

CRITICAL CARE ALERT®

A monthly update of developments in critical care and intensive care medicine

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Preventing Nosocomial Infection in Cardiac Surgery by Topical Oronasal Decontamination

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In adult patients undergoing elective cardiac surgical procedures, perioperative decontamination of the nasopharynx and oropharynx with chlorhexidine solution substantially reduced nosocomial infections and nasal carriage of S aureus, and was associated with a mean reduction in hospital stay of 0.8 days.*

Source: Segers P, et al. *JAMA* 2006;296:2460-2466.

SEGRS AND COLLEAGUES OF THE UNIVERSITY OF AMSTERDAM conducted this randomized, double-blind clinical trial at a 480-bed community hospital that performs 1200 cardiac surgical procedures annually. They sought to determine whether the routine application of the disinfectant chlorhexidine to the nasopharynx and oropharynx of patients undergoing cardiac surgery would decrease the incidence of nosocomial infection, nasal carriage of *Staphylococcus aureus*, and the duration of hospital stay.

All patients over 18 years of age who underwent sternotomy for electively-scheduled cardiac procedures and gave consent during the 25-month study period were included. They were randomized to receive 0.12% chlorhexidine gluconate both as a nasal gel and as a 10-mL mouth rinse or an apparently identical placebo. Application of the experimental solutions began on hospital admission and continued 4 times daily until the nasogastric tube was removed postoperatively, usually the day after surgery. Nosocomial infections were diagnosed using accepted criteria from the Centers for Disease Control and Prevention (CDC), and nasal surveillance cultures for *S. aureus* were performed at fixed intervals. All patients underwent perioperative skin cleansing and administration of intravenous cefuroxime according to institutional protocols.

In this study, 991 patients were randomly administered chlorhexidine decontamination or placebo. The overall incidence of nosocomial infection was 19.8% in the chlorhexidine group as

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compared to 26.2% in the placebo group (absolute risk reduction [ARR], 6.4%; 95% confidence interval [CI], 1.1%-11.7%; $P = 0.002$). The most severe infections—lower respiratory tract infections and deep surgical site infections—were significantly less common in the active treatment group: ARR, 6.5% and 3.2%, respectively, $P = 0.002$ for each. The number needed to treat in order to prevent 1 nosocomial infection was 16. In addition, *S. aureus* nasal carriage was reduced by 57.5% in the patients who received chlorhexidine, as compared with 18.1% in the placebo group ($P < 0.001$). Total hospital stay for patients treated with chlorhexidine gluconate was 9.5 days, compared with 10.3 days in the placebo group (ARR, 0.8 days; 95% CI, 0.24-1.88; $P = 0.04$). One patient in the active treatment group experienced temporary discoloration of the teeth; there were no other reported adverse effects.

■ COMMENTARY

Nosocomial infections occur in as many as 20% of patients who undergo cardiac surgery, and are an important cause of mortality, morbidity, prolongation of hospitalization, increased antibiotic utilization, and excess costs. The source of these infections is often the patient's own organisms, the suppression of which by

means of topical decontamination would seem a logical and practical strategy for reducing their incidence.

This was a study in patients undergoing elective cardiac surgery, whose ICU stays were generally short. Whether beneficial effects of routine naso- and oropharyngeal decontamination with chlorhexidine similar to those obtained in this study would be observed in medical ICU patients or in a general surgical ICU population is not known at this point.

The treatment as used in this study was both safe and inexpensive. The reported daily cost for the decontamination regimen employed was \$7.20. With an average duration of decontamination of 2 days, the cost to prevent one nosocomial infection was estimated to be \$230. Costs would undoubtedly be higher using the prepackaged commercial kits for oral hygiene and decontamination that are currently being marketed in the United States; an estimation of the cost to prevent one infection, assuming clinical effectiveness similar to the efficacy demonstrated by Segers et al and using actual current costs in your hospital, would be a worthwhile exercise prior to widespread adoption of this treatment. ■

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Nurses Caring for Elders at Home Report More Errors at Work

ABSTRACT & COMMENTARY

By Leslie A Hoffman, RN, PHD

Department of Acute/Tertiary Care, School of Nursing, University of Pittsburgh

Dr. Hoffman reports no financial relationship to this field of study.

