TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Volume 16, No. 4
April 2006

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, is a consultant for GlaxoSmithKline and Aventis, and receives funds from Johnson & Johnson. Peer Review, Lin Chen, MD reports no financial relationship relevant to this field of study.

Travel Medicine Advisor® is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305. Periodicals postage paid at Atlanta, GA. POSTMASTER: Send address changes to *Travel Medicine Advisor®,* P.O. Box 740059, Atlanta, GA 30374.
Customer Service:
1-800-688-2421.
Subscription Information:
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Rifaximin For Gastrointestinal Disorders

ABSTRACT AND COMMENTARY

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Synopsis: *Rifaximin, a poorly absorbed rifamycin drug, may have potential for the treatment of a variety of gastrointestinal disorders including hepatic encephalopathy,* Clostridium difficile*-associated diarrhea, and irritable bowel syndrome.*

Source: Adachi JA, DuPont HL. Rifaximin: A Novel Nonabsorbed Rifamycin for Gastrointestinal Disorders. *Clin Infect Dis*. 2006;42:541-547.

POTENTIAL NEW USES OF RIFAXIMIN ARE EXAMINED IN A RECENT CID ARTICLE by Adachi and DuPont. Rifaximin, a semisynthetic derivative of rifamycin, received FDA approval in May of 2004, for the treatment of traveler's diarrhea in patients 12 years of age and older caused by non-invasive strains of *E. coli*. The drug was first approved in Italy in 1987, and is now approved for use in 17 other countries throughout the world. Similar to other rifamycins, rifaximin binds to the β subunit of the bacterial DNA-dependent RNA polymerase, inhibiting the initiation of chain formation in RNA synthesis.

Gastric fluids do not inactivate rifaximin, and it is poorly absorbed with a bioavailability of < 0.4% in the blood following oral administration. The approved dosage of rifaximin for treatment of traveler's diarrhea is 200 mg 3 times a day for 3 days. Recently, in one randomized, double-blind, placebo-controlled study in Mexico, rifaximin was shown to be effective for prevention of traveler's diarrhea as well.[1] Rifaximin is not recommended for use in diarrhea accompanied by fever or blood in the stool, as efficacy has not yet been established for the treatment of diarrhea due to pathogens other than *E. coli*, such as *Campylobacter jejuni*, Shigella, and *Salmonella* spp. Because of negligible oral absorption, dosage adjustments in renal insufficiency and hepatic dysfunction, even patients with hepatic encephalopathy, are not necessary.

Attention is now shifting towards exploring some other potential uses of rifaximin in various gastrointestinal disorders. Several studies suggest there may be another role for rifaximin in the treatment of hepatic encephalopathy. In double-blind studies where rifaximin dosed at 400 mg 3 times a day, it was compared to lactulose. A reduction in ammonia levels and an improvement in cognitive function were also noted with rifaximin treatment. Another study showed rifaximin to be equivalent to neomycin in the treatment of hepatic encephalopathy.

Rifaximin may play a role in the treatment of *C. difficile*-associated diarrhea. Another possible use may include small bowel overgrowth. Rifaximin appears to be effective in reducing small bowel flora and intestinal gas production which should then improve the abdominal distention, bloating, and flatulence associated with irritable bowel syndrome. In one double-blind study, 34 patients with irritable bowel syndrome were randomized to receive rifaximin or activated charcoal. The rifaximin group did experience a reduced production of H_2, decreased severity of symptoms, and reduction in abdominal girth but neither group had improvement in bloating, abdominal pain, or production of CH_4.[2]

Lastly, the use of rifaximin is being examined for inflammatory bowel disease. In a small, randomized, double-blind, placebo-controlled study of 26 patients with ulcerative colitis refractory to steroids, the rifaximin group had a nonsignificant improvement in 64% of subjects compared to 42% of subjects in the placebo group.[3] Another study looked at the use of rifaximin plus ciprofloxacin in patients with pouchitis (inflammation of the ileal reservoir after pouch surgery for ulcerative colitis). Eighty-nine percent of the 18 patients treated with rifaximin plus ciprofloxacin for 15 days demonstrated clinical improvement.[4] For patients with active Crohn's disease, one open-label study of rifaximin given for 16 weeks showed clinical remission in 62% of patients.[5]

