TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media

INSIDE

Volume 21, No. 6
June 2011

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationships relevant to this field of study. Peer reviewers Lin Chen, MD, and Mary-Louise Scully, MD, Executive Editor Gary Evans, and Senior Managing Editor Paula Cousins report no financial relationships relevant to this field of study.

Vitamin B12 Deficiency in Resettled Bhutanese Refugees

ABSTRACT & COMMENTARY

By Michele Barry, MD, FACP, and Brian G. Blackburn, MD

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Dr. Barry is a retained consultant for the Ford Foundation and has received research or grant support from Johnson & Johnson Corporate Foundation, the Doris Duke Foundation, and the National Institutes of Health. Blackburn reports no financial relationship to this field of study.

Synopsis: *A recent survey detected vitamin B12 deficiency in 64% of Bhutanese refugees living in Nepali refugee camps. Post-resettlement sera drawn in the United States confirmed a vitamin B12 deficiency prevalence of 27%-32%. Any Bhutanese immigrant to the United States should be screened for B12 deficiency, megaloblastic anemia, and neurologic symptoms. Vitamin B12 supplementation and nutritional advice also should be offered.*

Source: Vitamin B12 Deficiency in resettled Bhutanese refugees — United States, 2008-2011. *MMWR Morb Mortal Wkly Rep* 2011;60:343-346.

Approximately 108,000 ethnic Nepalese people were forced to move from their long-standing homes in Bhutan in the 1990s and have since been living within refugee camps in Nepal. Since 2008, approximately 30,000 Bhutanese refugees have resettled in the United States, and more are expected to follow. Routine medical examinations of some of these resettled refugees revealed neurologic and hematologic abnormalities consistent with vitamin B12 deficiency, even in young adults. These cases prompted a Centers for Disease Control and Prevention (CDC) investigation of stored sera from overseas medical examinations that had occurred during 2007-2008, and post-arrival examinations that took place in three state health departments (Minnesota, Utah, and Texas) during 2010-2011. Records from a health clinic in St. Paul, MN, also were reviewed, to ascertain whether megaloblastic anemia or peripheral neuropathy were common findings in this refugee population.

Vitamin B12 deficiency was defined as a serum vitamin B12 concentration < 203 pg/ml. Low serum levels were found in 64% (63 of 99) of the specimens obtained from Bhutanese refugees living in Nepali camps during 2007-2008 *(see Table 1, page 30)*. The prevalence of serum B12 deficiency subsequently was assessed in serum samples of Bhutanese and other refugees, collected during post-arrival medical screening examinations in Minnesota, Utah, and Texas during 2010-2011 *(see Table 2, page 31)*.

Of refugees from 12 countries, only refugees from Bhutan (27%) and Somalia (12%) showed any significant B12 deficiency prevalence rates. The lower B12 deficiency rates seen in resettled Bhutanese refugees compared to those found in refugee camps might have been due to the higher proportion of children < 15 years of age tested in the domestic samples from resettled refugees. It takes approximately 5-10 years for body stores of vitamin B12 to become depleted. Macrocytosis, anemia, and peripheral neuropathy were observed in 10%-20% of refugees upon review of St. Paul (MN) health clinic charts. *H. pylori* infection, often a cause of chronic gastritis, and, in turn, vitamin B12 deficiency, was more prevalent among those with B12 deficiency than among those without deficiency in a small cohort, although inadequate dietary intake was felt to be the more likely cause of B12 deficiency. Further investigation is ongoing to determine the prevalence of other micronutrient deficiencies in this population.

Table 1. Vitamin B12 deficiency in adult Bhutanese refugees undergoing overseas medical screening examinations, by age group and sex — Nepal, 2007-2008.

	B12 < 203 pg/mL*	
Characteristic	Number	(%)
Sex		
Female	28/47	(60)
Male	35/52	(67)
Age group (years)		
15-29	26/44	(59)
30-49	14/30	(47)
≥ 50	23/25	(92)
Total	63/99	(64)

* Serum total vitamin B12 was measured at CDC using the Roche E-170 automated electrochemiluminescence immunoassay.

Source: Centers for Disease Control and Prevention Migrant Serum Bank

Adapted from: Centers for Disease Control and Prevention. Vitamin B12 deficiency in resettled Bhutanese refugees—United States, 2008-2011. *MMWR Morb Mortal Wkly Rep* 2011;60:343-346.