Synopsis: Compared with their peers, staff nurses with care-giving responsibilities for elders at home logged the least amount of sleep and also reported making significantly more errors at work.

Source: Scott, LD, et al. The impact of multiple care giving roles on fatigue, stress, and work performance among hospital staff nurses. *J Nurs Adm.* 2006;36:86-95.

THIS STUDY REPORTS FINDINGS FROM A SAMPLE OF 393 nurses who completed a daily log book for 28 days by recording information about work hours, sleep/wake patterns, perceptions of fatigue and stress,

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and errors or near errors during work shifts. The sample was randomly selected from the American Nurses Association national membership and consisted of nurses who provided direct patient care and were employed full time (≥ 36 h/wk). Nurses who worked for an agency or float pool were not eligible. The respondents were predominately female (79%), 45 ± 9 years of age (range, 22-66 yrs); 51% worked on medical-surgical floors or critical care units.

Of the respondents, 50% reported no dependents, 34% cared for children, 8% for elders, and 7% for elders and children. The proportion who reported drowsiness (struggling to remain awake) was similar among respondents who had no dependents (19%), cared for children (22%), cared for elders (23%), or cared for both children and elders (22%) ($P = \text{NS}$). A total of 199 errors and 213 near-errors were reported, including medication-related (56%), procedural (18%), charting (12%), and transcription mistakes (6%). Nurses who were providing elder care reported the least amount of sleep. When analyzed by logistic regression, the likelihood of making an error was doubled among nurses who were providing elder care at home (odds ratio [OR] = 2.38; $P = .005$). However, elder care was not associated with the risk of making near errors (OR = 1.33; $P = .33$). As anticipated, nurses caring for both elders and children reported higher levels of mental and physical fatigue ($P < .05$), compared to those without dependent care responsibilities.

■ COMMENTARY

Long work hours, once a hallmark of physician training, have been restricted for housestaff due to concerns about potential adverse effects. These restrictions were put in place to improve patient safety based on the belief that fatigue contributes to medical errors. Subsequently, several studies have reported that shorter work hours decreased errors and resulted in less stress and detrimental effects on morale and personal life.

This study reports a different and largely unrecognized source of stress that has the potential to impact patient safety. Informal (unpaid) care giving is an essential component of the health care system in the United States. More than 54 million Americans are estimated to be involved in family care giving, which often involves providing care for a chronically ill, disabled, or elderly family member. There is evidence that the profile of family caregivers is changing. Their mean age has decreased, making it more likely that care givers are full-time employees who are also responsible for dependent children. Combining these roles is difficult and the consequence is often sacrificing personal time

or restricting hours of sleep. Concurrently, the practice of working 12-hour shifts impacts the amount of sleep that is possible during the work week. A nurse who works a 12-hour shift and leaves work on time (which happens less than 20% of the time) has 12 hours to accomplish personal and family responsibilities, the daily commute, and sleep before the next shift.

Findings of this study provide interesting data regarding potential adverse effects of care giving responsibilities on medical errors. The strength of these findings is limited by the small sample and limited number of respondents who provided care for elders, and children and elders. Given the nursing shortage, escalating need for family care givers, and long work hours typical in nursing today, the topic is certainly worthy of further study. ■

Reversing Lung Collapse and Hypoxemia in Early ARDS

ABSTRACT & COMMENTARY

By David J. Pierson, MD

Synopsis: Using a stepwise lung recruitment protocol using airway pressures as high as 60 cm H₂O in patients with early ARDS, it was possible to achieve maximum reversal of atelectasis as determined by CT scan in 24 of 26 patients.

Source: Borges JB, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174:268-278.

BORGES AND COLLEAGUES IN SAO PALO, BRAZIL, studied 26 patients with acute lung injury or the acute respiratory distress syndrome (ARDS) to determine whether atelectatic lung areas could be fully recruited and oxygenation improved using a protocol employing progressively higher levels of positive end-expiratory pressure (PEEP). At the time of the study, the patients (median age 44 years, 46% women, with a variety of underlying pulmonary and non-pulmonary primary disease processes) had median PaO₂/FIO₂ ratios of 94 (range, 45-294) mm Hg, and had been receiving mechanical ventilation for a median of 2 (range, 1-7) days.