COMMENTARY

An effort to examine the use of rifaximin in other gastrointestinal diseases is welcome. As a medication for traveler's diarrhea, the cost, frequency of dosing, and the lack of approval for use of pathogens other than *E.coli* have limited its usefulness. For example, a 3-day course of a generic ciprofloxacin is now about $8.00, whereas 3 days of rifaximin will likely cost a traveler about $34.00. Also, the broader spectrum of activity of the quinolones or azithromycin for the bacterial pathogens of traveler's diarrhea other than just *E. coli* is an important reason why most physicians' prescribing practices have not widely changed. Of course, in the future, as drug resistance issues continue to emerge, rifaximin may play a greater role, especially if it is found to be effective against invasive forms of traveler's diarrhea, such as Campylobacter, Salmonella, and Shigella species. Studies are apparently being planned in Thailand to address this issue.

Three late-phase studies are now enrolling patients.[6] The first study will look at the efficacy of rifaximin dosed at 550 mg twice daily in the prevention of hepatic encephalopathy. The second study will address the usefulness of rifaximin in irritable bowel syndrome. A recent double-blind, placebo-controlled trial of 124 patients with irritable bowel syndrome showed rifaximin dosed at 400 mg twice a day was safe and effective for abdomi-

nal bloating and flatulence.[7] The newer study planned will examine more patients (525 patients) and higher doses of rifaximin (275 mg, 550 mg, or 1100 mg twice daily). The third study enrolling patients is to examine rifaximin use in treatment of *C. difficile*-associated diarrhea. It is a vancomycin comparator, 300 subject, Phase III trial of rifaximin dosed at 400 mg 3 times a day. This study is very timely amidst reports of increasing rates and severity of *C. difficile*-associated disease and the emergence of a strain of *C. difficile* capable of producing levels of toxin A and B that are 16 to 23 times higher than control strains.[8]

Development of resistance is an appropriate concern with any new antibacterial agent. Rifampin has a long track record of clinical use and is well known to be a stimulant of resistance, but so far this appears to occur at a lower frequency with rifaximin. Presently, there does not appear to be evidence of cross-resistance between rifampin and rifaximin but further studies on this important issue will be needed. ■

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Food and Water Safety: Geographic Variations

ABSTRACT & COMMENTARY

By Philip R. Fischer, MD, DTM&H

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

Synopsis: *Bacterial contamination of food and drinking water are global problems. Travelers should always exercise caution even though problems are less often noted in more developed regions of the world.*

Source: Beatty ME, et al. Epidemic Diarrhea Due to Enterotoxigenic *Escherichia coli*. *Clin Infect Dis*. 2006;42:329-334.

In June 1998, there were numerous reports of diarrheal illness in multiple attendees of events catered by a delicatessen in Chicago, Illinois. An investigation revealed that more than 16,000 individuals had attended many events catered by this delicatessen during a 3-day period. An epidemiological study was done on 612 attendees of 11 of these events. Approximately 20% of attendees developed acute gastroenteritis, but none were hospitalized, and no deaths were reported. Ingestion of several different food items (potato salad, macaroni salad, egg salad, and watermelon) was associated with illness. Stool and serologic testing implicated *Escherichia coli* O6:H16 in the epidemic, and this organism was found to produce both heat-stable and heat-labile toxins. (This organism is distinct from the O157:H7 strain that is commonly associated with beef products.)

No food handler admitted to having had recent illness, a history of recent foreign travel, or recent contact with foreign visitors. However, the food production of the delicatessen was about twice as great as usual during the week of the epidemic illness. (As an example, 2889 kg of potato salad were produced during the week and then stored in 22.5 kg containers. Due to limited refrigerator space, some salad was stored in a refrigerated truck without reliable temperature controls, and salads were delivered to some events without refrigeration.) Salad ingredient preparation and mixing was done manually. There were neither soap nor paper towels in the main kitchen. A new dishwasher had been installed in the delicatessen just prior to the beginning of the epidemic; during that time, there were areas where low-

Table 1

Bacterial Contamination of Water Samples Detained In a Ninth Grade Science Project

Site Country	Locality	Sample Source	Contamination (positive/total samples)
Bangladesh	Chakaria	hospital housing	1/2
	Dhaka	hotel	2/2
		airport restroom	1/1
Japan	Narita	airport restroom	0/2
Kenya	Limuru	conference center	0/1
	Nairobi	airport restroom	0/1
Mexico	Cabo San Lucas	resort	0/4
		home	1/1
		bus stop	1/1
		airport restroom	1/2
Thailand	Bangkok	hotel	1/2
United Kingdom	London	hotel, train	0/2
United States	Minnesota	home, restaurant	0/4

pressure water could stagnate and potentially mix with waste water. Serologic testing of delicatessen workers was performed 2 weeks after the initial cases of illness. By the time of the investigation, however, no enterotoxigenic *Escherichia coli* were found in either food handlers or in the delicatessen.