■ COMMENTARY

Vitamin B12, or cobalamin, is obtained naturally, but only from foods of animal origin including meat, eggs, and dairy products. Vitamin B12 deficiency leads to delayed DNA synthesis, resulting in megaloblastic anemia, peripheral neuropathy, and subacute combined degeneration of the spinal cord, as well as neuropsychiatric symptoms.[1,2] The deficiency can be caused by an inherited or acquired lack of intrinsic factor required for absorption of B12, and is commonly known as pernicious anemia, but in the developing world, it is often caused by low dietary intake or food/cobalamin malabsorption. At times, this malabsorption of cobalamin is associated with atrophic gastritis and with *H. pylori* infection.[1]

Bhutanese refugees living in the Nepal refugee camps have had their rations provided by the World Food Programme and the United Nations High Commissioner for Refugees and they consist of rice, lentils, chickpeas, vegetable oil, sugar, salt, and fresh vegetables.[1] Only certain refugees, including young, malnourished, pregnant,

Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone:
(404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor,*** PO Box 105109, Atlanta, GA 30348.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice @ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Table 2. Proportion of refugees with vitamin B12 deficiency in post-arrival serum samples — Minnesota, Utah, and Texas — September 2010-January 2011.

Characteristic	B12 < 203 pg/mL		B12 pg/mL	
	N	(%)	Median	Interquartile Range
Country				
Bhutan	17/64	(27)	262	(197-323)
Burma	0/107	—	480	(365-636)
Democratic Republic of the Congo	0/1	—	413	(413-413)
Cuba	0/3	—	278	(253-294)
Eritrea	0/5	—	401	(235-421)
Ethiopia	0/15	—	363	(297-526)
Iraq	0/33	—	368	(304-457)
Kyrgyzstan	0/4	—	695	(432-1,120)
Laos/Hmong	0/9	—	712	(247-753)
Liberia	0/2	—	881	(791-970)
Somalia	10/82	(12)	350	(257-498)
Sudan	0/1	—	486	(486-486)
Total	27/326	(8)	369	(272-517)

Adapted from: Centers for Disease Control and Prevention. Vitamin B12 deficiency in resettled Bhutanese refugees — United States, 2008-2011. *MMWR Morb Mortal Wkly Rep* 2011;60:343-346.

or lactating women are given multivitamin supplements. A locally made, fortified, blended food containing B12 and micronutrients is available, but is probably not being consumed — likely demonstrated by the results observed in this study, emphasizing how a culturally sensitive approach to food supplementation is imperative.

This excellent investigation should alert all physicians caring for Bhutanese or Nepalese immigrants to screen for B12 deficiency, both clinically and serologically. Moreover, the investigators strongly suggest that all refugees be provided with 30 days of oral B12 supplementation (500-1000 µg daily), as subclinical deficiencies may be present despite normal levels of B12. Any refugee exhibiting B12 deficiency should be screened for *H. pylori* infection and given antibiotic treatment if needed. Clinicians should consider the possibility of other nutritional deficiencies in this population as well. Lastly, one should think about offering all Bhutanese refugees nutritional advice that emphasizes culturally acceptably food containing B12. ■

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Japanese Encephalitis in Children

ABSTRACT & COMMENTARY

By Lin Chen, MD

Dr. Chen is Assistant Clinical Professor, Harvard Medical School; Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge MA

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

Synopsis: *Travelers visiting friends and relatives in endemic countries are at increased risk for Japanese encephalitis; their trip plans should be reviewed carefully, and they should be targeted for prevention with personal protective measures and Japanese encephalitis vaccine.*

Source: Centers for Disease Control and Prevention. Japanese encephalitis in two children — United States, 2010. *MMWR Morbid Mortal Wkly Rep* 2011;60:276-278.

Two children were diagnosed with Japanese encephalitis (JE) in the United States in July 2010. The first child, aged 11 years, had onset of fever, headache, nausea, vomiting, and neck pain 4 days after returning from a 21-day trip visiting relatives in the Philippines. She had

traveled with her relatives, and spent most of the time in Metro Manila. They stayed with relatives in a screened house, took day trips to coastal and rural areas, and also stayed for 2 nights at an island resort that was screened and air-conditioned.