The patients were sedated and paralyzed, and venti-

lated with tidal volumes of approximately 6 mL/kg predicted body weight (PBW) using pressure control ventilation. A pressure-volume curve was constructed for each of the first 11 patients, who were studied in the computed tomography (CT) suite. After a 40-second recruitment maneuver at 40 cm H₂O of continuous positive airway pressure, PEEP was set at 2 cm H₂O above the lower inflection point. A protocol was then carried out which consisted of setting PEEP at 25 cm H₂O and then sequentially increasing it by 5 cm H₂O increments (with 15 cm H₂O of additional inspiratory pressure) in 2-minute intervals with intervening “rest” periods on 25 cm H₂O. This was continued until an airway pressure of 60 cm H₂O was reached during inspiration, or the numerical sum of PaO₂ + PaCO₂ exceeded 400 mm Hg, or an adverse effect (mixed venous oxygen saturation < 80%, mean arterial pressure < 60 mm Hg, or overt barotrauma on CT) occurred. Arterial blood gases were assessed at each step, as was lung recruitment by CT scan. The last 15 patients had late recruitment evaluated in the ICU rather than in the CT suite.

With the stepwise recruitment protocol employed, all 26 patients were studied at step 1, 17 of them at step 2, 13 at step 3, 11 at step 4, and only 8 at step 5 (the highest airway pressure). Mean arterial PCO₂ values at these steps were 70, 75, 81, 89, and 95 mm Hg, respectively; the mean arterial pH fell from 7.15 at baseline to 6.94 at step 5. No patient required discontinuation of the protocol because of hemodynamic compromise, although one patient developed subcutaneous emphysema.

Oxygenation improved and CT-determined lung collapse decreased in all patients. In 24 of the 26 patients, the authors’ criteria for “maximum lung recruitment” were met. Maximum airway pressures required for this recruitment ranged from 40 to 60 cm H₂O. There was a strong and inverse correlation between arterial oxygenation and the percentage of collapsed lung by CT ($R = -0.91$; $P < 0.0001$). By their technique for assessing lung over-inflation by CT, the authors did not detect this effect in the non-dependent areas of their patients’ lungs.

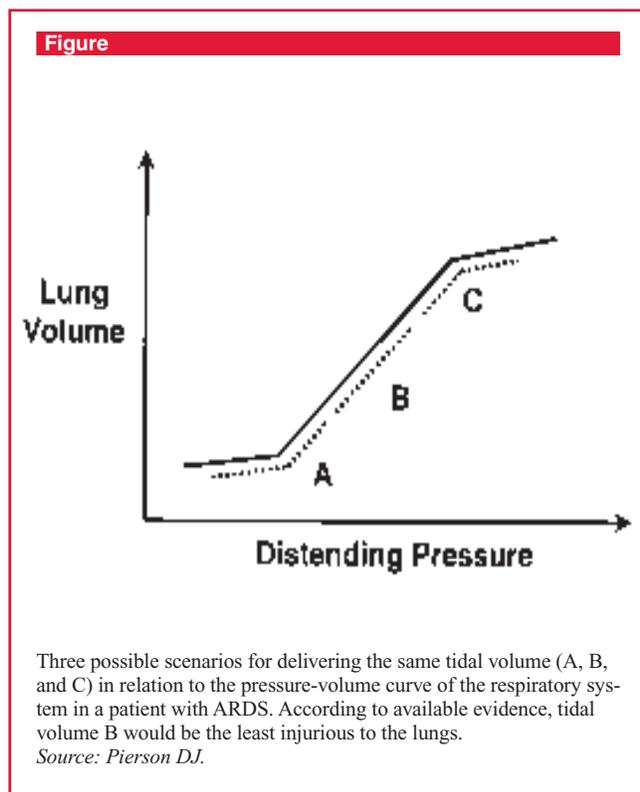
■ COMMENTARY

In managing patients with ARDS, using low tidal volumes (≤ 6 mL/kg PBW) and limiting lung distending pressures (keeping end-inspiratory plateau pressure ≤ 30 cm H₂O) saves lives—in comparison with the use of higher tidal volumes (12 mL/kg PBW) and higher plateau pressures.¹ A number of other interventions subjected to clinical trials—such as prone positioning, inhaled nitric oxide, high-frequency ventilation, and the

use of high levels of PEEP—have been shown to improve various indices of pulmonary mechanics and gas exchange, at least in the short term, but not to affect survival. So far, interventions to maximally recruit the lung in ARDS have demonstrated short-term physiologic benefits but have not been shown to improve clinical outcomes.