Thus, an epidemic of gastroenteritis due to enterotoxigenic *Escherichia coli* (ETEC) affected approximately 3300 people in Chicago in June 1998. The epidemic was linked to poorly stored food and potential mixing of wastewater with the potable water system in a single delicatessen.

COMMENTARY

Practitioners of travel medicine are well aware of the risk of ETEC gastroenteritis in travelers who ingest improperly prepared foods or beverages in developing countries. The paper from Beatty and colleagues at the CDC and at county and state public health agencies in Illinois serves to remind us, however, that ETEC diarrhea is not limited to locations outside of North America. Traveler's diarrhea is simply not limited just to travelers.

Much of travel medicine deals with balancing the risks and benefits of preventive interventions. Usually, it is not necessary to avoid salads at catered events in the United States, and previously cooked, stored foods may be eaten without worry. This paper, however, illustrates that any lapse in attention to food and water hygiene can prove disastrous.

Where in the world is water usually safe? The Cryptosporidium outbreak in Milwaukee in the early 1990s showed that even expensive, elaborate municipal water treatment systems can become contaminated.[1] Up to about half of travelers to developing countries develop diarrhea,[2,3] but the incidence of illness is greater in less developed countries. Unfortunately, most travelers do not follow routine food and water hygiene recommendations.[4] Interestingly, though, there is some evidence that implementation of food and water recommendations do not correlate with prevention of diarrhea.[5]

While traveler's diarrhea rates vary geographically,[6] there is no accurate way to predict an individual traveler's risk of bacterial contamination within and between foreign destinations. Anecdotal evidence from a 7th grade science project, however, provides a basis for some observations that could potentially be validated in a more rigorous study.

Joanna Fischer obtained water samples from several countries from her globe-trotting father as part of a science project at Schaeffer Academy in Rochester, Minnesota. Water samples were plated on blood agar, and the presence or absence of subsequent bacterial growth was noted. *Table 1* shows her results.

Water available for drinking in industrialized nations (Japan, United Kingdom, United States) seems relatively safer than water in less industrialized countries. One of the British samples came from a tap on a train that was labeled "not for drinking;" travelers should know that minerals and toxins can pose problems even when water is not contaminated with bacteria. Second, water from resorts and conference centers (such as the ones tested in Mexico and Kenya) with private treatment facilities likely poses less risk to travelers than does water obtained from taps throughout surrounding municipal areas. Third, even in seeming modern areas of developing countries such as Thailand, food and water precautions are still likely indicated. Indeed, a recent review of illness in returned travelers highlighted the frequency of traveler's diarrhea in individuals returned from Asia.[6]

Travel medicine specialists are concerned with the health of residents of developing countries.[7] In the developing world, resources should be allocated to improve the safety of locally available drinking water. And, even in seemingly developed nations, residents and visitors should remain vigilant to ensure that appropriate food and

water hygiene measures are implemented. Until then, the future development of an effective and affordable ETEC vaccine offers additional hope of protection.[8] ■

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Fevers Along the Thai-Myanmar Border

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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

Synopsis: *Malaria, leptospirosis, and rickettsiosis are the most commonly identified etiologies of fever in adult patients near the Thai-Myanmar border, and dual infections occur frequently. Travelers planning rural stays in this region should be advised regarding the risks and prevention.*

Source: Ellis RD, et al. Causes of Fever in Adults on the Thai-Myanmar Border. *Am J Trop Med Hyg*. 2006;74:108-113.

Collaborators from the Armed Forces Research Institute for Medical Sciences (AFRIMS) and the Kwai River Christian Hospital assessed the causes of febrile illness in the adult population in Sangkhlaburi, Thailand, near the border with Myanmar. Six hundred thirteen inpatients and outpatients were included in a study from June 1999 to March 2002, with an age range from 20-87 years. The patients were tested at fever presentations for complete blood count, malaria smears, biochemistry panel including alanine transferase (ALT), glutamyl transferase (GGT), blood urea nitrogen (BUN), and creatinine. Leptospirosis, dengue, and Japanese encephalitis serologies were tested. Subjects were selected for serology or PCR testing for rickettsioses, typhoid, melioidosis, Q fever (*Coxiella burnetii*), and other tests based on both clinical criteria and judgment. Testing was repeated 2-4 weeks after enrollment.