The patient was hospitalized 2 days after symptom onset in Nevada, and found to have leukocytosis and CSF pleocytosis. She deteriorated over the 2-3 days after admission with somnolence, focal motor seizures, pulmonary edema, bradycardia, and hypotension that led to placing her on mechanical ventilation. Her head CT showed cortical sulci effacement; her EEG showed little cerebral activity. She developed ventricular tachycardia and died 5 days after onset of illness.

The child's brain tissue obtained via autopsy showed meningoencephalitis, positive immunohistochemical staining for JE complex flavivirus antigens, and RT-PCR confirmed JE virus (JEV) RNA. CSF on admission was positive for JEV-specific IgM.

The second child, a refugee 6 years of age, was born in Thailand to Burmese parents. His symptoms included fever, somnolence, headache, vomiting, and refusal to walk, and started en route to the United States, 2 days before his presentation in Texas. He was found to have leukocytosis, CSF pleocytosis, and brain MRI showing a neurocysticercosis lesion in the left frontal lobe as well as an abnormal signal in the left thalamus. Subsequently an EEG showed generalized cerebral activity.

The second child's CSF on day 6 showed JEV-specific IgM and serum neutralizing antibodies rose fourfold between acute and convalescent serum samples. His cysticercosis serology was negative, but he was treated with a 21-day course of albendazole and corticosteroid for neurocysticercosis, and he recovered following a 24-day hospitalization.

■ COMMENTARY

Japanese encephalitis (JE) virus is a flavivirus transmitted by the bite of *Culex* mosquitoes, primarily *Culex tritaeniorhynchus*, and it is endemic in Asia and parts of the western Pacific. JEV is maintained in an enzootic cycle between mosquitoes and vertebrate hosts such as pigs and wading birds, and is particularly common in rural farming areas with rice paddies. Most infections are subclinical, but < 1% may present after 5-15 days of incubation with fever, headache, mental status change, vomiting, seizures, acute encephalitis or aseptic meningitis; among those with clinical infection, 20%-30% of cases may be fatal, and 30%-50% develop long-term neuropsychological sequelae.[1] Most infections occurring in endemic regions occur in children < 15 years of age.

JE infection occurs rarely in travelers, and the disease risk depends on season of travel, destination visited, trip duration, and activities. There have been 55 cases in citizens from 17 non-endemic countries reported in literature from 1973 to 2008, and the risk of acquiring JE is estimated to be < 1 case per 1 million travelers.[2] However, potentially severe consequences of infection underpin the recommendations for vaccination.

A new inactivated Vero cell-derived vaccine (IXIARO®, Intercell), a two-dose series, administered 28 days apart, became licensed in the United States, Europe, and Australia in 2009. In the United States, it is licensed for individuals aged ≥ 17 years and has been well tolerated. Recommendations from the Advisory Committee on Immunization Practices regarding JE vaccine include:[3]

- **Recommended:** Travelers who plan to spend a month or longer in endemic areas during the JEV transmission season
- **Consider:** Short-term travelers (< 1 month) to endemic areas during the transmission season if they have high-exposure activities
  - —Travelers to an area with ongoing JE outbreak
  - —Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel

For persons younger than 17 years of age in the United States, the currently indicated vaccine is JE-VAX®, but obtaining the vaccine requires contacting the distributor for each traveler. Several clinical trials are in progress to assess the safety and efficacy of the new Vero cell-derived vaccine in persons younger than 17 years.[4] A Phase II study on children ages 1-3 years in India was recently published and showed the vaccine to be safe and immunogenic.[5] A Phase II trial in Filipino children 3-12 years old also has been completed and is presented at the 12th Conference of the International Society of Travel Medicine in Boston, MA, USA, in May 2011.[6] Expanding the licensure for IXIARO for use in children would reduce barriers to vaccinate this vulnerable group of travelers.

The first case reported here illustrates some important issues regarding JE: 1) JE is under-reported in some countries; 2) travelers visiting friends and relatives (VFR) are at a significantly increased risk of exposure to JE; and 3) VFR travelers often lack pre-travel health advice. The report noted that the child was born in the United States, as were her parents who did not travel).[7,8]

The second case underscores the importance of considering the diagnosis of JE infection in febrile travelers with neurologic findings who have visited endemic areas, even when there is already a possible explanation. Travel medicine providers should be familiar with the common clinical presentations of JE: fever accompanied by headache, mental status change, seizure, vomiting, focal neurologic changes. Hemorrhagic lesions of the thalamus have been described.

