should be strongly considered in adults >50 years who develop unexplained encephalitis or meningitis in summer or early fall. The local presence of WNV enzootic activity or other human cases should further raise suspicion. Obtaining a recent travel history is also important. Severe neurological disease due to WNV infection has occurred in patients of all ages. Year-round transmission is possible in some areas. Therefore, WNV should be considered in all persons with unexplained encephalitis and meningitis.

#### Diagnosis and reporting

The most efficient diagnostic method is detection of IgM antibody to WNV in serum or cerebral spinal fluid (CSF) collected within 8 days of illness onset using the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Since IgM antibody does not cross the blood-brain barrier, IgM antibody in CSF strongly suggests central nervous system infection. Patients who have been recently vaccinated against or recently infected with related flaviviruses (e.g., yellow fever, Japanese encephalitis, dengue) may have positive WNV MAC-ELISA results. WNV encephalitis is on the list of designated nationally notifiable arboviral encephalitides. Aseptic meningitis is reportable in some jurisdictions. The timely identification of persons with acute WNV or other arboviral infection may have significant public health implications and will likely augment the public health response to reduce the risk of additional human infections.

#### Laboratory findings

Among patients in recent outbreaks: Total leukocyte counts in peripheral blood were mostly normal or elevated, with lymphocytopenia and anemia also

occurring. Hyponatraemia was sometimes present, particularly among patients with encephalitis.

Examination of the cerebrospinal fluid (CSF) showed pleocytosis, usually with a predominance of lymphocytes. Protein was universally elevated. Glucose was normal.

Computed tomographic scans of the brain mostly did not show evidence of acute disease, but in about one-third of patients, magnetic resonance imaging showed enhancement of the leptomeninges, the periventricular areas, or both.

#### Treatment

Treatment is supportive, often involving hospitalization, intravenous fluids, respiratory support, and prevention of secondary infections for patients with severe disease. Ribavirin in high doses and interferon alpha-2b were found to have some activity against WNV in vitro, but no controlled studies have been completed on the use of these or other medications, including steroids, anti-seizure drugs, or osmotic agents, in the management of WNV encephalitis.

(Source: Modified from CDC MMWR: [www.cdc.gov](http://www.cdc.gov))

#### **Oncology/surgery: twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer**

Umberto Veronesi, M.D., Natale Cascinelli, M.D., Luigi Mariani, M.D., Marco Greco, M.D., Roberto Saccozzi, M.D., Alberto Luini, M.D., Marisel Aguilar, M.D., and Ettore Marubini, Ph.D.

#### Aim

A 20 years follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast conserving surgery early breast cancer management.



### Methods

From 1973 to 1980, 701 women with breast cancers measuring no more than 2 cm in diameter were randomly assigned to undergo radical mastectomy (349 patients) or breast-conserving surgery (quadrantectomy) followed by radiotherapy to the ipsilateral mammary tissue (352 patients). After 1976, patients in both groups with positive axillary nodes also received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil.

### Result

Thirty women in the group that underwent breast-conserving therapy had a recurrence of tumor in the same breast, whereas eight women in the radical-mastectomy group had local recurrences ( $P < 0.001$ ). The crude cumulative incidence of these events was 8.8 percent and 2.3%, respectively, after 20 years. In contrast, there was no significant difference between the two groups in the rates of contralateral-breast carcinomas, distant metastases, or second primary cancers. After a median follow-up of 20 years, the rate of death from all causes was 41.7% in the group that underwent breast-conserving surgery and 41.2% in the radical-mastectomy group ( $p=10$ ). Mortality from breast cancer was 26.1% and 24.3% ( $p=0.8$ ) respectively.

### Conclusions

The long-term survival rate among women who undergo breast-conserving surgery is the same as those undergoing mastectomy.

(*N Engl J Med* 2002; 347:1227-32)

**HIV Medicine: A randomized trial of the discontinuation of primary and secondary prevention prophylaxis against *Pneumocystis carinii* pneumonia after highly active**

### antiretroviral therapy in patients with HIV infection

Lopez JC, de Quiros B, Miro JM et al.

### Aim

To determine if prophylaxis against *Pneumocystis carinii* pneumonia (PCP) can safely be stopped in patients with HIV infection who have sustained CD4 cells in response to antiretroviral therapy.

### Method

In a randomized multicenter trial, primary and secondary prophylaxis against PCP was discontinued in patients with sustained response to antiretroviral therapy, defined by a CD4 count greater than 200/cubic mL and a plasma HIV-1 RNA level of less than 5000 copies/mL for at least three months. Prophylactic therapy was restarted if the CD4 count dropped to less than 200.

### Results

Four hundred seventy four patients were receiving primary prophylaxis (median CD4 count 342; 38% detectable HIV RNA). Two hundred forty of these patients discontinued prophylaxis and after a median follow-up of 20 months, there have been no episodes of PCP. Similarly, 113 patients were receiving secondary prophylaxis (median CD4 count 355; 245 detectable HIV 1 RNA). Prophylaxis was discontinued in 60, and after a median follow-up of 12 months there had not been instances of PCP.

### Conclusion

It is safe to discontinue primary and secondary prophylaxis against PCP in HIV-infected patients who respond to antiretroviral therapy when the CD4 count has increased to 200 or more per cubic millimeter for more than three months even in those with incomplete suppression of viral replication.

