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The Rabies Symposium at CISTM 2007

SPECIAL REPORT

By Lin Chen, MD

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Dr. Lin H. Chen reports no financial relationship relevant to this field of study.

THE RABIES SYMPOSIUM AT THE CONFERENCE OF THE INTERNATIONAL Society of Travel Medicine in Vancouver, Canada, featured Drs. David Warrell, David Shlim, and Kanitta Suvansrinon. Professor Warrell presented Rabies Update: Epidemiology and Risk including Host Range. He described a 26-year-old woman from the United Kingdom who traveled to Himachal Pradesh, India, where she was bitten by a dog. The wound was cleaned with whisky and the patient treated with antibiotics and homeopathy. One month later, she returned to the UK still needing dressing changes. Two months later, she became tired, had back pain, and was described as "catching her breath when drinking liquids or felt wind." Two days later she experienced cardiac arrest and died 36 hours later.

The annual human deaths from rabies are ~24,000 in India, 3,200 in China, < 40 in North America, 36 in South America, 9 in Russia. In India during 2005, most bites were due to dogs; there were 16 million bites, 20,000 deaths, and 4 million courses of post exposure rabies prophylaxis given. In China for the year 2006, there were 3293 deaths (27% increase from 2005), and 8 million courses post-exposure prophylaxis administered. Rabies was the leading cause of infectious diseases from May 2006 to March 2007. About 95% of bites were from dogs, whose population ranges from 80-150 million. In rural China, 70% of households have guard dogs or pet dogs; only 2% are vaccinated, and usually they are not leashed. There are also many feral dogs. Use of post-exposure prophylaxis is inadequate in rural China. Among 178 rabies victims in Guizhou Province, 66% had no wound treatment, 72% received no vaccine, 28% received too few doses or delayed vaccination, and 99% had no rabies immune globulin (RIG).

Regarding the epidemiology of rabies, the UK had been free of indigenous rabies since 1902. However, in 1996 European bat lyssavirus (EBLV-2a)-infected Daubenton's bats (*Myotis daubentonii*) were discovered. In South Africa, rabies carriers include dog (southeast), fox (west), kudu (north), mongoose (central). In the Middle East, camels are common carriers. In the United States, carriers include skunks and raccoons, as well as bats. In Latin America, vampire bats are common rabies carriers. Less than 500 human deaths have occurred since 1975; children are bitten more commonly on their ears, while adults are bitten on their toes.

In Puerto Maldonado, Peru, bats are present in caves. Between July 2006 and

February 2007, 527 people had bites. In arid coastal Peru, irrigation tunnels house vampire bats. Local bat control uses an anticoagulant that is lethal for bats. In Melbourne, flying foxes are of concern. In 1996 and 1998, 2 females died of rabies-like illnesses. The usual perception of rabies is the "mad dog" form but a paralytic type of rabies is also very dangerous.

Rabies transmission can occur through bites, scratches, inhalation, transplanted cornea (1979-1996: 8 recipients in 6 countries), organ transplants (2004: 4 recipients died after receiving transplants of liver, kidneys, iliac artery; more than 1000 contacts were traced, and 20% did get post-exposure prophylaxis). A study found that among 1,882 foreigners living in Thailand, 1.3% had dig bites, and 8.9% had dog licks. [1]

Rabies is uncontrolled in most countries, and some countries have experienced a recent increase in incidence. It is important to educate travelers, advise that they clean bite wounds immediately and seek effective western post-exposure prophylaxis. Following bites, victims should receive rabies vaccine and rabies immune globulin (RIG). However, the latter may be unavailable or unreliable. Therefore, consider pre-exposure prophlaxis in consideration of time and peace of mind. Pre exposure prophylaxis has never failed, when boosted after exposure. Intradermal route is an economic solution in some countries, and it is well worth interrupting a trip to get complete post-exposure prophylaxis.