The concept of lung recruitment holds that, particularly in early ARDS, much of the lung is collapsed, and that optimally opening the collapsed alveoli and keeping them open throughout the ventilatory cycle will improve not only lung compliance and gas exchange but also clinical outcomes. This study by Borges et al deals with this last approach to managing patients with ARDS, and uses an approach to lung recruitment that is more vigorous than those used in many studies.

In many patients with ARDS, when they are completely relaxed and making no respiratory efforts, the relationship between airway pressure and lung volume has the 3-part shape illustrated in the Figure below. As distending pressure is initially increased from functional residual capacity in the absence of PEEP, much of the lung is atelectatic and little increase in volume occurs. As distal lung tissue opens with increasing pressure, an inflection point can often be identified, such that the slope of the curve of volume change over pressure change (compliance) increases. During tidal ventilation in



this portion of the curve (using PEEP to maintain end-expiratory lung volume), alveoli are presumably open but not over-inflated.

Above a certain pressure, however, hyperinflation occurs, as shown by a decrease in the slope of the curve. Theoretically, ventilation with a given tidal volume that occurs on the steep portion of the curve (corresponding to the dotted line labeled B in the Figure) will yield better gas exchange and produce less shear injury than the same tidal volume delivered at a lower lung volume (breath A), and also less injury from overdistension than if delivered at a higher lung volume (breath C). Tidal ventilation at A would subject collapsed alveoli to repetitive opening and closing, while tidal ventilation at C would stretch their walls and risk both overdistension injury and overt barotrauma.

In the present study, Borges et al have shown that maximum lung recruitment can be achieved in patients with early ARDS (moving them from position A to position B on the curve in the Figure), and that this is accompanied by optimization of gas exchange. The investigators also present evidence to support their contention that severe hyperinflation (ventilation at position C) was generally avoided. They conclude that, using their protocol of sequential lung recruitment and very high airway pressures, the index of $(\text{PaO}_2 + \text{PaCO}_2) \geq 400$ mm Hg, on 100% oxygen and with the patient paralyzed, 5% or less of collapsed lung units have been opened.

In the TV ads that show the latest luxury car swooping effortlessly through tight curves, there is always a disclaimer saying “Closed circuit with professional driver: do not attempt.” While the results presented in this article are intriguing, the interventions involved are potentially dangerous, and the message here should be the same as in the TV ads. As the authors state, “It is often possible to reverse hypoxemia and fully recruit the lung in early ARDS. Due to transient side effects, the required maneuver still awaits further evaluation before routine clinical application.” Also unknown at this point is whether the non-intuitive $\text{PaO}_2 + \text{PaCO}_2$ index will prove to be clinically relevant, and whether maximally recruiting the lung will be shown to benefit patients in terms of outcome. ■

Reference

- 1) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342:1301-1308.

Special Feature

What You Need To Know About West Nile Virus

By **Saadia R. Akhtar MD, MSc**

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WEST NILE VIRUS (WNV) INFECTION IS A GROWING epidemic that impacts more persons and more aspects of our health care system yearly. A significant percentage of affected patients require admission to and care in an intensive care unit (ICU). Those with the most severe manifestations—meningoencephalitis and/or acute flaccid paralysis—may have prolonged ICU stays with considerable long-term morbidity and mortality. Thus it is essential that all health care personnel in the critical care community become familiar with WNV.

Epidemiology

WNV is a single-stranded RNA virus of the family Flaviviridae which includes the arboviruses Japanese encephalitis and St. Louis encephalitis viruses. It was first discovered about 70 years ago in Uganda. It was not until the 1990s that it began to spread across the world and ultimately appeared in the United States in 1999.¹⁻² (The strain found in the United States is genetically almost identical to a strain from the Middle East and has not changed significantly since 1999.) Most human WNV infections occur at the times of peak mosquito activity which in the United States is July through October. However, cases have been reported from April to December. Persons of all ages may be affected.²