(*N Engl J Med*. 2001; 344 159-167)

**Infectious diseases/ critical care medicine: efficacy and safety of recombinant human activated protein C for severe sepsis**

Bernard GR, Vincent J-L, Laterre P-F et al.

**Aim**

To investigate whether drotrecogin alfa (activated) (recombinant human activated protein C), a compound demonstrated to have anti-inflammatory, antithrombotic, and profibrinolytic properties, could reduce overall 28-day mortality in patients with severe sepsis.

**Methods**

A randomized, double blind, placebo-controlled multi-center trial was performed in patients with evidence of systemic inflammation, acute infection, and organ failure due to the infection. Once enrolled, patients received a 96-hour infusion of either drotrecogin alfa (activated) dose of 24g/kg/hr or placebo. The primary end point was all-cause 28-day mortality.

**Results**

A total of 1690 total patients were studied, 840 in the placebo group and 850 in the treatment group. Demographics and severity of illness were similar in the control and treatment groups. Seventy-five percent of all patients had at least two organ dysfunctions. Seventy-five percent were on vasopressors and receiving mechanical ventilation at the time of enrollment. The lung and abdomen were the most common sources of infection, and the incidence of gram-positive and gram-negative infections was similar in both groups. Patients in both groups had similar laboratory evidence of ongoing inflammation and both fibrinolytic and coagulation abnormalities. The absolute reduction in mortality in the treatment group was 6.1% (24.7% vs. 30.8%,  $P=0.0005$ ). The

relative risk of death was reduced by 19.4% in the treatment group. Consistent treatment effect was observed in all the predefined subgroups. Biological markers (IL-6 levels and D-dimer) were also reduced in the treatment group. The incidence of serious bleeding was higher in the treatment group (3.5% vs. 2.0%,  $p=0.06$ )

**Conclusion**

Treatment of patients with severe sepsis with drotrecogin alfa (activated) significantly reduced mortality but was associated with a slightly increased risk of bleeding.

(*N Engl J Med.* 2001; 344:699-709)

**Comments**

Over the years, there has been a desperate search for interventions that modify the course of severe sepsis. Antibiotics and vasopressors remained the corner stones of treatment for severe sepsis. This is the first "novel" treatment agent for severe sepsis to have an impact on mortality with a favorable safety profile.

Where this drug will fit in with standard ICU practice is yet to be determined, but clinicians now have an alternative therapy for a disease with a mortality rate of 28% - 50%.

**Related reference**

Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101:1644-1655.

**Surgery/ critical care: Intensive insulin therapy in critically ill patients**

Van Den Berghe G, Wouters P, Weekers F, et al.

**Aim**

To investigate whether normalization of blood sugar in critically ill patients



improves prognosis and outcome.

#### Methods

This study was a prospective, randomized controlled trial in adults who were admitted to surgical intensive care units and who were also receiving mechanical ventilation. Patients were randomized to receive either intensive insulin therapy (maintaining blood glucose levels between 80 and 110 mg/dL) or conventional treatment (insulin only if blood glucose levels exceed a level between 180 and 200 mg/dL). The primary outcome measure was all-cause mortality during intensive care unit stay.

#### Results

A total of 1548 patients were enrolled. In the intensive insulin therapy group, mortality was reduced when compared to the conventional group (4.6% vs. 8%;  $p$  less than 0.04). The effect of intensive insulin therapy was attributable to its effect on mortality in patients who remained in the intensive care unit for more than 5 days (20.2% vs. 10.6%,  $p=0.005$ ). Intensive insulin therapy also reduced in-hospital mortality by 34% (10.9% vs. 7.2%;  $p$  less than 0.01), bloodstream infections by 46% (7.8% vs. 4.2%;  $p=0.003$ ), acute renal failure requiring any type of renal replacement therapy by 41% (8.2% vs. 4.8%;  $p$  less than 0.007), the median number of red blood cell transfusions by 50% (2 vs. 1;  $p$  less than 0.001), and critical illness polyneuropathy by 44% (51.9% vs. 28.7%;  $p$  less than 0.001). Patients receiving intensive insulin therapy were also less likely to require prolonged mechanical ventilation and intensive care.

#### Conclusion

Intensive insulin therapy used to maintain blood glucose levels between 80 and 110 mg/dL in critically ill surgical patients reduced both morbidity and

mortality. This effect was seen regardless of whether or not the patients had any prior history of diabetes mellitus (*N Engl J Med* 2001; 345:1359-1367)

#### Comments

This study has the potential to have a huge impact on the practice in both surgical and medical critical care. The authors are the first to note, however, that their data may not be extrapolated to a cohort of critically ill medical patients. Data already exists regarding glycaemic control in patients with stroke, myocardial infarction, and cardiac surgery. The results of this study add surgical ICU patients to a growing list where glycaemic control appears to impact outcome.

#### Related references

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2. Scott JF, Robinson GM, French JM et al. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST)/ *Stroke* 1999; 30: 793-799.
3. Rassias AJ, Marrin CA, Arruda J, et al. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. *Anesth Analg* 1999; 88:1011-1016.

#### **Zakari Y. Aliyu, MD, Msc, MPH**

Adjunct Assistant Professor of International Health, School of Public Health and Health Services, Department of International Public Health, George Washington University, 2300 I Street, NW, Washington DC 20037, U. S. A.  
E-mail: [zaliyu@cs.com](mailto:zaliyu@cs.com)