Dr. Shlim discussed pre-exposure rabies immunization for travelers, and highlighted the unique nature of rabies: 1) the time and source of exposure is almost always known and almost always preventable; 2) it is the most lethal infection of humans; 3) it has 100% fatality when encephalitis develops. He addressed the benefits of pre-exposure prophylaxis, what is adequate pre exposure prophylaxis, and when boosters should begin.

What are benefits of pre-exposure prophylaxis?

- Omits need for human rabies immune globulin (HRIG), which may be unavailable following exposure
- Reduces vaccine doses from 5 to 3 doses
- Simplifies treatment from complicated 28 days to 3 days
- Increases protection if post-exposure prophylaxis (PEP) delayed
- Possibly protects against unreported or unrecognized exposure
- Reduces overall cost if treatment becomes necessary (pre-exposure prophylaxis + boosters = $1000, PEP + Human RIG = $4000)
- Decreases or eliminates chance of PEP failure* due to mistakes (studies performed on 28 PEP failures found 26 cases to have errors in PEP)

Pre-exposure rabies vaccine was initially developed by Louis Pasteur in the 1880s, by drying infected rabbit spinal cord to attenuate the rabies virus. Subsequently, vaccines were developed using nerve tissue and duck embryo. Brain-derived vaccine was associated with neuroparalytic reactions in >1/400 recipients. In the late 1970s, cell culture vaccines were developed: human diploid cell vaccine (HDCV), purified chick embryo culture vaccine (PCECV), purified Vero cell rabies vaccine (PVRV).

What is an adequate dosing schedule?

Adequate pre-exposure prophylaxis is given on a 3-dose schedule on days 0, 7, 21 or 28. Due to the

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expense of the vaccine, intradermal administration using a fraction of the intramuscular dose was introduced in the 1980s, but vaccines had to be used within hours of reconstitution. In 1986, manufacturers repackaged the vaccine into 0.1 ml individual syringe for intradermal administration. Ten studies in the 1970s-80s showed adequate antibody response, but antibody levels following intradermal administration were lower than intramuscular administration.

How long can you go?

Volunteers injected with 0.1 cc of rabies vaccine intradermally at 2 sites were tested at 1 year, and 13/16 had > 0.5 IU/ml. After a booster, the mean titer was 49+ at 2 weeks (good).[2] Minimum protective antibody level was considered to be 0.5 IU/ml according to the WHO, but this level should be interpreted as evidence of "boostability" rather than protection.

In 1983, a United States Peace Corps volunteer, a 23-year-old woman who had been immunized with the intradermal series was bitten by a puppy. No PEP was given, and she developed rabies 6 weeks later and died. A study of her cohort in Kenya found 9 of 11 had no seroconversion. Among Peace Corps volunteers in other countries, a 34%-40% failure rate was associated with intradermal rabies vaccines given in destination countries.[3] Hypotheses were tested regarding the failure, and suggested that concurrent administration of chloroquine reduced total immune response though antibodies still achieved adequate level.

When should boosters be given?

Anamnestic response persists for many years. In the 1980s, CDC advised boosters every 2 years. However, it is evident that the initial series produces boostability, and boostability lasts for years, as boostability is currently felt to last lifelong. No tourist has ever died while trying to get PEP, but tourists have died from no PEP or inadequate administration. Education is the key pre-travel measure.

Dr. Suvansrinon presented post-exposure diagnosis and treatment, focusing on human rabies deaths related to PEP in Thailand. She emphasized that WHO advocated strongly against neuro tissue rabies vaccines such as Semple.

Exposure categories (WHO) are:

- III - deep wounds, must have PEP
- II - minor scratch
- I - touching, feeding of animals or licks on intact skin

The WHO recommendations for PEP mandate wound cleansing, RIG and modern vaccines immediately.[4] The WHO approves of 4 rabies post-exposure vaccine schedules, 2 intramuscular and 2 intradermal regimens. Among these, the Essen (administered on days 0, 3, 7, 14, and 28) is the regimen recommended and used in the United States.[4] (See Table 1.)