Between January 1 and November 28, 2006, 4028 cases of human WNV infection from across the continental U.S. were reported to the Centers for Disease Control and Prevention (CDC). This number represents a 27-fold increase in cases since 2001. The largest numbers of cases were detected in Idaho (889). Neuroinvasive disease (meningitis, encephalitis or myelitis) occurred in 34.4% or 1386 of these cases. Overall mortality was 3.4% (135 persons). This year the median age of affected patients was 51 years and 55% of patients were male.³

Transmission

Mosquitoes (of the *Culex* species) serve as the primary transmitters of WNV. They acquire infection by

feeding on infected birds and subsequently transmit the virus by biting humans or other birds and animals. (Birds of more than 100 species may be affected by WNV but the most common hosts are crows, jays and ravens in the Corvidae family.) Although fecal-oral transmission may occur among birds, its significance remains unclear. Humans and other animals do not develop high enough levels of viremia to be carriers of disease that uninfected mosquitoes can acquire: that is, there is no human-to-human transmission by mosquitoes and no animal-to-human transmission. There is, however, WNV transmission via human tissue and body fluids. This includes blood products (packed red cells, platelets and plasma), solid organs (either via organ transplantation or exposure of health care workers during autopsy), and breast milk. Transplacental transmission with devastating fetal outcomes has also been reported although this appears to be rare.^{4,5}

Clinical Features and Outcomes^{2,4,6-7}

The incubation period for human WNV infection is 2-14 days. It is estimated that 80% of infected persons are asymptomatic. The most common clinical presentation is that of a mild flu-like illness or what is termed West Nile fever: general malaise, fever, headache, myalgias and anorexia lasting 3-6 days, but more protracted courses have been described. Lymphadenopathy or a transient erythematous fine maculopapular rash of the face and trunk may be seen. Symptoms resolve fully with supportive care.

Neuroinvasive disease is the next most common manifestation: meningitis, encephalitis and/or myelitis with acute flaccid paralysis are well-described. These are estimated to represent less than 1% of WNV infections.⁸ Advanced age (> 50 years) is a clear risk factor for development of neuroinvasive disease. There is suggestion that diabetes and alcohol abuse may be factors as well.⁹

WNV meningitis resembles other viral meningitides and presents with fever, headache, nausea, vomiting, nuchal rigidity and photophobia. WNV encephalitis may present with all of these plus altered mental status, focal neurological changes and, less commonly, seizures. In WNV encephalitis, tremor is common and other movement disorders have also been reported. WNV acute flaccid paralysis may be symmetric or asymmetric and clinically and pathologically resembles poliomyelitis. There is hypo- or a-reflexia and often bowel and bladder dysfunction. Sensation, however, is intact. Pathology generally reveals destruction of anterior horn cells. Rarely, demyelinating syndromes have

been reported. Guillain-Barré syndrome is in the differential and must be ruled out with history, serological testing (see below) and, if needed, electromyographic and nerve conduction studies. Finally, WNV has also been reported to cause chorioretinitis and vitritis.⁸

On routine blood work, patients may have a mild leukocytosis or leukopenia and mild hyponatremia. With neuroinvasive disease, spinal fluid reveals mild to moderate pleocytosis (typically < 500 cells/mm³ although > 2000 have been reported), usually lymphocytic, with elevated protein and normal glucose. Head CT is generally unremarkable. Brain and spine MRI are normal in the majority of patients but in about 1/3 may reveal leptomeningeal or periventricular enhancement or increased signal on T2-weighted images of the thalamus, basal ganglia, brainstem or spinal cord.

Rarely, WNV has been reported to cause acute pancreatitis, hepatitis, nephritis, myocarditis or a septic shock-like syndrome with multisystem organ failure.

Overall, about one third of patients with WNV infection are hospitalized. In one series from the Colorado experience in 2003, 34-38% of patients with encephalitis or limb weakness required intubation and mechanical ventilation⁹: in another recent review of WNV-associated acute flaccid paralysis, 54% of patients required ventilatory support.¹⁰ ICU lengths of stay for these patients may be quite long (up to 118 days in one study).¹¹ Mortality of those with neuroinvasive disease is up to 7-18% and even higher in patients with acute flaccid paralysis with quadriplegia or those requiring mechanical ventilatory support.^{7,10,12} Significant neuropsychological impairments remain at 8-12 months of follow-up of patients with WNV neuroinvasive disease, with complaints including general fatigue and weakness, memory loss, cognitive dysfunction, tremor, gait abnormalities and depression. Those with acute flaccid paralysis in particular appear to have only limited recovery at best.¹²⁻¹³

Diagnostic Studies^{4,6}

Presence of WNV virus in any body fluid or tissue (usually detected by PCR) confirms the diagnosis of WNV infection. However, the likelihood of isolating the virus is quite low: by the time symptoms of illness develop, only very low levels of viremia are present. For instance, sensitivity of WNV PCR of CSF for patients with neuroinvasive disease is ≤ 50%.