About half of the subjects had specific etiologies identified. Malaria was the most common etiology, diagnosed in 25% of subjects, with 61% being *Plasmodium falciparum*. Leptospirosis was the second most frequent etiology, diagnosed in 17.5% of subjects. Rickettsiosis was diagnosed in 6%, followed by dengue (1.5%), pulmonary tuberculosis (1.1%), typhoid fever (0.8%), and Japanese encephalitis (0.2%).

Among the subjects who had clinical diagnoses (but no etiologic diagnoses), fever not specified was the most common category (25%), followed by respiratory infections, gastroenteritis, and urinary tract infections. There were 8 deaths, ultimately attributed to typhoid (2), leptospirosis (1), clinical end-stage AIDS (2), fever not specified (2), and hepatitis of unidentified etiology (1).

Dual diagnoses were common among the subjects involving 17% of smear-positive malaria cases, 26% of leptospirosis cases, 11% of rickettsial cases, and 22% of dengue cases. Comparison of age, sex, admission status, symptoms at presentation, and laboratory abnormalities showed association for malaria with outpatient status, documented fever, and thrombocytopenia. Leptospirosis was associated with elevated ALT. Rickettsial disease was associated with older age, elevated GGT, and rash, although the latter was a criteria for serologic testing.

■ COMMENTARY

The landscape around Sangkhlaburi near the Thai-Myanmar border is rural, with rice fields, farms, lakes, streams, and forests. There is frequent flooding, and the area is endemic for malaria. This study confirms that *Plasmodium falciparum* is the most commonly identified etiology for fever in adults residing in the area, which is consistent with other data that have shown *P. falciparum* to cause 56% of malaria cases in Thailand.[1] Travelers visiting border areas of Thailand should take precautions to reduce the risk of acquiring malaria in this region.

The study highlights the prevalence of leptospirosis and rickettsiosis as causes of fever in rural Thailand. Leptospirosis is the second most frequent etiologic diagnosis identified, caused by a zoonotic spirochete usually infecting rodents and domestic animals. Leptospires are shed in animal urine, which can contaminate fresh water. Humans are exposed through contact with fresh water, soil, or direct contact with infected animals, and the organisms enter through abraded skin. After the infection, there is an incubation period of 7-12 days (range, 3-30 days) before onset of symptoms, which include fever, myalgia, headaches, rash, conjunctival suffusion, nausea, and vomiting.[2] Severe symptoms, including aseptic meningitis, pulmonary hemorrhage, liver dysfunction, and renal failure can occur.[2] Residents in this region with much exposure to fresh water in the environment are understandably at significant risk of acquiring leptospirosis.

Similarly, the local population has significant exposure to rickettsioses through their outdoor occupations in farming or forestry. In addition, many houses are open wood and thatch constructions, some with walls made of scrap materials only. Many village homes in the area have domestic animals all around them. There is likely an abundance of ticks, mites, and fleas, vectors of spotted fever group (SFG) rickettsiosis, scrub typhus, and murine typhus, respectively. Spotted fever group (SFG) rickettsioses are zoonoses caused by obligate intracellular gram-negative coccobacilli within the genus Rickettsia. The etiologic agent of scrub typhus is *Orientia tsutsugamushi*, known to be endemic in Asia, and the agent of murine typhus is *Rickettsia typhi*, with worldwide distribution.

Infections with SFG rickettsiosis, scrub typhus, and murine typhus generally have incubation periods of 1-2 weeks (4-7 days for SFG and up to 20 days for scrub typhus).[3-5] The diseases are associated with fever, myalgias, headache, eschar, rash, abdominal pain, nausea, vomiting, and sometimes cough, renal failure, confusion, seizures and arrhythmias.[3-5] Skin manifestations include eschars, maculopapular, or vesicular rash.[3-5]

Ellis and colleagues found dengue and Japanese encephalitis to be less common causes of fever in this study on adults, due to the fact that these infections occur more frequently in childhood. Adults in rural Thailand may be immune against Japanese encephalitis from childhood immunization. The majority of dengue cases in Thailand occur in children, and adults are often immune to dengue from prior exposures.