Table 1. Who Rabies Post-Exposure Vaccine Schedule

Type of administration and regimen	Abbreviation	Explanation
Intramuscular		
• Essen	**0, 3, 7, 14, 28**	**1 dose on days 0, 3, 7, 14, 28**
• Zagreb	2-1-1 (0, 7, 21)	2 doses on day 0, 1 dose on days 7 and 21
Intradermal		
• Oxford	8-0-4-0-1-1	Indicated for PVRV or PCECV; 0.1mL at 2 sites on days 0, 7, 21, and 1 site on days 30 and 90
• Thai Red Cross	2-2-2-0-1-1	Indicated for HDCV or PCECV; 0.1mL at 8 sites on day 0, 4 sites on day 7, 1 site on days 28 and 90

Dr. Suvansrnon discussed PEP failures and described a number of cases from 1985 to date. The reasons for failure included: 1) RIG was not used or not injected into all wounds; 2) vaccine or RIG were of poor quality; 3) a large viral load was inoculated through the bite; 4) virus was introduced into the nerve; 5) possible deviations from recommended dosing schedule. A sobering case for this associate editor was the case of an adult that was bitten by a dog, managed by observing the dog. The dog was suspected of having rabies on the 4th day. The patient received post exposure prophylaxis starting on the 6th day, but still succumbed to rabies. ■

References:

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2. Khawplod P, et al. Immunogenicity study of abbreviated rabies preexposure vaccination schedules. *J Travel Med* 2007;14(3):173-176.

3. Bernard KW et al. Pre-exposure rabies immunization with human diploid cell vaccine: decreased antibody responses in persons immunized in developing countries. *Am J Trop Med Hyg* 1985;34(3):633-647.
4. Meslin FX. Rabies as a traveler's risk, especially in high-endemicity areas. *J Travel Med* 2005;12:S30-S40.

Under the Deep Blue Sea

Updates from the 10th Conference of the International Society of Travel Medicine

SPECIAL REPORT

By Mary-Louise Scully, MD

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Dr. Scully reports no financial relationship relevant to this field of study.

AT THE RECENT 10TH CONFERENCE OF THE International Society of Travel Medicine (CISTM10) in Vancouver, Canada in May an informative overview of diving medicine was given by Michael Callahan MD as part of a Plenary Session Medicine at the Extremes (PLO1).[1] Since scuba diving first began in the mid 1940s, it has grown to now include more than 9 million certified divers in the United States alone. With recent advancements in scuba equipment and its growing popularity, more adventure-minded persons of all ages and degrees of physical fitness are participating in scuba diving. This expansion of participation carries with it increased risk of diving-related injury or illness, especially in persons with underlying medical conditions or disabilities. As such, physicians need to be knowledgeable about assessing their patients' medical fitness for diving.

A diving examination should include an assessment of patients pulmonary, otolaryngologic, cardiac, neurologic systems, as well as their psychological stability. Medical contraindications for diving are often related to the pressure changes that occur with submersion underwater. Some absolute contraindications include pregnancy, a history of spontaneous pneumothorax, atrial septal defectf, and chronic or restrictive lung disease. A complete listing of contraindications is provided in Table 1.[2] Some relative contraindications generally include age less than 12 years, significant visual impairment, and arteriovenous malformations (AVMs). Insulin-dependent diabetes mellitus (IDDM) was previously considered a contraindication for diving but many patients with well-controlled IDDM have been diving safely for years and the American Diabetes Association has guidelines for divers with IDDM. Therefore, well-controlled IDDM patients that are knowledgeable, used to vigorous exercise, and who have a prepared diving companion can sometimes be medically cleared for diving. Patients with well-controlled asthma or hypertension can also generally be given medical clearance to dive.