Finally, recent clinical trials on the duration of immunity found that 15 months after primary vaccination with IXIARO, the proportion of vaccinees with protective levels of antibody titer (≥ 1:10) declined to 58%-83% of subjects. One month after a booster dose, 100% achieved $PRNT_{50}$ of ≥ 1:10, and > 98% remained protected serologically 12 months later.[9] The ACIP voted in February 2011 to recommend a booster dose of IXIARO at 12 months after the primary series for travelers who remain at risk for JE infection. ■

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Pets in the Bedroom — Move Over Rover!

ABSTRACT & COMMENTARY

By Mary-Louise Scully, MD

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

Synopsis: *The increasingly close and almost intimate relationships with our pets can lead to increased numbers of cases and the emergence of zoonotic diseases, including human plague (*Yersinia pestis*)*

Source: Chomel BB, Sun B. Zoonoses in the bedroom. *Emer Infect Dis* 2011;17:167-172.

The numbers of households with pets, both traditional such as dogs and cats, as well as exotic pets, are increasing in many countries across the world. In addition, data obtained from media sources note a trend in the percentage of these pets sleeping in, or on, the owner's bed. To address whether this behavior is associated with the acquisition of zoonotic disease(s), the authors searched PubMed for peer-reviewed publications that demonstrated disease likely to have been acquired by sleeping with, sharing a bed with, kissing, or being licked by pets.

The results encompassed bacterial, parasitic, and viral associated zoonoses. The bacterial zoonoses included those with known animal associations such as *Yersinia pestis* (plague), *Bartonella* species (cat-scratch disease), *Pasturella* species, and *Capnocytophaga camimorsus*. In the case of a plague outbreak, 1 patient had the onset of his illness the morning after noting bites from his flea-infested cat who had shared his bed.[1] Another case-control study of plague survivors found 44% of survivors vs. 10% of controls reported sleeping in the same bed with a pet dog.[2] Although *Bartonella* infections are often associated with a scratch of a cat that harbors *Bartonella henselae*-infected fleas, a 9-year-old girl from Taiwan with multi-organ (hepatic, splenic, and renal) disease from *Bartonella*, became ill after sleeping with her cat at night.[3] Various Pasturella-associated diseases are reported in the literature; meningitis cases in infants especially support an animal exposure. In one study of *P. multicida* meningitis, 27 (87%) of 31 infants exposed to animals had been exposed in various ways to oropharyngeal animal secretions through either licking or sniffing.[4] In addition, *Pasturella* wound infections have been reported when the animals had been observed licking the wounds prior to onset of illness.[5]

Capnocytophaga camimorsus is a gram-negative bacillus that is known for its presentation of a purpura fulminans-like sepsis, especially in asplenic, alcoholic, or steroid-dependant patients. Several cases in the literature exist for which the portal of entry was felt to be a direct result of a pet licking an ulcer or abraded skin of the patient. For example, a patient with chronic ulcerous eczema of the legs whose dog used to lick his legs, died of septic shock and renal failure caused by *C. camimorsus*.[6]

Other literature cited includes references to rabies,

hookworms, and roundworms — diseases commonly associated with animal exposure, though these exposures were not, for the most part, usually from the bedroom.

■ **COMMENTARY**

These are just some of the highlighted cases discussed in this article analyzing the reports in the literature about diseases acquired from close association with pets. *Staphylococcus intermedius* and methicillin-resistant *Staphylococcus aureus* (MRSA) are mentioned only briefly in this article. *S. intermedius* is a coagulase-positive zoonotic organism that is a common commensal of oral, nasal, and skin flora in healthy dogs. In humans, it can cause invasive disease, especially in immunocompromised patients. The name of this species reflects that the organism has some phenotypic properties of *S. aureus*, but it also has some properties of *Staphylococcus epidermidis*. I recently saw a patient with a post-surgical septic olecranon bursitis caused by *S. intermedius*. The patient admitted his dog may have licked the wound or provided saliva exposure during their playful nightly wrestling on the floor. Also, there is increasing reference and media attention to MRSA and animal/pet exposure. The most recent reference I found to include data on this evolving topic is from the Center for Food Security & Public Health from Iowa State University from January 2011 — an MRSA article with more than 180 references![7] We are very likely just seeing the tip of the iceberg on this emerging issue.