Leptospirosis is an emerging disease, and outbreaks have occurred in travelers participating in water sports or competitions.[6] Because of leptospirosis' worldwide distribution, travelers with possible exposure to fresh water should be advised of the risk of acquiring leptospirosis.

SFG rickettsiosis has previously been reported in travelers, most frequently in travelers to Africa,[7-9] but this study in Thailand illustrates the presence of the disease and its significance as a cause of febrile illnesses. This is probably the tip of the iceberg, and rickettsiosis should be considered an emerging disease. Travelers with rural destinations, especially with outdoors activities, should be advised of the risk.

Unfortunately, cultures could not be performed in this study to ascertain the true prevalence of typhoid fever and melioidosis, as well as endocarditis and bacteremia of various causes. However, typhoid fever was identified by PCR, and its association with deaths and bowel perforation supports its significance as a cause of fever in rural areas of Thailand. Melioidosis is prevalent in other parts of Thailand, and confirmation of presence of the infection in this region is important for therapeutic considerations. Tuberculosis is probably a more common cause of fever, but the study only classified cavitary lesions and/or acid-fast bacilli on sputum smear to be pulmonary tuberculosis.

Finally, coinfections appear to be common. It is important to keep in mind the possibility of coinfection in assessing patients returning from the tropics with multiple possible exposures. If a febrile traveler is not responding to treatment for an identified pathogen, a second etiology must be sought. Because of its efficacy against leptospirosis and rickettsiosis, and because of mefloquine-resistant *P. falciparum* in the region, doxycycline appears to be an optimal malaria chemoprophylaxis for travelers visiting the Thai-Myanmar border. This study provides additional emphasis on preventing arthropod bites and fresh water exposure for travelers visiting rural Thailand and Myanmar, and likely most SE Asian countries. ■

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Management of Occupational Exposures to HIV

ABSTRACT & COMMENTARY

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Dr. Mileno is a consultant for GlaxoSmithKline, and does research for Merck.

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

Synopsis: *Exposures to blood-borne pathogens continue to pose serious risks to health-care personnel (HCP) and may be especially serious for those working in the developing world. The most likely blood-borne exposures of concern include Hepatitis B, Hepatitis C, and HIV. The field is evolving such that travel medicine specialists advising students and other health providers must take many issues into consideration when advising on appropriate post exposure prophylaxis for potential HIV infection.*

Source: Panlilio, AL, et al. Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis. *MMWR Recomm Rep*. 2005;54:1-17.

Exposure of healthcare personnel to either blood or the bloody secretions of an HIV-seropositive person has only occasionally resulted in HIV infection. This *MMWR* article cites risks after exposure to HIV-infected blood: transmission of HIV occurs at a rate of approximately 0.3% after percutaneous exposure, 0.1% after mucous membrane exposure, and < 0.1% after exposure to the non-intact skin. We will focus on post-exposure prophylaxis (PEP) and current management strategies, which have been twice updated since 1996, concerning potential exposures to HIV in the healthcare setting.

COMMENTARY

At the moment of exposure to blood or other body fluids, it is imperative to provide both counseling and medical evaluation to delineate the type and degree of exposure encountered. It is also important to obtain as much detail about the source patient's HIV status as possible. If the source patient is HIV seropositive, one must determine what HIV drug regimens the patient has been using as well. Such information will determine both who should receive prophylaxis and which drugs are likely to be effective.

It is important to understand the types of potentially infectious exposes in the healthcare setting, as well as the degrees of the exposures. Various types of infectious materials include whole blood and bodily fluids that are visibly bloody. Highest risk is associated with a needlestick from a large bore needle that contains blood from a known HIV-infected individual. Percutaneous injury might include a cut with a sharp object, contact of mucous membranes or exposed skin that is chapped, abraded, or affected with dermatitis, by blood, tissue, and open body fluids that are potentially infectious. Fluids that are potentially infectious but for which the risk of HIV transmission is simply unknown include: pleural, cerebrospinal, peritoneal, pericardial, amniotic, and synovial fluids. Those fluids that are considered non-infectious, unless they are visibly bloody, include saliva, tears, urine, feces, vomitus,nasal secretions, sputum, and sweat.[1]

The level or degree of exposure encountered can help to determine which PEP regimen to utilize. The CDC categorizes less severe vs more severe percutaneous injuries and small versus large volume exposures. The quantity of blood is considered large if a device is visibly contaminated with blood; if a procedure involved a needle placed directly into a vein or artery or if a deep injury occurred. PEP should be initiated within hours depending on the type and degree of exposure. Examples of recommended basic and expanded regimens are provided in the review. Healthcare workers seeking experiences abroad in countries with burgeoning HIV disease should carry an initial phase of a PEP regimen (Combivir one tablet orally twice each day with Kaletra 3 capsules orally twice per day, taken with food) provided with complete instructions for high risk exposures because testing and treatment for HIV infection may not be readily available).