Table 1. Some Absolute Contraindications for Diving

History of spontaneous pneumothorax
Acute asthma with abnormal pulmonary function
Cystic or cavitary lung disease
Obstructive or restrictive lung disease
Epilepsy or seizure disorder
Atrial septal defect (ASD)
Symptomatic coronary artery disease
Chronic perforated tympanic membrane
Chronic inability to equalize sinus and/or middle ear
Intraorbital gas
Pregnancy
Sickle cell disease
Ménière's disease

Even with adequate screening, diving complications can occur, the most serious being the pulmonary overpressurization syndrome and decompression sickness . In 1980, the Divers Alert Network, a private, nonprofit dive safety organization was established to provide emergency medical assistance to recreational divers. It is now a worldwide organization with a broad range of activities (www. DiversAlertNetwork.org). Some practical advice for recreational divers is to be sure that there is supplemental oxygen available on the dive boat and to check the status and accessibility of the nearest decompression chamber prior to any diving excursion.

Paul Auerbach, MD, both entertained and educated his audience in an excellent presentation entitled "Shark Attack" as part of the symposium *When Nature Bites Back* (SY04).[3] Sharks are indeed man's most feared underwater creatures. Some 35 of about 375 species of

sharks account for the 75 to 100 shark attacks that are estimated to occur annually. There are between 6-10 deaths from shark attacks each year. The most common types of sharks accounting for attacks are the great white sharks, bull sharks, and tiger sharks. However, smaller sharks such as blacktip and spinner sharks are involved in the minor incidents common in the offshore areas of Florida. The greatest numbers of shack attacks are reported from North America, especially Florida's central east coast, and the danger of shark attack is greatest during the summer months.

Sharks are extreme predators that possess remarkable sensory systems, including olfactory and vibratory systems that allow them to track prey up to ½ mile away by motion. Sharks eyes are specially adapted for night vision as well. The possible attraction of sharks to certain colors such as international orange has caused some shark researchers to refer to this color as "yum yum yellow." The concept that sharks appear to be more attracted to bright colors in preference to black seems to be accepted, yet unproven. It is clear that sharks are attracted to bright, reflective type objects so avoidance of jewelry such as ankle bracelets or barrettes is strongly suggested.

There are 2 basic patterns of shark feeding: (1) normal or subdued, with slow purposeful group movements, and (2) frenzied or mob feeding as a result of an inciting event such as the presentation of food or blood in the water. Blood and other body fluids can attract sharks and woman have historically been advised to avoid diving during menstruation, although there is little actual data to support the attraction of sharks to menstrual discharge. Certain sharks will bump a person prior to attack. This so-called "bump and bite" technique is perhaps a shark's way of assessing the defensive abilities of its prey. Severe bruising and abrasions have occurred secondary to even such bumping incidents. If a shark does bump a person, one should prepare for a likely attack.

Sharks commonly attack young, old, or sick prey. It is thought that humans splashing at or near the water's surface are misinterpreted by sharks as struggling prey. Some other important advice about preventing shark attacks include : (1) avoid known shark-inhabited water, particularly at dusk and at night, (2) swim in groups, (3) avoid turbid water, drop-offs, deep channels, mouths of rivers, and sanitation waste outlets, (4) do not carry dead or tethered fish as fish blood is a strong chemical attractant for sharks, (5) do not tease or corner a shark, and (6) do not splash on the surface or behave in a manner that could mimic that of a struggling fish. Lastly, if approached by a shark in shallow water, swimmers should leave the water if possible, facing the shark, with slow purposeful movements. If a shark approaches in deep water, a diver should stay submerged and descend to the ocean floor seeking shelter with posterior protection so as to better defend against a frontal attack. Blunt blows, ideally with a knife or a weapon, aimed at the eyes, snout, or gills are a victim's best tactic to defend against a definite attack. "Bang sticks" and electronic shark deterrent devices are in use and evolving but, unfortunately, they are not fully protective. A powerhead, bang stick, or shark stick is actually specialized type of a firearm for underwater use and firing in direct contact with the target. ■

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1. Callahan M. *Diving Medicine: Pre-travel Screening, Education and Itinerary-based Assessment for Recreational Divers*. (PL01.02). 10th Conference of the International Society of Travel Medicine. Vancouver, Canada. May 20-24, 2007.
2. Kizer K, Van Hoesen K. *Diving Medicine. In: Wilderness Medicine.* Auerbach PS. (ed) Fifth Edition. 2007, Mosby - Elsevier, Amsterdam, Netherlands.
3. Auerbach P. *Shark Attack.* (SY04.01). 10th Conference of the International Society of Travel Medicine. Vancouver, Canada. May 20-24, 2007.