In May of 2011, shortly after the Chomel article was published, the Centers for Disease Control and Prevention published two cases of human plague in *MMWR* from Oregon in 2010. These were the first cases reported from Oregon since 1995 and they were the only plague cases reported in the United States in 2010. The patients, ages 17 and 42, lived in the same household with a dog that was later found to be seropositive for *Y. pestis* by passive hemagglutination-inhibition assay. Both patients had clinical illness compatible with human plague, including bilateral inguinal buboes, fever, and hypotension. Though plague was not suspected initially, one patient's blood culture specimen was later identified as positive at the Spokane (Washington) Regional Health District, and the other patient had a positive serology. One of the patients admitted sleeping in the same bed with the dog during the 2 weeks prior to the onset of illness. Fortunately, both patients recovered after empiric therapy with doxycycline.

Pets are known to provide company and assuage the loneliness of countless human beings worldwide and as such, they are often considered "part of the family." Although transmission of zoonotic infections from pets is rare, it would seem prudent to ensure our pets are properly de-wormed, free of fleas, and defer from sharing the same bed with them to prevent serious and potentially fatal infections such as human plague. ■

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Schistosomiasis in Travelers

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

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

Synopsis: *Schistosomiasis is a potential problem for international travelers, especially adventure travelers involved in water sports; it is also encountered in migrants to developed countries. Diagnosis is made using urine and stool microscopy or serologic testing. Praziquantel is the medication of choice for effective therapy.*

Source: Clerinx J, Van Gompel A. Schistosomiasis in travellers and migrants. *Trav Med Infect Dis* 2011;9:6-24.

Tropical medicine specialists Jan Clerinx and Alfons Van Gompel from Belgium provide a practical review of current knowledge about schistosomiasis as it relates to travelers and migrants, including good images of parasite lifestyle, maps, parasite eggs, and 223 references. Overall, about 83% of imported schistosomiasis originates from Africa. The severity of symptoms depends upon the intensity of the infection, the individual's immune responses and the pre-treatment duration of the infection.

Non-immune travelers may present an itchy, papular rash soon after the skin is penetrated by the cercarial form of the parasites; penetration may take up to 72 hours. This

"swimmers' itch" occurs with human schistosome infections as well as with the abortive non-infecting contact of animal schistosomes with human skin.

Acute schistosomiasis, still sometimes referred to as Katayama fever, is a systemic hypersensitivity reaction directed toward the maturing parasites; it usually occurs 3 weeks to 3 months after initial infection. Patients may have fever, cough, abdominal discomfort, and sometimes an urticarial rash.

The presentations for chronic schistosomiasis vary between parasite species. *Schistosoma haematobium* causes a granulomatous inflammation within the bladder and ureteral walls and patients may present with dysuria and hematuria. *S. mansoni* infection in the intestinal tract has been associated with abdominal discomfort and fecal blood loss, but most infected patients have no intestinal symptoms. Portal hypertension results from long-term infection with *S. mansoni*, *S. japonicum*, and *S. mekongi*. Neuroschistosomiasis results from the "ectopic" migration of adult worm pairs into small cerebral or spinal vessels with a secondary destructive eosinophilic granulomatous immune response to ova.

Schistosoma infection is best documented by finding ova in either urine or feces, but not all infections are heavy enough to produce detectable excretion of eggs. Antibody tests are very useful, but seroconversion is not assured until 2 or more months after infection. Antigen tests show some promise.

Praziquantel (single dose of 40 mg/kg) is the most cost-effective and widely used medication for treatment of schistosomiasis. Corticosteroids are helpful in acute schistosomiasis, but dosing regimens have not been well studied. They may also be combined with praziquantel treatment in the management of travelers with neuroschistosomiasis. Artemisinin derivatives are being evaluated and might prove adequately effective.