Once PEP has been initiated, it is important to provide a structure for post-exposure monitoring. Baseline HIV antibody tests should be drawn from the healthcare provider (HCP), as well as the source patient. HIV seronegative HCPs should have follow-up testing performed at 6 weeks, 12 weeks, and 6 months after exposure to determine whether transmission has occurred. The average duration of time to seroconversion of exposed individuals who have been infected is within 3 months.[2] Some studies have shown 4 weeks of zidovudine to be protective although the optimal duration for PEP is unknown. We suggest 4 weeks of HIV PEP be administered. If it is determined, however, that the HIV status of the source patient is negative, then PEP should be discontinued.

Several additional considerations exist regarding selection of HIV PEP regimens although these complexities should not delay the timing and initiation of PEP. Although choice of agents is primarily empiric, some patients with high body burden of HIV deliver higher levels of viral exposure, and 3 or more drugs may be indicated. Second, resistance of source patients' HIV virus to antiviral agents is a serious concern when choosing a PEP regimen. Since publication of the last set of guidelines, an additional report of an occupational HIV seroconversion, occurring despite combination therapy HIV PEP, has been published. This exposure was a percutaneous injury sustained by a nurse performing a phlebotomy on a heavily treatment-experienced patient. In addition, all approved antiviral agents may have adverse effects and potentially serious drug interactions when used with certain other medications. During pregnancy, primate data indicate that we should not use efavirenz. Indinavir can lead to hyperbilirubinemia and renal stones. Combination therapy with d4T and ddI should be avoided in treatment of HIV due to reports of mitochondrial dysfunction and fatal lactic acidosis, particularly during pregnancy.

First and foremost, emphasis must be given to providing counseling to HCP who have had exposures, particularly during those weeks of uncertainty requiring both emotional support and monitoring of adverse events, as well as advice for safe sexual practices until viral transmission has been excluded. ■

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CME Questions

5. Which of the following is true regarding rifaximin?

a. It requires dose adjustment in renal failure.
b. It is FDA approved for use in *Salmonella enteritis*.
c. It achieves high serum drug levels
d. It is being studied for possible use in hepatic encephalopathy, irritable bowel syndrome, and *C. difficile*-associated diarrhea.
e. It is approved for treatment of traveler's diarrhea in children under 12.

6. Enterotoxigenic *Escherichia coli*:

a. may cause gastroenteritis, but generally only in developing countries.
b. rarely causes diarrhea in travelers who have received pre-travel health advice.
c. frequently causes traveler's diarrhea through contamination of beef products.
d. may contaminate food and beverages in industrialized as well as developing countries.
e. are the most common cause of spontaneous dysentery syndromes.

7. Which of the following statements regarding causes of fever in rural Thailand is correct?

A. The predominant species of malaria in Thailand is *Plasmodium vivax*.
B. Japanese encephalitis is found to be the cause of fever more frequently than malaria.
C. Malaria ought not be considered in the work up of febrile patients returning from the Thai-Myanmar border since it is uncommonly found there.
D. Leptospirosis should be considered strongly in febrile travelers returning from rural Thailand.
E. Coinfection with malaria rarely occurs, and continued fevers need no further work up.

8. Which of the following criteria is not considered during the selection of post exposure HIV prophylaxis (PEP)?

a. The number of prior exposures the Health Care Provider has received in their work.
b. The volume of blood to which the provider has been exposed.
c. The size or bore of the needle which provided the exposure to the provider.
d. The experience of the infected patient who provided the exposure to previous antiretroviral therapy.
e. Whether the exposed provider is pregnant or not.

Answers: 5. (d); 6. (d); 7. (d); 8. (a)

CME Objectives

The objectives of Travel Medicine Advisor are:

• 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.

Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

Treatment of Benign Prostatic Hyperplasia

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

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commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■