Thus diagnosis is generally made by detection of serum or CSF antibodies to WNV in the appropriate clinical setting. Measurement of WNV IgM and IgG by antibody capture enzyme linked immunoabsorbent

Table

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 (e.g., 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 (less than or equal to 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.

CDC West Nile Virus Case Definition for Epidemiological Surveillance, from <http://www.cdc.gov/ncidod/dvbid/westnile/clinicians/surveillance.htm#casedef>

assay (MAC-ELISA) is the recommended method for confirming diagnosis. WNV IgM antibodies become positive by the 8th day of illness in $\geq 90\%$ of patients: it is important to note that they may persist for ≥ 6 -12 months. Presence of WNV IgM in the CSF confirms neuroinvasive disease. WNV IgG antibodies begin to appear at 1 week and are positive by 3 weeks in most infected patients: thus an increase in titer over this time period is strongly suggestive of acute infection. (The CDC case epidemiological case definitions for WNV infection are listed in the Table above.)

The duration of viremia and time to development of antibodies may be delayed in immunocompromised patients.

There is cross-reactivity between antibodies against WNV and antibodies against other viruses of the Flaviviridae family. Thus it is important to obtain appropriate clinical history to evaluate for these and to confirm any positive WNV antibody result by MAC-ELISA with further, more specific testing (plaque reduction neutralization assay).

Treatment¹⁴⁻¹⁶

Supportive care is the mainstay of therapy for WNV infection. There have been in vitro or animal studies and anecdotal human reports of therapy with WNV-specific-IV-immunoglobulin, ribavirin, interferon-alpha and corticosteroids. Results have been mixed. At this time there is insufficient evidence to recommend any of these therapies. PREVENTION^{2,4,7}

An equine WNV vaccine was licensed in 2003 and is currently in use. No human vaccine is yet available

although studies of candidate vaccines are ongoing.

Avoiding exposure to infected mosquitoes is the primary route of prevention of WNV infection. This is particularly important for persons who are elderly, pregnant or immunocompromised. Recommended methods include using insect repellent (containing DEET, permethrin, picaridin or oil of lemon eucalyptus), wearing long-sleeved and long-legged clothing, limiting outdoor activity during dusk to dawn (the peak mosquito hours), using door and window screens on homes and draining standing water to avoid creating mosquito breeding areas. Local mosquito control programs including spraying of large areas with larvicides or insecticides may be necessary in some locations.

The Food and Drug Administration recommends routine screening of blood products for WNV between June 1 and November 30. Furthermore, donors with symptoms of flu-like illness in the week prior to presentation to blood banks are asked to defer donation for one month. Cases of persons who are found to develop WNV infection after donation or persons with WNV illness who received transfusion in the month preceding onset of illness are also investigated in order to identify and remove infected blood products from the supply.

Summary

WNV infection is an increasing problem in the U.S. Our knowledge of its epidemiology and clinical impact is still developing. Until targeted therapies and a specific preventive vaccine are identified, supportive care remains the mainstay of treatment. It is clear that for now we will continue to encounter WNV infection cases resulting in severe illness, substantial morbidity including need for prolonged critical care services and support for long term neurological deficits, and significant mortality. ■

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CME Questions

16. Among patients undergoing elective cardiac surgical procedures, which of the following was associated with the routine perioperative use of topical decontamination of the nasopharynx and oropharynx with chlorhexidine solution?
 - a. An overall reduction in the incidence of nosocomial infections
 - b. A reduction in the rate of lower respiratory tract infection
 - c. A reduced hospital length of stay
 - d All of the above
 - e None of the above
17. Nurses who reported making an error were more likely to be:
 - a. providing care for dependent children.
 - b. providing care for elders and dependent children at home.
 - c. providing care for an elder at home.
 - d. assigned to a medical-surgical unit.
 - e. assigned to a critical care unit.
18. Which of the following interventions has been shown to reduce

mortality in patients with ARDS?