■ COMMENTARY

Travel medicine practitioners must confront the issue of schistosomiasis during pre-travel consultations when they give advice about fresh-water contact occurring in many areas of Africa. Again, they must deal with schistosomiasis on seeing returned travelers inquiring as to whether the returnees are asymptomatic or had pruritus after water contact, unexplained itchiness or fever, perhaps with respiratory and intestinal symptoms associated with headache and eosinophilia. In reviewing the topic of schistosomiasis, Clerinx and Van Gompel have provided us with a useful resource.

Additional new information has become available to guide travel medicine practitioners in caring for people who might come in contact with fresh water in schistosomiasis-endemic areas. Several new reports remind physicians of the frequency of schistosomal infections and, thus, the importance of appropriate testing and treatment.

In May, Verani and colleagues reported on a cross-sectional survey of children in Kenya. While anti-schistosomiasis efforts had previously been directed at older children, Verani found that 14% of 1-year-olds were already infected and that 90% of children were infected by age 10 years.[1] All travelers, even very young ones, should either avoid contact with fresh water in schistosomiasis-endemic areas or ensure good post-exposure testing and/or treatment.

At the International Society of Travel Medicine (ISTM) meetings in Boston this May, several studies reported new information on schistosomiasis. First, 7% of 132 Dutch travelers (median age 25, median duration of trip 12 weeks, 47% backpackers) were found to have schistosomiasis-positive serology. Just 2 (of 9) had had symptoms of acute schistosomiasis; the others had no symptoms suggestive of schistosomiasis.[2] Second, a group of 29 Irish school children visited Uganda for a cultural experience that included some lake, river, and waterfall exposure. Two of the returned students developed illness that prompted blood counts to be done and had significant eosinophilia (19% and 51%). Twenty of the 29 tested children were seropositive for schistosomiasis. In retrospect, 8 of the children had had symptoms suggestive of Katayama fever, and only 6 had been totally asymptomatic.[3] Finally, Belgian groups of 9 and 7 travelers visited the Dogon Valley in Mali for an adventurous vacation.[4,5] All 9 in one group (each of whom had experienced cercarial dermatitis, 1 of whom developed terminal hematuria) and 1 of 7 in the other group developed positive schistosomiasis tests.

During a symposium on "Water-Related Hazards" at the May 2011 ISTM meetings, Eli Schwartz of Israel noted that more water-related infections arise via skin contact than by ingestion. In some groups of adventure travelers who acquire schistosomiasis, the attack rate is frequently near 100%; most cases in travelers are from Africa, although schistosomiasis has emerged as a problem among river rafters in Laos. Most travelers with schistosomiasis experience acute schistosomiasis, and only about 7% present with cercarial dermatitis. Marc Mendelson from South Africa discussed common challenges in managing schistosomiasis. He pointed out that early post-exposure praziquantel is not effective in preventing disease; the use of DEET prior to water contact and vigorous toweling after exposure can partially prevent infection from getting established. Acute schistosomiasis occurs 1-12 weeks after exposure, and symptoms that arise are mostly from a hypersensitivity reactions to migrating larvae rather than from new ova that are laid 4 or more weeks after cercarial contact; thus, corticosteroids would be more useful in acute schistosomiasis

treatment than would be praziquantel, which is effective for established infections, 3 months or more after the exposure. Interestingly, mefloquine is somewhat effective against juvenile forms of schistosomiasis. Diagnostic tests are helpful, but sensitivities vary with the stage of infection. Schistosomiasis also has been linked to false-positive HIV test results and false-positive tests for some malaria antibodies. Eosinophilia can persist for up to a year after effective treatment of schistosomiasis. Even with advanced disease, treatment does help reduce hepatic fibrosis and splenomegaly.

Clearly, schistosomiasis should be of concern to travelers, especially adventurous travelers who are wading, splashing, swimming, or boating in fresh water in regions where schistosomiasis is endemic. Whether symptomatic or not, patients with such exposures can be tested and/or treated following their travels. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

• discuss the latest data regarding the diagnosis and treatment of various travel-related diseases;

• explain new data concerning recommended precautions and prophylaxis for patients traveling to specific areas of the world;

• implement strategies in the practice setting to inform patients of disease outbreaks and epidemics relevant to their travel plans.