Severe Dengue Virus Infection in Travelers

ABSTRACT & COMMENTARY

By Omega Edwards, MD, and Maria D. Mileno, MD

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Dr. Edwards reports no financial relationships relevant to this field of study.

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Dr. Mileno is a consultant for GlaxoSmithKline.

Synopsis: *There is no uniformly useful definition for severe dengue virus infection and severe dengue may go undiagnosed in returning travelers, if we use the WHO classification scheme for strict diagnosis. Preexisting dengue antibodies were the most significant risk factor for spontaneous bleeding and other severe manifestations of dengue, according to these authors.*

Source: Wichmann O, et al. Severe Dengue Virus Infections in Travelers: Risk Factors and Laboratory Indicators. *J Infec Dis* 2007:195 (15 April) 1089-1096.

Global travel continues to increase, with over 800 million tourist arrivals recorded worldwide in 2005. Increasing numbers of international travelers are returning with dengue fever. The GeoSentinel surveillance network reported that dengue virus infection was the leading cause of febrile illness among travelers returning from every geographic area except for sub-Saharan Africa and Central America. Wichmann et al described 219 patients with acute or recent dengue virus infection in their surveillance of dengue fever among returning European travelers, as reported by the European Network on Surveillance of Imported Infections Diseases.

Intensified study since May 2004 included an additional standardized questionnaire covering dengue-specific symptoms, serological results, hematological values, chemical blood constituents, and history of previous travel and immunizations. Fully 64% of the 219 travelers acquired their dengue infections in either southeast Asia or India. Central America accounted for another 17.8% of cases. There were confirmed diagnoses in 133 patients and probable diagnoses recorded in the remaining 86 individuals. Most cases had documented increasing dengue antibody titers using commercially available Panbio-ELISA assays. PCR confirmation alone was used in two patients. A combination of methods confirmed the diagnosis in 17 patients. There were no significant differences in clinical, laboratory or demographic characteristics between persons with probable and confirmed dengue virus infection. Most common clinical manifestations of dengue included fever (93%), headache (69%), fatigue (57%), rash (53%), muscle pain (50%), retroorbital pain (44%) and a positive tourniquet test in 44% of those tested. In terms of dengue antibody titers, 77% of patients had primary immune response and 23% had a secondary response. Forty-five persons had missing data, and 13 with a secondary response were excluded, due to history of prior flavivirus immunization. Seventeen percent had acquired a secondary dengue virus infection.

In further describing disease severity, 28 patients showed petechiae, 17 had spontaneous bleeding, most often from the nose or gums. One individual showed hematemesis and GI bleeding. Eighty-two patients underwent a tourniquet test and 44% showed positive results.

A positive tourniquet test was associated with occurrence of petechiae but not with spontaneous bleeding. No significant association was noted between a positive tourniquet test and the frequency of severe clinical manifestations, low platelet counts (less than 100,000/µL), non-European origin, secondary immune response or increased liver enzyme (AST) levels to greater than 3 times normal. Leukopenia and thrombocytopenia occurred between day 3 and 6 of illness. Abnormal AST, ALT, and LDH values occurred later than day 6.

Twenty-three percent of patients required hospitalization and the average hospital stay was 4 days. One individual with significant bleeding developed atrial fibrillation and required treatment in the ICU. On patient had dengue infection complicated by visual disturbances manifesting itself as black dots in the field of vision, which resolved gradually over 2 months. One individual had hypotension. A total of 11% (23 patients) demonstrated severe dengue related disease: four had internal hemorrhage; 2 had plasma leakage; one developed shock, and 18 had platelet counts less than or equal to 50,000/µL. In multivariate analysis, only secondary immune responses to dengue viruses and a greater than 3-fold increased serum AST level were independent predictors of severe dengue associated disease.