- a. Ventilation with tidal volumes of 6 rather than 12 mL/kg predicted body weight
- b. Inhaled nitric oxide
- c. Prone positioning
- d. All of the above
- e. None of the above

19. West Nile virus infection may be transmitted to humans in all of the following ways except:

- a. Blood transfusion
- b. Breast feeding
- c. Organ transplantation
- d. Bite of an infected dog
- e. Bite of an infected mosquito

20. Clinical manifestations of west Nile virus infection include:

- a. Flu-like illness
- b. Meningoencephalitis
- c. Chorioretinitis
- d. Flaccid paralysis
- e. All of the above

21. Diagnosis of west Nile virus infection is most commonly made by:

- a. Clinical history
- b. Head MRI
- c. Antibody detection
- d. Viral culture
- e. Positive response to ribavarin

22. Recommended preventive strategies for west Nile virus infection include:

- a. Avoiding contact with birds
- b. Limiting outdoor activity at midday
- c. Obtaining equine west Nile virus vaccine
- d. Applying insect repellents
- e. Refusing blood transfusions from July to October

Answers: 16 d; 17 c; 18 a; 19 d; 20 e; 21 c; 22 e;

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *Critical Care Alert*. Send your questions to: Robert Kimball, *Critical Care Alert* c/o AHC Media, LLC, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *Critical Care Alert* via the internet by sending e-mail to robert.kimball@ahcmedia.com. ■

In Future Issues:

Life-Sustaining Treatment and Surrogate Decision Makers

PHARMACOLOGY WATCH



Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Study: Long-Term Use of Clopidogrel for DES Patients

Patients with coronary artery disease who have received intra-coronary, drug-eluting stents (DES) may benefit from longer courses of clopidogrel than is currently standard. Researchers at Duke looked at 4,666 patients undergoing percutaneous coronary interventions with bare metal stents (BMS) (n = 365) or DES (n = 1501). Patients were followed up at 6, 12, and 24 months with the main outcomes being death, non-fatal MI, and the composite of death or MI at 24-month follow-up. For patients who received DES and were event free at 6 months, use of clopidogrel was a significant predictor of fewer events at 24 months (death rate 2.0% with clopidogrel vs 5.3% without, $P = 0.3$; death/MI 3.1% vs 7.2%, $P = 0.02$). However the same was not seen for BMS patients, with no significant difference in death rate or death/MI in the patients who took clopidogrel. For DES patients who were event free at 12 months, use of clopidogrel continued to improve outcomes (death rate 0% with clopidogrel versus 3.5% without, $P = .004$; death/MI 0% versus 4.5%, $P < 0.001$). For patients with BMS who were event free at 12 months, use of clopidogrel was still not associated with any change in death rate (3.3% vs 2.7% $P = 0.57$) or death/MI (4.7% vs 3.6%, $P = 0.44$). The authors conclude that extended use of clopidogrel in patients with drug-eluting stents may reduce the rate of death and MI. However the appropriate duration of clopidogrel administration has not yet been determined. (*JAMA* early release article posted 12/05/06). Implications of the study are significant in that current recommendations following PCI with drug eluting stents is for 3 to 6 months of clopidogrel. Several

studies have shown that these stents have increase risk of catastrophic stent thrombosis, higher than bare metal stents, months after the procedure. This has led some experts to recommend long-term use of clopidogrel, perhaps even lifetime use in patients who have received a DES. While the study does not make recommendations, it does confirm the fact that clopidogrel is beneficial for patients who received a DES for up to 2 years.

Drug Labels — A Prescription for Misunderstanding?

Prescription drug labels are commonly misunderstood according to a new study in the *Annals of Internal Medicine*. Nearly 400 English-speaking patients were enrolled in the study to assess their understanding of 5 different medication labels, all had relatively common instructions. Patients with low literacy, defined as 6th-grade level or less, were less likely to understand all 5 labels. Patients with low literacy read the instruction, "Take two tablets by mouth twice daily," but only 35% could demonstrate the number of pills to be taken daily. Patients who had multiple prescriptions were significantly

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. 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. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

more likely to misunderstand prescription labels. The authors admit that the patient's actual drug-taking behaviors were not observed, so authors could not demonstrate a link between misunderstanding the labels and actual medication errors. Still the authors suggest that patients of all ages would benefit from additional efforts to improve the clarity of prescription labels and suggest that the text and format of existing prescription containers should be redesigned and standardized (*Ann Int Med.* 2006;145: Epub ahead of print).