CME Questions

1. **Which of the following is *not* a contributor to or potential cause of vitamin B12 deficiency?**
   a. Diet lacking meat, eggs, and dairy products
   b. Infection with the beef tapeworm, *Taenia saginata*
   c. Infection with *H. pylori*
   d. Pernicious anemia
   e. Atrophic gastritis

2. **Japanese encephalitis virus infection:**
   a. is a significant risk for short-term travelers visiting popular destinations such as Bangkok and Hanoi.
   b. presents in the vast majority of infected persons with mental status change and fever.
   c. can be prevented with vaccines that are FDA-approved for children including newborns.
   d. occurs more commonly in rural areas of Asia near rice paddies.

3. **All of the following organisms are associated with animal pet exposure *except*:**
   a. *Capnocytophaga camimorsus*
   b. *Yersinia pestis*
   c. *Bartonella henselae*
   d. *Vibrio vulnificus*
   e. *Staphylococcus intermedius*

4. **Schistosomiasis has been associated with:**
   a. itchy skin (pruritis).
   b. fever with cough.
   c. portal hypertension.
   d. false positive HIV test results.
   e. All of the above

Answers: 1. b, 2. d, 3. d, 4. e.

PHARMACOLOGY WATCH

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

Women's Health Issue — Adverse Medication Effects

In this issue: Calcium supplements and MI; birth control pills and VTE; ACE inhibitors and breast cancer risk; spending on pharmaceuticals; and FDA actions.

Calcium supplements and MI risk

Do calcium supplements increase the risk of myocardial infarction (MI)? Researchers from New Zealand recently reanalyzed data from the Women's Health Initiative (WHI) in an attempt to answer this question. In 2008 the same group published a randomized, placebo-controlled trial of calcium supplements in nearly 1500 healthy postmenopausal women that showed upward trends in cardiovascular event rates with calcium use (*BMJ* 2008;336:262-266). The same group subsequently carried out a meta-analysis of cardiovascular events in randomized, placebo-controlled trials of women taking calcium supplementation without vitamin D. In that study, calcium supplementation significantly increased the risk of MI by about 30% (*BMJ* 2010;341:c3691). Although these studies garnered some interest, they were also viewed with skepticism, and most physicians, especially in this country, did not change their practice of recommending calcium supplementation for postmenopausal women. The New Zealand group then turned to the WHI data, a rather strange place to look considering that one of the main outcomes of WHI was the finding of no adverse effect of calcium and vitamin D on cardiovascular risk. However, the researchers found one major caveat: WHI did not consider whether women were taking calcium on their own prior to entry into the study. The New Zealand group got access to the original NIH data and were able to tease out women who were not using personal calcium supplements at randomization. They found nearly 17,000 women who fit that category. Women in this subgroup who were randomized to calcium and vitamin D had small but significant increased risk for cardiovascular events with hazard ratios that ranged from 1.13-1.22 ($P = 0.05$ for clinical MI or stroke, $P = 0.04$ for clinical MI or revascularization). When the WHI data were added to the previously done meta-analysis of three placebo-controlled trials, calcium and vitamin D were found to increase the risk of MI (relative risk [RR] 1.21 [95% confidence interval [CI] 1.01-1.44]; $P = 0.04$), stroke (1.20 [CI 1.00-1.43], $P = 0.05$), and the composite of MI or stroke (1.16 [CI 1.02-1.32], $P = 0.02$). Trial level data was available for more than 28,000 women who were randomly assigned to calcium plus vitamin D or placebo. Calcium or calcium plus vitamin D increased the risk of MI (RR 1.24 [CI 1.07-1.45], $P = 0.004$) and a composite of MI or stroke (1.15 [CI 1.03-1.27], $P = 0.009$). The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially MI. They suggest that a reassessment of the role of calcium supplementation in osteoporosis management is warranted (*BMJ* 2011;342:d2040 doi:1136/*BMJ*.d2040, published April 19, 2011). This study has been hotly debated and was even criticized in an editorial in the same issue of *BMJ*. Nonetheless there is a bit of irony in using WHI data, which are largely responsible for millions of women stopping hormone replacement therapy, to show a relationship between calcium and

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cardiovascular disease disease. There is no suggestion in any of these data that dietary calcium leads to adverse events. It is postulated that the rapid increases in calcium that occur with calcium supplementation may somehow play a role in increased cardiovascular risk.