COMMENTARY

The WHO clinical case definition for Dengue Hemorrhagic Fever requires the presence of 4 criteria: fever, platelet count less than 100,000 cells/µL, hemorrhagic tendency in addition to evidence for capillary leakage as shown by either an hematocrit increase of greater than 20% from baseline, a pleural effusion, ascites or hypoproteinemia. Only 0.9% of patients in this study met the criteria for severe dengue infection based upon the WHO classification system - it failed to accurately categorize the spectrum of dengue virus infections observed. The authors found that returning travelers with fever, high liver enzymes, and thrombocytopenia are far more likely to have a severe form of dengue virus infection than would be predicted from these criteria. The tourniquet test, although visually stimulating and convincing when positive, also appears to have limited clinical utility. Preexisting dengue antibodies were the most significant predictor of severe disease.

Travel Medicine practitioners may take home a message that persons with prior travel to dengue endemic areas are at risk for a severe dengue infection, keeping in mind that 8 individuals in this cohort visited a dengue endemic country for the first time and yet they still presented with severe dengue. A heightened discussion of personal protection measures is just as necessary for travelers visiting dengue endemic regions and should be as rigorous as the

measures recommended for travelers to malaria endemic regions. ■

Additional Sources:

Freedman DO, et al. Spectrum of Disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006:354:119-130.

Wilder-Smith, A and Tambyah, PA. Severe Dengue Virus Infection in Travelers. *J Infect Dis* 2007:195:1081-1083.

Malaria and Travelers

ABSTRACT & COMMENTARY

By Philip Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Division of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer reports no financial relationship relevant to this field of study.

Synopsis: *Helpful summary information can guide travel medicine practitioners through a maze of controversy toward appropriate use of incompletely understood malaria chemoprophylactic agents as well as toward evidence-based treatment of patients with malaria.*

Sources: Chen LH et al. Controversies and misconceptions in malaria chemoprophylaxis for travelers. *JAMA* 2007; 297:2251-2263.

Griffith KS et al. Treatment of malaria in the United States. *JAMA* 2007; 297:2264-2277.

THE MAY 23/30, 2007, ISSUE OF *JAMA* WAS DEVOTED to malaria and contained an informative selection of papers. In particular, two articles were of particular interest to practitioners of travel medicine. *Travel Medicine Advisor* associate editor, Lin Chen, joined with collaborators on each side of the Atlantic to discuss myths and controversies about malaria chemoprophylaxis. While the prevention of malaria in travelers requires detailed knowledge of malaria epidemiology and host-vector-parasite interactions, they wrote, decisions are also complicated by lack of standardized recommendations. The Centers for Disease Control and Prevention's (CDC's) Monica Parise MD and some of her public health colleagues suggested that U.S. clinicians' unfamiliarity with malaria and drug resistance patterns have contributed to delays in diagnosis and treatment with resulting poor outcomes. Then, with text, tables, and a helpful algorithm, they systematically reviewed the details of medications used in the treatment of malaria.

■ **COMMENTARY**

Chemoprophylaxis: Data are not complete, and various national groups have offered differing recommendations in regard to the use of chemoprophylaxis for travelers. In addition, travelers and public media sometimes share misconceptions. Thus, health care providers providing pre-travel care must be aware of factual material while being ready to discuss controversies - particularly in regard to mefloquine and to primaquine.

Since it became available in Europe in 1985, mefloquine has been used by more than 30 million individuals. Many individual reports document both serious and minor adverse events, but larger studies are not completely comparable due to variations in design, methods, and study populations. Some studies have shown similar rates of abnormal dreams and insomnia between travelers taking mefloquine and those taking other antimalarials such as chloroquine. Recent studies, however, show more sleep trouble, headache, and psychological disturbance in travelers, especially women, taking mefloquine. While disabling adverse reactions are uncommon (less than 1%) with mefloquine, they are even less common for individuals taking other medications. Mefloquine does not cause difficulty with driving, concentration, balance, or diving.