Osteonecrosis of the Jaw — New Side-Effect to Bisphosphate Use

With the widespread use of bisphosphonates for the prevention and treatment of osteoporosis, a new side effect, osteonecrosis of the jaw, has emerged as a concern. A new "Perspective" piece in the *New England Journal of Medicine* (November 30) helps answer the question, "Osteonecrosis of the Jaw—Do Bisphosphonates Pose a Risk?" Osteonecrosis of the jaw is characterized by exposed bone in the mandible, maxilla, or palate, and is often associated with dental disease, dental surgery, oral trauma, periodontitis, and poor dental hygiene. The author points out that the first case of osteonecrosis associated with bisphosphonates was reported in 2003, nearly 10 years after the drugs were first approved. Most reported cases are associated with high-dose intravenous bisphosphonates given to control metastatic bone disease where the rate is reported from 1.3% to 7%. The average patient with osteonecrosis had been receiving intravenous bisphosphonate therapy for 1.5 to 3 years. Use of oral bisphosphonates to treat osteoporosis involves doses that are often 10 times lower than intravenous doses. Fewer than 50 cases of osteonecrosis of the jaw have been associated with oral bisphosphonates, or approximately 1 in 100,000 patient years. There is concern that with long-term use of oral bisphosphonates, the rate of osteonecrosis may increase in the future. Some have even suggested that osteoporosis patients take a "drug holiday" after 5 years of therapy to reduce the risk; however, the benefit of the strategy is unclear at this time. A routine dental evaluation is reasonable prior to starting bisphosphonates; however, there is no reason to stop the drugs prior to dental treatment. Some oral surgeons advocate temporarily withholding drugs if invasive dental care is needed, but given the very long half-life of these drugs, it is unclear whether temporary cessation will have any effect on reducing the risk of

osteonecrosis, and more research is needed (*N Eng J Med.* 2006; 355:2278-2281).

Beta-Blockers and Depression — Unlinked?

Many physicians are cautious about the use of beta-blockers after myocardial infarction because of the risk of depression. A new study suggests that this concern may be unwarranted. Researchers from the Netherlands looked at 127 patients who had a myocardial infarction and were not taking beta-blockers versus 254 MI patients who were taking beta-blockers at 3, 6, and 12 months post MI. Outcomes were scores on 2 commonly used depression scales. No significant differences were found between beta-blocker users and non-beta-blocker users regarding the presence of depressive symptoms or depressive disorder, although a trend towards more depression was seen in patients with long-term use of beta-blockers and patients on higher doses. Use of a hydrophilic versus lipophilic beta blocker made no significant difference. The authors conclude that in post MI patients, use of beta-blockers is not associated with an increase in depressive symptoms or depressive disorders in the first year (*J Am Coll Cardio.* 2006;48:2209-2214).

FDA Actions

The FDA has approved telbivudine for the treatment of chronic hepatitis B virus (HBV) infections in adults. The drug is approved for patients with evidence of viral complication in either persistent elevations in serum transaminases or histologically active disease. The approval was based on a one-year study, and more than 1,300 patients showed significant decreases in HBV-virus DNA levels compared with lamivudine. Telbivudine, which is given as a 600 mg oral daily dose, will be marketed by Idenix Pharmaceuticals and Novartis as "Tyzeka."

FDA has approved the first generic version of ondansetron injection (Zofran) for the prevention of nausea and vomiting associated with chemotherapy and prevention of postoperative nausea and vomiting. The generic product will be manufactured by Teva and SICOR Pharmaceuticals. GlaxoSmithKline, which previously held the patent for Zofran, had 2005 sales of nearly \$850 million.

The FDA has approved expanded use of Herceptin for HER2-positive, early-stage breast cancer after mastectomy or lumpectomy. Previously, the drug was only approved for HER2-positive, metastatic breast cancer. ■