Birth control pills and VTE risk

A progestin commonly used in birth control pills may increase the risk of venous thromboembolism (VTE). A recent report suggests that women taking oral contraceptives containing drospirenone may be at increased risk of VTE compared to women taking contraceptives containing other progestins. Two studies were recently published in *BMJ*. The first was a case-controlled study of U.S. women that showed that women taking drospirenone-containing contraceptives were twice as likely to develop nonfatal VTE compared to women taking levonorgestrel (*BMJ* 2011;342:d2151). The other study, a case-controlled study of British women, showed a three-fold higher rate of VTE with drospirenone-containing contraceptives compared to levonorgestrel (*BMJ* 2011;342:d2139). Oral contraceptives containing drospirenone include Yaz, Yasmin, and Angeliq.

ACE inhibitors and breast cancer risk

Researchers at UCLA and Kaiser Permanente in northern California recently published data suggesting that angiotensin converting enzyme inhibitors (ACEi) may increase the risk of breast cancer recurrence in breast cancer survivors. Using a database of nearly 1800 women with a history of breast cancer, there were 292 recurrences, 174 breast cancer deaths, and 323 total deaths. Twenty-three percent of the women in the study were exposed to either a beta-blocker or an ACEi. ACEi exposure was associated with breast cancer recurrence 1.5 times baseline (HR 1.56, 95% CI 1.02-2.39, $P = 0.04$) but not increased cause-specific or overall mortality. Beta-blocker exposure was associated with lower hazard of recurrence and cause-specific mortality. There was no dose-response with either medication. When a beta-blocker was combined with an ACEi, there was a lower hazard ratio for recurrence than with ACEi alone. The authors suggest that ACEis may be associated with an increased risk of breast cancer recurrence; although beta-blockers may be somewhat protective, more research is needed (*Breast Cancer Res Treat*, published online, DOI: 1007/s10549-011-1503-3). Beta-blockers have been shown to be protective against breast cancer recurrence in other studies, but the ACEi findings were unexpected.

Spending on U.S. pharmaceuticals

Spending on pharmaceuticals in the United States grew at its smallest level in years in 2010, according to a report by the IMS Institute for Healthcare Informatics. Pharmaceutical spending increased 2.3% in 2010 compared to 5.1% in 2009. Generics dominated the pharmaceutical market in 2010 making up 78% of total market share compared to 63% in 2006. Of the top 25 drugs by volume, only three were brand-name products: atorvastatin (Lipitor), clopidogrel (Plavix), and montelukast (Singulair). By spending dollars, however, Lipitor was the top grossing product at $7.2 billion in 2010, down from $7.6 billion in 2009. Esomeprazole (Nexium) was second at $6.3 billion, while Plavix ranked third at $6.1 billion. The domination of generics is of major concern to the pharmaceutical industry since there are few new drugs in the development pipeline and several high-profile drugs are due to lose protection soon. Foremost among these is Pfizer's Lipitor. Pfizer has been battling to maintain its patent protection, but generic manufacturer Watson Pharmaceuticals is expected to introduce the first generic atorvastatin in November of this year. Likewise, Merck's Singulair will likely lose its patent protection next year. The economy also has played a role in the decrease in pharmaceutical spending as the total volume of medicines consumed decreased 0.5% in 2010 along with a decrease in the number of doctor office visits of 4.2%. This extends a decline that began in mid 2009 — likely due to higher unemployment and rising health care costs.

FDA actions

The FDA has approved rituximab (Rituxan) for the expanded indication to treat Wegener's granulomatosis and microscopic polyangiitis, two rare vasculitides. The effectiveness of rituximab was demonstrated in a single control trial in which 197 patients with either condition were randomized to rituximab plus glucocorticoids or oral cyclophosphamide plus glucocorticoids. After 6 months, 64% of the patients treated with rituximab had a complete remission compared to 53% of patients treated with cyclophosphamide. Rituximab is manufactured by Genentech.

The FDA has approved gabapentin enacarbil for the treatment of moderate-to-severe restless leg syndrome. The approval was based on two 12-week clinical trials in adults showing the effectiveness of the drug vs placebo. Gabapentin enacarbil is formulated as a once a day extended-release tablet. It is marketed by GlaxoSmithKline and Xenoport as Horizant. ■