Malaria chemoprophylaxis is designed to prevent life-threatening disease but does not effectively prevent later illness due to recrudescence of Plasmodium vivax. Even atovaquone-proguanil, which has some activity against liver stages of malaria, does not prevent hypnozoites from causing later bouts of vivax malaria. Primaquine also offers the potential for providing both primary and post-exposure prevention of malaria and is effective against all species of human malaria. Prior to even prophylactic treatment with primaquine, however, glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out. Until primaquine becomes routinely recommended, travelers to areas endemic for *Plasmodium vivax* or *ovale* must be warned that febrile illness, even up to a year or more after return from the endemic area, should prompt a diagnostic evaluation for malaria.

Treatment

Prompt diagnosis of malaria is the key to effective treatment, and clinicians in all settings should consider the diagnosis of malaria in febrile patients who have visited malaria endemic areas within the past year. Blood smears should be obtained and examined promptly; the CDC provides a telediagnosis service as well as physician consultation (770-488-7788 during regular working hours and 770-488-7100 after normal working hours).

Oral quinine (in combination with either tetracycline,

doxycycline, or clindamycin), atovaquone-proguanil, and mefloquine are effective in most cases of uncomplicated malaria. Mefloquine use is limited by resistance of malaria parasites originating in some parts of southeast Asia and by its association, in treatment doses, with adverse neuropsychiatric events. Resistance to atovaquone-proguanil has only been reported in 12 patients, but is certainly possible. The combination of atovaquone and proguanil is also probably the best choice for treatment of chloroquine-resistant *P. vivax* malaria from Papua New Guinea and Indonesia. Primaquine can prevent *P. vivax* relapses and is now recommended in a dose of 0.5 mg primaquine base/kg by mouth daily for 14 days with a maximum daily dose of 30 mg. Because of either resistance or toxicity, the use of sulfadoxine-pyrimethamine, amodiaquine, and halofantrine is not recommended in the United States.

Treatment of severe malaria should be initiated with parenteral therapy, and quinidine is the only parenteral product available in the U.S. Artemisinin derivatives are effective in cases of severe malaria and will likely be available in the U.S. through the CDC by later this year. Exchange transfusions seem beneficial in some cases of severe malaria. Other treatment modalities including prophylactic phenobarbital, dexamethasone, heparin, and iron chelators are either unproven or harmful and are not recommended.

Children less than 8 years of age should not receive doxycycline or tetracycline due to effects on bone and teeth. Clindamycin is, however, effective in combination with quinine and can replace tetracycline for the treatment of young children. Mefloquine is adequately tolerated in children as small as 5 kg. Primaquine can be used at any age, as long as G6PD testing has been normal.

Atovaquone-proguanil and mefloquine are not currently recommended at treatment doses during pregnancy but can be considered if quinine and clindamycin are not available or are not tolerated. Primaquine should not be used during pregnancy due to the potential risk of undiagnosed G6PD deficiency in the pre-born child. ■

CME Question

11. Which of the following statements regarding shark attacks is incorrect?

a. Fish blood is a powerful chemical attractant for sharks.
b. "Bump and bite" is likely a pre-attack technique of some sharks.
c. Sharks are attracted to bright, shiny, objects.
d. If threatened by a shark in deep water, one should swim quickly to the surface.
e. Surface splashing of humans may mimic struggling prey to a shark.

12. Valid available option(s) for the initial treatment of severe malaria in the United States at this time include:

a. oral mefloquine
b. oral quinine
c. parenteral quinine
d. parenteral quinidine

13. The World Health Organization requires each of the following to make a diagnosis of severe dengue infection except:

a. fever
b. thrombocytopenia
c. headache and meningismus
d. hemorrhagic tendency
e. evidence of capillary leakage

Answers: 11. (d) 12.(d) 13.(c)

CME Objectives

• To present the latest data regarding the diagnosis and treatment of various travel-related diseases;
• To present new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world; and
• To alert the readers to recent disease outbreaks and epidemics. ■

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.

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■